High vs. Standard Dose Flu Vaccine in Adult Stem Cell Transplant Recipients

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Statement of Compliance

This clinical trial will be conducted in accordance with the protocol and Good Clinical Practice (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, 54 and 56; 21 CFR Part 312).
- International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule-Final Modification (45 CFR Parts 160 and 164);
- National Institutes of Health (NIH) Clinical Terms of Award

Compliance with these standards provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

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

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.

Principal Investigator: Natasha B. Halasa, MD, MPH
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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 (signatures(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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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 ≥4-fold rise and HAI titer ≥1:40 and higher* geometric mean titer *(GMT) to influenza A antigens compared to the standard dose quadrivalent inactivated influenza vaccine (SD-QIV) group.*

   Specific Aim #1: To determine whether HD-TIV compared with SD-QIV will increase the probability of achieving either a ≥4-fold rise in HAI titer, a HAI titer ≥1:40, or a higher GMT to influenza A antigens in adult HSCT recipients.

2. **Hypothesis 2:** *We hypothesize that HD-TIV will be well tolerated, with a safety profile similar to SD-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 SD-QIV in adult HSCT recipients.

3. **Hypothesis 3:** *We hypothesize that 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 SD-QIV.*

   Specific Aim #3: To define the relationship between HAI titers, *in vivo* T and B cell phenotype, and *in vitro* influenza-specific T and B cell responses in adult HSCT recipients receiving either HD-TIV or SD-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.[1] Mortality due to infections is seen in 8-17% of HSCT patients who died within 100 days post-transplant.[1] Influenza A and B are important causes of morbidity and mortality in high-risk individuals, including HSCT recipients;[2] however, the majority of disease is due to circulating influenza A/H3N2 or influenza A/H1N1.[3,4] 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 confirmed influenza patients, 23% died.[5] Reported mortality rates in HSCT associated to influenza range around 15-17%;[5,6] 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%.[2,5-8] In the general population, an influenza epidemic can be associated with attack rates of 10–20%; however, increased attack rates are seen in individuals with cancer, including HSCT recipients.[9-12]

Moreover, significant morbidity and mortality were noted in HSCT recipients during the recent influenza A/H1N1 pandemic, with several reports showed increased rates of pneumonia, lower respiratory tract infections, and even death.[13-19] Since immunosuppressed individuals can shed influenza virus for prolonged periods after infection, they pose significant risk for promoting nosocomial influenza outbreaks,[20-22] and the development of antiviral resistance.[23] HSCT recipients infected with pandemic influenza A/H1N1 and treated with oseltamivir have been shown to develop high rates of antiviral resistance while on antiviral therapy.[18,24-26] The risks for severe influenza or fatal outcome in HSCT recipients include lymphopenia, older age, neutropenia, influenza soon after transplantation or chemotherapy, steroid treatment, and late initiation of antiviral therapy.[8,11,27,28] 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.[2] 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 who 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%.[2] 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.[29]

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, and functional recovery of B and T lymphocytes can take up to 2 years or even longer.[30] Prior studies of influenza vaccines in HSCT recipients have been reported; however, the majority of these studies were conducted at single centers.[31-45]

Despite limited clinical data for influenza vaccine efficacy in this population, yearly vaccination is recommended, beginning 3-6 months after HSCT.[46] 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,[46] with little data to support vaccinating earlier post-transplant.[46] The percentage of HSCT recipients that achieve seroprotective hemagglutinin inhibition (HAI) titers (defined as ≥1:40) one month after standard influenza vaccination is very low when compared to healthy controls. While impaired vaccine-induced immune responses are likely due to incomplete immune reconstitution or ongoing immunosuppressive therapy, 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 $CD19^+$ B cells, and early post-transplant vaccination have been implicated as factors associated with lower titers after influenza vaccine.[8]

Authors of the 2013 *European Guidelines for the Prevention and Management of Influenza in HSCT and Leukemia Patients,* recommend 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 it may only have marginal benefit.[8] Results from trials comparing two doses of influenza vaccine are conflicting: some suggest no benefit from a second dose, while others demonstrate an increase in influenza titers after the second dose in HSCT recipients.[18,31,41,44,47] 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.[18,44,47]

In contrast, the *2013* Infectious Disease Society of America (IDSA*) Clinical Practice Guidelines for Vaccination of the Immunocompromised Host* recommends yearly vaccine with IIV to be administered 6 months after HSCT or as early as 4 months after HSCT during an influenza outbreak.[48] Thus, both the optimal timing of influenza vaccination and the ideal number of IIV 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.[49] This strategy is successful in individuals ≥65 years, a group with a historically poor response to influenza vaccines compared to healthy young adults.[50-52]

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.[50] The first trial enrolled 202 adults ≥65 years who were randomly assigned to 15, 30, or 60 µg of hemagglutinin per strain or placebo.[52] Mean serum HAI antibody titers one month after immunization in groups given 0, 15, 30 and 60 µg 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.[52] Mean serum HAI and neutralizing antibody levels against the three vaccine antigens in participants given the 60µg dosage were 44% to 71% and 54% to 79%, respectively, higher than those in participants given the standard 15 µg dosage. Among recipients with low pre-immunization antibody titers, the rate of seroconversion was nearly double for

those who received 60 µg, as compared to 15 µg dosage level.[52] 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 ≥65 years of age to receive either 15 µg versus 60 µg of TIV.[51] 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 (SD-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 serum antibody increases (≥4-fold) 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.[51] Mean titers of antibody attained, the magnitude of antibody increases, and the frequencies of persons with final HAI antibody titers ≥1:32, ≥1:64, and ≥1:128 were all greater for the HD-TIV group in both serologic tests (e.g., HAI and neutralization assays), for all titer groups ≥1:32, ≥1:64, and ≥1:128), and for all vaccine viral strains compared to the SD-TIV.[51]

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 ≥65 years of age to compare HD-TIV to SD-TIV.[53] HD-TIV was administered to 2575 subjects and SD-TIV was administered to 1262 subjects. Individuals who received HD-TIV had higher mean post-vaccination GMT **(Table 1).** The HD-TIV vaccine met 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 SD-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 SD-TIV group in this phase III trial led to the licensure of HD-TIV in individuals ≥65 years.[50] 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 SD-TIV.[54]

Table 1.	HD-TIV	SD-TIV	GMT ratio
H1N1	116	67	**1.7**
H3N2	609	333	**1.8**
B	69	52	1.3

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 Medical Center, compared HD to SD-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 HD-TIV or SD-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. Twenty-nine subjects received HD-TIV and 15 subjects received SD-TIV. The HD-TIV group had higher median IgG levels (676 vs. 469, p=0.025). The HD group reported more local symptoms compared to SD. No serious adverse events (SAEs) were attributed to the vaccine, and no differences in systemic reactions were noted. The HD-TIV group had a higher percentage of individuals with a HAI titer ≥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 of 6.9. These results are published in *Biology of Blood and Marrow Transplant*.[55]

b. Pediatric Solid Organ Transplant (SOT) Recipients. This multi-center, randomized, double-blind, phase I safety and immunogenicity trial, conducted at Vanderbilt University Medical Center and the Children's Hospital of Pittsburgh during the 2011-12 influenza season, compared HD to SD-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 SD-TIV. No individuals had rejection associated with vaccination. Fatigue and body ache were greater in the HD group compared to the SD 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 SD group (56% versus 13%, p=0.08). These results are published in *Pediatric Transplantation.*[49]

c. Pediatric Acute Lymphoblastic Leukemia (ALL) Subjects. This single-center, randomized, double-blind, phase I safety and immunogenicity trial was conducted at Vanderbilt University Medical Center, comparing HD to SD-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 SD. Safety data revealed no differences between the groups for total solicited systemic and local reactions; however, the SD group reported more fatigue and headache. No SAEs were attributed to vaccination. The immune response, measured by a ≥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.*[56]

d. Adult Oncology Patients Receiving Chemotherapy. This single-center, randomized, double-blind safety and immunogenicity trial was conducted at Rochester General Hospital, comparing HD to SD-TIV in adults 18-64 years of age who were receiving chemotherapy for malignancy.[57] One hundred five subjects were enrolled (47 in year 1 and 58 in year 2), with a mean age of 53.4 years, 53% were male, and 10% had hematological malignancies. Fifty four subjects were given HD and 51 were given SD. Safety data revealed no differences between the groups for total solicited systemic and local reactions; however, the HD group reported more localized pain.[57] No SAEs were attributed to vaccination. The immune response, measured by HAI GMT, was improved in the HD group, as post vaccination HAI GMT for H3N2 and B were significantly higher than those documented in the SD group. Additionally, the HD group had a higher percentage who achieved a 4-fold rise in H1N1, H3N2 and B titers [72% versus 46% (p=0.014), 80% versus 58% (p=0.029), 80% versus 44% (p=0.0004) respectively].[57]

e. Children and Young Adults with Cancer or Human Immunodeficiency Virus (HIV) infection. This single-center, randomized, open-label safety and immunogenicity trial was conducted at St. Jude Children's Research Hospital, comparing HD to SD-TIV in subjects aged 3-21 years old who were receiving chemotherapy for malignancy or had HIV infection.[58] Eighty five participants were enrolled (27 with leukemia, 17 with solid tumor, and 41 with HIV), with a mean age of 14.8 years and 66% were male. Forty one subjects received 2 doses of HD and 42 received 2 doses of SD (administered at least 21 days apart). HD subjects with leukemia had a greater fold increase in HAI titers compared to SD leukemia subjects to B antigen [geometric mean ratio (GMR), post second dose/pre-vaccine; 11.2 versus 3.9, p=0.04] and HD subjects with solid tumors had a greater fold increase in HAI titers compared to SD solid tumor subjects to H1 antigen (GMR 10.2 versus 3.7, p=0.04).[58] There were no differences in the proportions of subjects who seroconverted, defined by a ≥4-fold rise in HAI titer if HAI titer was ≥1:10 pre-vaccine or HAI titer ≥1:40 if pre-vaccine titer was <1:10, between those that received HD versus SD. However, higher proportions of subjects in both groups (HD and SD combined) seroconverted after the second dose of vaccine compared to the first dose (67% versus 42% for antigen H1, 80% versus 46% for antigen B, p<0.0001 for both). Safety data revealed no differences between the groups for total solicited systemic and local reactions; however, the HD group reported more localized pain and fatigue. One adverse event was attributed to the first HD vaccination (somnolence that spontaneously recovered within 2-3 hours).

f. Adult Kidney and Liver Transplant Recipients. This single-center, randomized safety and immunogenicity trial was conducted at Lausanne University Hospital, comparing HD to SD-TIV in subjects at least 18 years of age and at least 3 months out from either kidney or liver transplantation. Seventy-nine subjects were enrolled with a mean age of 58 years and 61% were male. Safety data revealed no differences between the groups for systemic or local reactions. The HD group had higher GMT to B antigen than the SD group, and also higher seroconversion (defined as ≥ 4 fold rise in HAI) rates to B antigen two weeks after vaccination.[59]

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 virus infections have been antigenically related to the B virus component of the trivalent flu vaccines.[3] A SD-QIV is currently available and provides additional protection against the second B strain while retaining non-inferior immunogenicity to the other 3 TIV strains.[60,61]

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 SD IIV. HD-TIV has increased immunogenicity and efficacy in adults ≥65 years compared with SD,[54] and in many phase I studies in an immunocompromised population, there are data suggesting that HD may have increased immunogenicity. Therefore, the use of HD-TIV appears to be a promising and practical alternative intervention to improve vaccine-induced immune responses in adult HSCT recipients. ***We hypothesize that HD-TIV will be more immunogenic compared with SD-QIV and will remain well tolerated in this vulnerable population.*** Thus, for this protocol we propose to conduct a phase II trial and compare the immunogenicity and safety of HD-TIV to SD-QIV in adult stem cell transplant recipients.

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, including in those patients without co-morbidities.[62] Moreover, this study has significant potential to impact clinical practice in adult HSCT patients. Demonstration of safety and greater immunogenicity of HD-TIV versus SD-QIV in this population could alter current influenza vaccine recommendations. Administering two doses of vaccine creates the opportunity to separately examine the immunogenicity induced after the first and second dosage. Additionally, successful use of HD-TIV to enhance influenza-specific immune responses in adult 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 SD-QIV in adult HSCT recipients. 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 SD-QIV (15µg of each influenza antigen) of the season-specific vaccine 28-42 days apart. Approximately 30-60 mLs of blood will be collected for HAI and microneutralization (MN) assays to influenza virus antigens, phenotypic B, and T cell responses, B and T cell specific influenza responses, complete blood count with differential and platelet count (CBC d/p), quantitative $CD4^+/CD8^+/CD19^+$ levels, and quantitative serum IgG and IgM concentrations prior to and 4-6 weeks after the first and second dose of each influenza vaccine and 7 months after second vaccine. If subjects are receiving intravenous (IV)/ subcutaneous (SC) IG during any visit, additional sera will be collected to measure HAI and MN titers after IVIG/SCIG. Subjects will record solicited events for 7+ days (Day 0-7) after each vaccination. On days 1-3 and 8-10, an electronic communication will be attempted to assess for solicited AEs following each vaccination, unless a subject is seen within this window period for an optional visit. Each female of childbearing potential will be given a pregnancy test before each vaccination. If she is pregnant, she will not be eligible for the study. An optional visit 5-10 days after each vaccination will be included for those subjects who volunteer to come back for a blood draw only, and approximately 30-60 mLs of blood will be collected for B and T cells responses. If within the 8-10 day telephone and/or electronic communication window, this would replace the 8-10 day communication.

   *Note, if blood is drawn and discarded for clinical reasons, blood volumes can exceed 60 mLs.

Subjects enrolled during the 2017-2018 season were approached for repeated enrollment during the 2018-2019 season. Subjects enrolled for the first time during the 2018-2019 season will be approached for repeated enrollment during the 2019-2020 season.

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.[63,64] During the influenza season, the participants will be carefully followed for influenza like illness (ILI) with weekly telephone and/or electronic communications by the study staff.

If subjects meet ILI criteria (see below), a nasal swab will be collected and PCR testing for influenza and other respiratory viruses will be performed at VUMC.

If they have any of the following:

1. **Fever:** ≥38.3°C (101°F); or
2. **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).

Additionally, we will attempt to collect nasal swabs from subjects who meet the ILI criteria during the study time (out of the flu season). Nasal swabs will be obtained at all scheduled visits to document the occurrence of influenza virus detection both prior to and after vaccination.
Data regarding about any breakthrough clinical influenza illness will be collected during the study period and until June 30th.

2. Primary and Secondary Study Objectives:

a. Primary Objectives:

- **i.** To determine whether HD-TIV compared with SD-QIV will increase the probability of achieving a ≥4-fold rise in HAI titers, ≥1:40 HAI titer, or higher GMT titers to influenza A antigens in adult HSCT recipients.

b. Secondary Objectives:

- **i.** To determine whether HD-TIV compared with SD-QIV will increase the probability of achieving a ≥4-fold rise in HAI titers, ≥1:40 HAI titer, or higher GMT titers to influenza B antigens in adult HSCT recipients.
- **ii.** 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 SD-QIV in adult HSCT recipients.
- **iii.** 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 SD-QIV in adult HSCT recipients.
- **iv.** To define the relationship between HAI titers, *in vivo* T and B cell phenotype, and *in vitro* influenza-specific T and B cell response in adult HSCT recipients receiving either HD-TIV or SD-QIV.
- **v.** To correlate HAI responses to MN responses.
- **vi.** To compare the persistent HAI and MN titers for all four antigen seven months after the last vaccine dose to assess for persistence of antibody titers.
- **vii.** To compare influenza detection by PCR during influenza season in adult HSCT recipients receiving either HD-TIV or SD-QIV.
- **viii.** To assess HAI and MN response in patients (e.g. repeaters) undergoing two-consecutive years revaccination using the same antigen dose
- **ix.** To correlate HAI responses to neuraminidase inhibition titers (NAI).

3. Study Area: The study will be conducted in the Oncology Units or Clinics, or Clinical Trial Centers at the following sites: **Table 2** includes the yearly average number of transplants per site.

Table 2. Clinical Sites	**Average Number of Yearly Allogeneic Transplants**
Northwestern University Feinberg School of Medicine	167
Fred Hutchinson Cancer Research Center	300
University Hospital, University of Alabama at Birmingham	90
Vanderbilt University Medical Center	108
TOTAL	**665**

4. Study Population:

1. **A target of at least 138 new subjects who received an allogeneic HSCT over two enrollment years: 2017-18 and 2018-2019. The following were the inclusion/exclusion criteria that were used:**

a. Inclusion criteria

1. Allogeneic HSCT recipients who are 3-23 months post-transplant;
2. ≥ 18 years of age;
3. Available for duration of study;
4. 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).
5. Can be reached by telephone and/or electronic communication
6. Subjects must have a platelet count of ≥30,000 to receive the immunizations. Patients requiring platelet transfusions are eligible to enroll and must have a platelet count ≥30,000 within 72 hours prior to their immunization, or platelet count ≥75,000 without transfusion documented within 30 days for subjects <12 months post-transplant and within 90 days for subjects 12-23 months post-transplant.

b. Exclusion criteria

1. History of hypersensitivity to previous influenza vaccination or severe hypersensitivity to eggs/egg protein;
2. History of Guillain-Barre syndrome;
3. Evidence of hematologic malignancy or disease relapse post-transplant (stable mixed chimerism is permitted);
4. History of receiving current seasonal influenza vaccine post-transplant;
5. Pregnant female;
6. History of proven influenza disease after September 1, 2018 prior to enrollment;
7. Non-allogeneic (e.g. autologous) or syngeneic hematopoietic SCT recipients;
8. History of known active infection with HIV
9. History of cirrhosis
10. History of known latex hypersensitivity;
11. Subjects who have received stem cell boost or delayed donor lymphocyte infusion within 90 days of enrollment, including day of enrollment
12. Receipt of. IVIG/SCIG <28 days prior to vaccination

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 ≥100.4ºF/38.0ºC (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.

For subjects who were enrolled and vaccinated in 2017-18, and 2018-19, the goal is to enroll these same subjects who participated the previous influenza season year and then administer the same vaccination as the previous year. These subjects are referred to as repeaters.
For example, subjects enrolled in 2017-18 year were eligible to enroll again in 2018-19 as repeaters. For subjects enrolled in 2018-19 year and received at least one vaccine, will be eligible to be enrolled as repeaters for 2019-2020 season.

Enrollment Criteria for Repeaters - Subjects who Participated in a previous influenza season:

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

1. **Inclusion Criteria for Repeaters**
    a. Available for duration of study;
    b. Can be reached by telephone and/or electronic communication
    c. 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).
    d. Subjects must have a platelet count of ≥30,000 to receive the immunizations. Patients requiring platelet transfusions are eligible to enroll and must have a platelet count ≥30,000 within 72 hours prior to their immunization, or platelet count ≥75,000 without transfusion documented within 30 days for subjects <12 months post-transplant and within 90 days for subjects 12-23 months post-transplant.

2. **Exclusion Criteria for Repeaters**
    a. Evidence of hematologic malignancy or disease relapse post-transplant (stable mixed chimerism is permitted);
    b. History of receiving current seasonal influenza vaccine post-transplant.
    c. Pregnant female.
    d. History of proven influenza disease after September 1, 2019 prior to enrollment.
    e. History of known active infection with HIV
    f. History of cirrhosis
    g. Subjects who have received stem cell boost or delayed donor lymphocyte infusion within 90 days of enrollment, including day of enrollment
    h. Receipt of IVIG/SCIG <28 days prior to calendar day of vaccination

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 ≥100.4ºF/38.0ºC (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 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.

Table 3.	**Screening Period**	**Visit 1**	electronic communication	**Optional Visit**	**Visit 2**	electronic communication	**Optional Visit**	**Visit 3**	**Influenza Season**	**Visit 4 Optional for repeaters for 2019-2020**	**June 30th**
Days		**0**	**1-3 and 8-10* days after visit 1**	**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 ±56 days after visit 3**	**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 and IgM#		X			X			X		X	
Study vaccine administration (HD-TIV or SD-QIV)		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 electronic communication			X			X			Weekly		
Pregnancy Test (if applicable)		X			X						
Collection of Nasal Swab for PCR testing for Influenza and other respiratory viruses ***		X		X	X		X	X		X	X
Proven clinical influenza illness review ##		X	X	X	X	X	X	X	X	X	X

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

*** Study staff will attempt to collect nose swabs from symptomatic patients throughout the study period.
Proven clinical influenza illness is any breakthrough influenza illness confirmed by laboratory testing (ie Rapid antigen assay, PCR, virus culture, etc.)

5. Treatment Groups:
There will be two groups – HD-TIV versus SD-QIV. The subjects will be randomized in a 1:1 HD-TIV versus SD-QIV.

Treatment Group	Target Total N
Group 1 0.5 mL HD-TIV	69
Group 2 0.5 mL SD-QIV	69

a. **Randomization:** Subjects will be randomized 1:1 to either HD-TIV or SD-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 Research Electronic Data Capture (REDCap) database. The investigational pharmacy at each of the 4 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 42 (30%) subjects to ≥12 months post-transplant.

For block randomization

1. For subjects 12-23 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 Oncology units or 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 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:

a. Type of transplant: (Bone marrow, peripheral blood, both bone marrow and peripheral blood, cord blood [single or double] or cord blood and peripheral blood; type of HSCT (HLA-identical sibling, HLA-mismatched relative, unrelated)
b. Underlying disease 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 grade
g. HLA match
h. History of IVIG/SCIG administration since transplant
i. Chimerism status
j. Gender (patient/donor gender)
k. Race/ethnicity
l. Age
m. Social History (work, marital status, , etc.)
n. Smoking History (is the subject exposed to secondhand cigarette/cigar/e-cigarette smoke)

o. Household members (# people live in the subject's primary household as of date of visit-1, # of children less than 18 years , # of adults)
p. History of influenza vaccination (pre and post-transplant)
q. Past medical history
r. CMV status (donor/recipient) and CMV viral end points
s. 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 each 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 to contact 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 SAEs 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 Institutional Review Board (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
    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. 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 in the Vanderbilt University Medical Center. With the permission of the subjects any leftover samples will be kept and used for future research and will be stored at Vanderbilt University Medical Center. A separate IRB approval will be sought prior to the use of these samples.

10. Investigational Product and Risk Information:

Fluzone Quadrivalent® is a Federal Drug Administration (FDA)-approved vaccine and is recommended for all patients ≥6 months.[65]

Fluzone® HD-TIV has not yet been approved for individuals <65 years of age. The current seasonal influenza vaccine will be used throughout the entire study.

a. Acquisition: Fluzone Quadrivalent® and Fluzone® HD, preservative free, licensed product formulated for the 2017-2018,2018/2019, and/or 2019/2020 influenza season will be donated by Sanofi Pasteur and distributed to each site of the 4 institutions.

b. Formulation, Packaging, and Labeling: Fluzone Quadrivalent® and Fluzone® HD, preservative free, licensed product, Sanofi Pasteur, Swiftwater, PA. The 2017-2018 influenza strain recommendations are the following: A/Michigan/45/2015 (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) for both HD-TIV and SD-QIV; 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.

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

d. 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 SD-QIV or HD-TIV (Fluzone Quadrivalent®, Sanofi Pasteur or Fluzone® HD-TIV, 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 SD-QIV/HD-TIV may normally be clear to slightly opalescent). If either condition exists, the pre-filled syringe will not be used.

Subjects are randomized in a 1:1 fashion to receive either 2 doses of 0.5ml of HD-TIV (60µg of each influenza antigen) or 2 doses of SD-QIV (15 µg of each influenza antigen) of the current seasonal influenza vaccine (e.g.2017-2018 or 2018/2019), 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. 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 immunocompromised recipients has been comparable to that reported in healthy individuals receiving TIV.[66] With the exception of soreness at the injection site, adverse reactions to TIV are uncommon.[67] 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.[67-69]

12. Risk Information:

a. Influenza vaccine: The adverse event profile of TIV administration in HSCT recipients has been comparable to that reported in healthy individuals receiving TIV.[34,35,46] With the exception of soreness at the injection site, adverse reactions to TIV or QIV are uncommon.[67] 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.[68,69]

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, and IgG/IgM 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, prior to visit 1, consent may be obtained.
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 ± 56 after visit 3.
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:

<u>Screening Periods/Supplemental Visit, prior to Visit 1, Day 0.</u>

- Subjects 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 on that day, this will 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.

<u>Days -1 to -90 days:</u>

- Subjects must have a platelet count of ≥30,000 to receive the immunizations. Patients requiring platelet transfusions are eligible to enroll and must have a platelet count ≥30,000 within 72 hours prior to their immunization, or platelet count ≥75,000 without transfusion documented within 30 days for subjects <12 months post-transplant and within 90 days for subjects 12-23 months post-transplant.

<u>Visit 1: Day 0:</u>

- Subject will sign written Informed Consent if not already signed prior to Visit 1.
- Brief review of Medical history
    - Inclusion/exclusion criteria will be checked.
    - Prior/concomitant medications will be recorded.
    - Written documentation of prior influenza immunizations post-transplant will be collected.
- Targeted physical examination will be conducted including measurement of oral temperature (must be <u>≤</u>100.4ºF/38ºC). 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 potential a pregnancy test will be performed.

- Approximately 30-60 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 IgG and IgM 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).
- Study vaccine will be administered.
- Study 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 must be given 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.
- A nasal swab for PCR testing for influenza and other respiratory viruses will be obtained regardless of symptoms.

Days 0-7: After the first 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: 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 medications 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.

Optional visit: 5-10 days after first vaccination for B/T cell responses:

- Only those subjects who volunteer will return for a blood draw only.
- Approximately 30-60 mL of blood will be collected for B and T cells responses.
- If within the 8-10 days phone/email window, this would replace the 8-10 day telephone and/or electronic communication.
- A nasal swab for PCR testing for influenza and other respiratory viruses will be obtained regardless of symptoms.

Visit 2: Days 28-42:

- Solicited AEs/unsolicited AEs will be reviewed and recorded.
- Medical history changes

- Concomitant medications will be recorded.
- 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 the changes need to be documented.
- Targeted physical examination will be conducted including measurement of oral temperature (must be <100.4°F/38°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 potential a pregnancy test will be performed
- Approximately 30-60 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 IgG and IgM concentrations.
- Study vaccine will be administered
- Study 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 must be given 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 from the memory aid form will be collected from the subject through telephone calls or emails in the week following vaccination. 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.
- A nasal swab for PCR testing for influenza and other respiratory viruses 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:

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

Optional visit: 5-10 days after second vaccination for B/T cell responses:

- Only those subjects who volunteer will return for a blood draw only.
- Approximately 30-60 mL of blood will be collected for B and T cells responses.
- If within the 8-10 days phone/email window, this would replace the 8-10 day telephone and/or electronic communication.
- A nasal swab for PCR testing for influenza and other respiratory viruses will be obtained regardless of symptoms.

Visit 3: 28-42 Days after Visit 2:

- Solicited AEs/unsolicited AEs will be reviewed and recorded if within 7 days following vaccination #2.
- Approximately 30-60 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 $CD4^+/CD8^+/CD19^+$ levels, and quantitative serum IgG and IgM concentrations.
- If IVIG/SCIG is given the same day, it must be given after the vaccination, and a second blood draw will be obtained post-IVIG/SCIG if administered on same calendar day.
- A nasal swab for PCR for influenza testing will be obtained regardless of symptoms.

All attempts will be made for these visits to be done at each site; however, if distance is an issue, the site PI will work with PI (Halasa) to arrange for a local lab to perform study labs, and then draw and send blood samples to Vanderbilt directly. This will be evaluated on a case by case basis.

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.[63,64]

ILI Visit: Supplemental visit

If research participants have any of the following:

a. **Fever:** ≥38.3°C (101°F); or
b. **Two 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).

If the patient presents to the clinic with ILI criteria they will be seen by the investigator or study staff and a nasal swab will be collected, and tested by PCR for influenza and other respiratory viruses at Vanderbilt University Medical Center. If distance is an issue and they can't be seen within 48 hours of symptom onset, subjects will be given a Swab with training instructions for self-collection and arrangements will be made for specimens to be sent either to the local academic center or directly to Vanderbilt University Medical Center. Specimens should be collected within 7 days of onset of symptoms, ideally within 48 hours.

Additionally, we will attempt to collect nasal swabs from patients who meet the ILI criteria during the study time (out of the flu season). And nasal swabs will be obtained at all scheduled visits to document the occurrence of influenza virus detection both prior to and after vaccination.

Also, data about any breakthrough clinical influenza illness will be collected during the study period and until June 30th.

Visit 4: 180 Days ±56 after Visit 3:

- Approximately 30-60 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 $CD4^+/CD8^+/CD19^+$ levels, and quantitative serum IgG and IgM concentrations.
- A nasal swab will be obtained, regardless of symptoms.
- For 2019-2020 enrollment season, visit 4 will be optional and subjects who volunteer to participate will have the procedures mentioned above completed.
- 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.

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 or clinic nurse 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 Vanderbilt University Medical Center for HAI, MN testing, B and T cell influenza-specific responses. Other clinical labs will be sent the local lab.
b. **Hemagglutination Inhibition Assays (HAI):** Sera HAI testing will tested at Vanderbilt University Medical Center. Sera will be initially diluted 1:10 per protocol.[70] 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 2017-2018 or 2018-2019.
c. **Microneutralization assays**: Sera will be shipped to at Vanderbilt University Medical Center for MN testing and results will be compared to HAI.[71]
d. **Neuraminidase inhibition titers.** Sera will be shipped to at Vanderbilt University Medical Center for NAI testing and results will be compared to HAI.
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 5-9 months after second vaccination. After ficolle 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 and shipped to Vanderbilt University Medical Center 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, nurse practitioner (NP), or Licensed practical nurse (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, NP, 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.

Adverse events 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 (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.

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

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
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 interfere 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

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fatigue/Malaise	No interference with activity	Some interference with activity	Incapacitating, prevent s 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 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
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
Systemic (Quantitative)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Fever (°C) – ORAL	≥38.0 - <38.3 ≥100.4 < 101° F	≥38.3 - <39 ≥ 101 - < 102° F	≥39 ≥ 102° 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.
- A congenital anomaly/birth defect.
- 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.

The SAE 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. 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 Investigational New Drug (IND) Sponsor/Lead primary investigator (PI) (Dr. Natasha Halasa) local site PI and/or Sub-Investigators and The Division of Microbiology and Infectious Diseases (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.
- SAEs deemed related to the study vaccine and unexpected will be reported to Sanofi within 7-15 calendar days after SAE awareness.

SAEs occurring within 7days of vaccination that are deemed related 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

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. All ISMs and future ISMs will be assessed for Conflict of Interest (COI) according to the National Institute of Allergy and Infectious Diseases (NIAID) policy, and only those ISMs who have no COI will be allowed to serve.

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 appraised of all new safety information relevant to the study product and the study.

Safety oversight will be conducted by a 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. All DSMB members and future DSMB members will be assessed for COI according to the NIAID policy, and only those DSMB members who have no COI will be allowed to serve. The DSMB will consist of a minimum of 3 members. A simple majority will be considered a quorum for meeting purposes.

The DSMB operations will be in compliance with the NIAID policy and will be so described in the charter which will be shared with DMID. 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, and reactogenicity 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 un-blinded fashion, and may request the treatment assignment be un-blinded for an individual subject if required for safety assessment. The DSMB will review grouped and un-blinded 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 IND sponsor and/or DMID Medical Monitor is empowered to stop enrollment and study vaccinations if adverse events that meet the halting criteria are reported. The IND sponsor, 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, and reactogenicity 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 un-blinded safety, and reactogenicity data for this study. The data will be provided in a standard 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.

The DMID Medical Monitor will:

- receive access to the open session materials;
- be invited to the open session of the DSMB discussion;
- be informed promptly on the DSMB recommendations; and
- be copied on the official DSMB recommendations.

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:

1. If two or more subjects have an SAE within 7 days of vaccine that is determined to be related to the study vaccine after reviewing the case by the site ISM, site PI and study PI , no new subjects will be enrolled. The SAEs will be reviewed by ISM for the relationship with the study vaccine and further discussed with DMID and the Data Safety Monitoring Board.
2. If eight or more subjects have the same Grade 3 event in any reactogenicity category (excluding grade 3 redness/induration size grade 3 fatigue 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.
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. Center for Biologics Evaluation and Research (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- National Cancer Institute (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.

l. 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 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.

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:
Either the vaccines will be blinded and/or an un-blinded vaccinator will be available to administer the vaccine. All study staff and subjects will be blinded to which vaccine the subject will receive, except for an un-blinded vaccinator, if applicable. This individual will not inform the study team, subjects to 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 will be informed of this during the consent process.

17. Statistical Considerations:

a. **Sample Size Calculations**: A target of 138 subjects will be targeted, with 69 in each group. This is based on the assumption, with 80% power, that 25-30% of the subjects in the SD group will achieve a protective titer compared to 50-60% of the HD-TIV group for at least one influenza antigen. Accounting for a 20% drop out rate, 138 subjects will be recruited.

Strain	Expected Seroprotection HD-TIV	Expected Seroprotection SD-QIV	N (HD)	N (SD)	Power	Total N with 20% drop out
Expected HD-TIV seroprotection is twice as of SD-QIV						
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, using the full analysis set. We will calculate the Bayesian posterior distribution of the probabilities under all 4 combinations of SD- 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 $CD4^+/CD8^+/CD19^+$, and IgG/IgM 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. We will use normal priors with standard deviation of 5 for all logit-linear coefficients and the baseline mean, which are not informative when transformed to the probability scale. Scale (standard deviation) parameters will be given long-tailed half-Cauchy priors, also in the interest of being uninformative. In addition, the distributions of geometric mean HAI titers for high and SD-QIV 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. The scale parameters for priors under the log-normal model will be increased by an order of magnitude relative to the logit-linear models to ensure that they do not influence the posterior estimates. 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≥1:40).[72] Subjects with missing data will be excluded from the analysis, but the sensitivity of the results to missingness will be formally analyzed by comparing posterior estimates under the range of possible outcomes for the missing individuals.

c. **Safety analysis:** For the primary analysis of the safety data, the proportion of subjects in each group (using full analysis set) 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 continuous-valued events (e.g. size of swelling) uninformative priors will be used as described in (17.b); for discrete events, a flat beta parameter with scale=shape=1 will be used as uninformative priors. 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. Subjects with missing data will be excluded from analysis, but the sensitivity of the results to missingness will be formally analyzed by comparing posterior estimates under the range of possible outcomes for the missing individuals.

d. **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, DMID, 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 to 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 subject. 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 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.
5. Subjects may receive IRB approved information about the vaccines to be used in the study.

d. Exclusion of Women, Minorities, and Children (Special Populations):
This study will be inclusive of subjects 18 years of age and older 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.
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 and/or OnCore 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.[73] 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 may be transferred to **ON**-line **C**linical **O**ncology **R**esearch Environment = **ONCORE (OnCore)**, 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 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 clinical data update system (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.

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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