Title: Assessing Immunological Basis of Durable Antibody Responses to 9-valent HPV Vaccination

NCT# NCT05031078

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PROTOCOL TITLE: Assessing immunological basis of durable antibody responses to 9-valent HPV vaccination

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EXTERNAL (NON-EMORY) COLLABORATORS

EPFL (École Polytechnique Fédérale de Lausanne) will map epitopes of antibodies
Lausanne, Switzerland
*EPFL IRB will provide oversight for any reviews necessary

Centers for Disease Control and Prevention will test for HPV-specific antibody responses in microsamplers and paired serum samples and conduct immunological screening tests
Atlanta, Georgia, USA
*CDC IRB will provide oversight for any reviews necessary

VERSION: Version 11 May 08, 2025

FUNDING SOURCE: Department funding

REVISION HISTORY
Version 11 adds the option to re-attempt a bone marrow aspiration for Visit 19 or 24 once per each visit if 1) unsuccessful in the first attempt, 2) clinician performing the procedure agrees, and if 3) participant is willing. Must be within 30 days of safety labs or safety labs must also be repeated. Conducted as unscheduled visit (s) with vital signs, pregnancy test (if indicated), and follow-up phone call within 7±1 days.

Version 10 edits the schedule of events (Appendix A) to be consistent with the text regarding the visit window for visits 18 and 23 being up to 30 days prior to bone marrow aspiration procedure visits. Secondary endpoint #2 has been corrected to an exploratory endpoint for consistency with required reporting. An external collaboration with EPFL was added; and CDC was added as an external collaborator on Page 1 to be consistent with language already in protocol regarding this collaboration.

Version 9 reduces the number of visits in the secondary endpoint to be consistent with an upcoming related study and adds language regarding an unscheduled visit. Administrative changes throughout.

Version 8 adds a blood draw at 36 months (Study Day 1095), 48 months (Study Day 1460), and 60 months (Study Day 1825) for immunological assays, as well as a bone marrow aspiration procedure at 60 months (Study Day 1825) for immunological assays and associated safety visit and follow-up phone call. The rationale for these additional visits/specimen collections are 1. To assess the half-life/decay kinetics/durability of HPV-specific antibody responses in blood following vaccination and 2. To assess the half-life/decay kinetics/durability of HPV-specific plasma responses in the bone marrow following vaccination. We do not anticipate that a second bone marrow aspirate will incur any additional risks to participants on basis that participants in other tissue sampling studies at Hope Clinic that have had more than one bone marrow aspiration procedure with no complications to date. Version 8 also adds an anonymous survey by email or text about the bone marrow aspiration procedure at the time of the two follow-up phone calls and minor changes to language for consistency.

Version 7 changes compensation of bone marrow aspiration from $200 to $350 and adds Hope Clinic as a site for bone marrow aspiration, as well as lorazepam, an anxiolytic, as a study medication that may be administered sublingually per manufacturer dosing recommendations prior to the bone marrow aspirate procedure per the clinician performing the procedure. It also corrects some information about the immunological screening assay and laboratory conducting that assay; makes consistent the time to notify ISM of SAEs (and IRB if study related) as 24 hours; and changes the lidocaine dosage for bone marrow aspiration from 2% to 1-2% to be consistent with other tissue sampling protocols at Hope Clinic.

Version 6 changes the study enrollment number to 50. The eligibility based on age has been changed to 18 – 45 instead of > 18 – 45. Visit window days have been updated as follows: Day 61 to Visit 8 +1 day; Day 67 to Visit 8 + 7 ±1 days; Day 74 to Visit 8 + 14 ±5 days; Day 90 to Visit 8 + 30 ±5 days; Day 187 to Visit 13 + 7 ±1 day; Day 194 to Visit 13 + 14 ±5 days; Day 210 to Visit 13 + 30 ±5 days. Study of procedures table has been edited to reflect the aforementioned changes.

Version 5 changes visit window timelines to expand the Visit 2 window from Day -30 to Day 0 (currently Day -30 +/-1) and makes minor changes to visits included for endpoint analyses for consistency throughout protocol

Version 4 changes requirements for Visit 4 and Visit 9, which are now optional. Windows for Visit 8 and Visit 13 have been extended to +/- 5 days. Visit windows for FNA in Group 1, Group 2, and Group 3 have been extended to +/- 5 days. Baseline FNA for Group 2 has been moved to before dose 2 and for Group 3 to before dose 3. The version number, date, and version history were updated.

Version 3 removes blood chemistry and blood count values from inclusion criteria, modifies interpretation of vital signs and safety labs, adds optional finger prick blood collection by microsampler at five visits, and makes minor changes to follow up visit days and saliva sampling visit days for consistency throughout protocol. The version number, date, and version history were updated. The table of contents formatting was updated. Grammatical and formatting changes were updated throughout the document.

Version 2 was updated to add HIPAA Compliant Emory RedCap database and HIPAA compliant clinical management database - Clinical Conductor. The version number and date were updated throughout the document; 2021 November 30. The table of contents formatting was updated. Grammatical and formatting changes were updated throughout the document.

Table of Contents

1. Study Summary

Study Title	**Assessing immunological basis of protection by and durable antibody responses to 9-valent HPV vaccination**
Study Design	Single center, longitudinal cohort study in which participants will receive 9-valent HPV vaccine according to package insert (i.e., one dose of 9-valent HPV vaccine on D0 followed by a second dose 2 months later and a third dose 6 months later). Immune responses in the blood, saliva, bone marrow, and lymph nodes will be assessed in participants receiving the HPV vaccine. Blood samples for immunologic testing will be collected at screening (from D-60 to D-45), on D0 (before vaccination), D1 (optional visit), D7, D14, D30, D60 (before vaccination), Visit 8 + 1 day (optional visit), Visit 8 + 7±1 days, Visit 8 + 14±5 days, Visit 8 + 30±5 days, D180 (before vaccination), Visit 13 + 7±1 days, Visit 13 + 14±5 days, Visit 13 + 30±5 days, D365, D730, D1095, D1460, and D1825. Saliva samples for antibody testing will be collected on D0 (before vaccination), D30, D60 (before vaccination), Visit 8 + 30±5 days, D180 (before vaccination), Visit 13 + 30±5 days, D365, and D730. Axillary lymph node sampling by fine needle aspiration will be done 3 times per group. Group 1 will have lymph node sampling done D-30 to D0, D14, and D30. Group 2 will have lymph node sampling done D60, Visit 8 + 14±5 days and Visit 8 + 30±5 days. Group 3 will have lymph node sampling D180, Visit 13 + 14±5 days, and Visit 13 + 30±5 days. Bone marrow sampling will be done for all groups at D730 and D1825.
Primary Objective	• Determine number of participants with a minimum four-fold rise in post-vaccination HPV-16 and HPV-18 neutralizing antibody titers

Secondary Objective	1. Assess magnitude and durability of HPV specific Bmem responses at baseline and following 9-valent HPV vaccination
Exploratory Objectives	1. Determine if 9-valent HPV vaccination induces germinal center formation in humans by assessing the generation of germinal center T follicular cell (GCTfh) and germinal center B cell (GCB) responses in lymph nodes 2. Test whether the magnitude or quality of GCTfh responses correlates with the durability of antibody and B cell responses induced by 9-valent HPV vaccination 3. Assess correlations between the phenotype of GCB and the magnitude, type, and durability of B cell memory induced by 9-valent HPV vaccination. 4. Compare B cell antibody repertoires and gene expression (RNA sequencing) profiles of HPV-specific memory B cells (Bmem), plasmablasts (PB), GCB, and plasma cells (PC) following 9-valent HPV vaccination 5. Define gene expression changes in blood following HPV vaccination relative to baseline 6. Examine the magnitude and kinetics of the PB response at baseline and following 9-valent HPV vaccination 7. Characterize the magnitude, phenotype, and durability of HPV-specific PC following 9-valent HPV vaccination 8. To compare the isotypes, magnitude, kinetics, durability of saliva Ab responses with those serum Ab responses at baseline and following 9-valent HPV vaccination 9. Evaluate associations between the magnitude or quality of circulating T follicular helper cells (cTfh) and the magnitude of Ab and PB responses induced by 9-valent HPV vaccination. 10. Characterize magnitude, type, and functions of CD4 T cells at baseline and following 9-valent HPV vaccination 11. Map HPV L1 CD4 T cell epitopes 12. Determine if vaccine-elicited antibody responses collected with a blood microsampler

	correlate with antibody responses found in serum to demonstrate feasibility for surveillance programs 13. Measure isotypes, magnitude, kinetics, durability, and neutralizing potency of HPV-specific serum Ab responses at baseline and following 9-valent HPV vaccination 14. Map antibody epitopes (polyclonal antibodies in blood or monoclonal antibodies cloned from B cells)
Research Intervention(s)/Interactions	• 3 doses of 9-valent HPV vaccine (Gardasil 9) at D0, D60, and D180 • 1-2% lidocaine injections • Lorazepam
Study Population	Men and women aged 18-45 years
Sample Size	8 female and 8 male participants split into 3 groups (Group 1 = 8 participants, Group 2 = 4 participants; Group 3 = 4 participants; with equal numbers female and male participants per group)
Study Duration for individual participants	Approximately 1892 days (~63 months)
Study Specific Abbreviations/ Definitions	HPV – human papillomavirus GCTfh – germinal center T follicular helper cells cTfh – circulating T follicular helper cell Bmem – memory B cell PC – plasma cell (bone marrow) PB – plasmablast (circulating)
Funding Source (if any)	Departmental Funding

2. Objectives

Specific aims

1. Determine if 9-valent HPV vaccination induces germinal centers in humans. We hypothesize that the HPV vaccine generates germinal centers as these structures are important for the formation of Bmem and we have previously shown that the 4-valent HPV vaccine elicits Bmem[1,2].
2. To determine if the magnitude or quality of GCTfh responses correlates with the durability of Ab and B cell responses induced by 9-valent HPV vaccination. We hypothesize that the quality of GCTfh will be a better predictor of Ab durability than GCTfh magnitude.
3. To assess correlations between the phenotype of GCB and the magnitude, type, and durability of B cell memory induced by 9-valent HPV vaccination. We hypothesize that we will observe more PC precursors than Bmem precursors in the germinal center given

that HPV Bmem rapidly wane to near baseline levels, whereas antibody levels are high and stable (suggesting potent and durable PC responses).

4. To compare B cell Ab repertoires and gene expression profiles of HPV-specific Bmem, GCB, and PC following 9-valent HPV vaccination. Previous work in mice suggests that Bmem repertoires are less somatically mutated and harbor more breadth than PC repertoires, which is what we expect to observe in our comparison here. However, we have also found that human anti-HPV Abs require little somatic hypermutation to potently neutralize HPV and thus we may find that fewer differences between these repertoires in the case of HPV.
5. To define gene expression changes occurring post-vaccination in blood relative to baseline. Little is known about the gene expression changes that coincide with HPV vaccination, yet this information can advance our understanding of what innate and adaptive immune pathways are being activated by the HPV vaccine so that we can further investigate mechanism in vitro and in pre-clinical models.
6. To compare the isotypes, magnitude, kinetics, durability of saliva Ab responses with those serum Ab responses at baseline and following 9-valent HPV vaccination. Less is known about the composition, kinetics, and durability of mucosal anti-HPV Ab responses following vaccination compared to serum anti-HPV Ab responses. Although the isotypes and magnitude of the saliva Ab responses may differ with respect to serum Ab responses, we hypothesize that the kinetics and durability of saliva Ab responses will be similar to serum Ab responses, if saliva antibodies can be detected.
7. To determine if a microsampler can be used an alternative to venous blood collection for measuring antibody responses in blood for surveillance programs

3. Background

Human papillomaviruses (HPV) cause cervical, anal, oropharyngeal, vulvar, vaginal, and penile cancers. There are over 200 types of HPV[3], of those, 12 are known to cause cancer and are considered carcinogens and high risk (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59)[4], though other types are capable of causing disease (e.g., genital warts)[5]. Currently, the 9-valent HPV vaccine is licensed and available in the U.S. It prevents infection by types that cause 90% of cancer cases (HPV 16, 18, 31, 33, 45, 52, and 58)[6] and 90% of genital warts cases (HPV 6 and 11)[7]. The 9-valent vaccine was >96% effective at preventing high-grade cervical, vulvar, and vaginal disease in 16-26 year old women who did not have evidence of ongoing or prior infection (i.e., seronegative and PCR negative)[8,9], and the 4-valent HPV vaccine was >74% effective at preventing high-grade anal disease in 16-26 year old men without evidence of ongoing or prior infection[10]. Importantly, in persons aged 9-26 years at vaccination, the 4-valent (HPV 6, 11, 16, and 18) and 9-valent vaccines have shown to induce highly durable antibody responses for 10-14 and 7.5 years, respectively[11-14]. Based on this data, mathematical modeling has predicted that antibody titers will remain above the antibody levels induced by natural infection for at least 15 years post-initial vaccine dose[15]. This is exceptional compared to many other approved and candidate subunit vaccines, whose antibodies drop to baseline more rapidly (e.g., influenza, acellular pertussis, tetanus,

hepatitis B virus, HIV-1 RV144 vaccine, herpes simplex virus 2 gB2 and gD2 vaccine)[16-21]. Moreover, in ~10% of persons who became seronegative for one of the HPV types by year 12, vaccine efficacy against cervical intraepithelial neoplasia grade 2 or worse remained at 100%, suggesting either a role for cellular memory or that antibodies at levels lower than those elicited by natural infection are protective[11]. Moreover, Bmem elicited by a previous version of this vaccine (4-valent) have been shown to persist a minimum of 4.5 years post-vaccination[22].

Most vaccines protect by generating antibodies. However, how this benchmark subunit vaccine – let alone any vaccine – elicits durable antibodies and Bmem is not understood. Is it dependent on antigen valency/avidity, given that the HPV vaccine antigen (L1) spontaneously assembles into virus like particles with 72 L1 subunits? Or is it due to trace amounts of DNA in the vaccine, which could provide B cell co-stimulation through pattern recognition receptors (e.g., TLR9) on B cells or other antigen-presenting cells (e.g., macrophages or dendritic cells)? Or does the vaccine induce and require GCTfh, which are critical to the formation of Bmem and long-lived PC? Further studies into how vaccines elicit potent, durable antibody responses will aid our ability to successfully and reliably design subunit vaccines that recapitulate these highly desired antibody responses.

Therefore, we designed this study to better understand how the 9-valent HPV vaccine elicits such potent and durable antibody responses in humans. We hypothesize that the HPV vaccine induces germinal center formation and propose to test this hypothesis by evaluating fine needle aspirates for the presence of GCTfh or GCB, which correlate with germinal center formation assessed by more comprehensive, albeit more invasive, methods (e.g., lymph node biopsy and immunohistology)[23,24]. We also propose to measure HPV-specific GCB. In measuring GCB, we propose to assess the fraction of Bmem and PC precursors and how these numbers correlate with the magnitude and durability of Bmem responses and magnitude and durability of PC and antibody responses. We also propose to assess the gene expression profiles of single GCTfh and GCB cells to learn, for example, whether genes associated with B cell help (IL-21) or specific pattern recognition receptor pathways (TLR9) are upregulated in these cells. We also propose to examine the gene expression changes in blood activated by the first and second dose of this vaccine relative to baseline. These analyses will enable us to study associations between the innate immune activation and GC magnitude and between GCTfh or GCB gene expression profiles and the magnitude and durability of the antibody, PC, and Bmem responses. Moreover, these analyses will establish important benchmarks for future studies aimed at understanding the durability of immunity for candidate vaccines or natural infections (e.g., SARS-CoV-2).

In addition to understanding how effective vaccines work, a tremendous amount of resources is also being invested into the development of vaccines that maximize germinal centers to generate diverse B cell repertoires against highly variant pathogens (e.g., HIV and influenza). The general consensus from a very limited number of studies is that the Bmem repertoire is more diverse, lower affinity, and less somatically mutated than the plasma cell repertoire[25] and thus research efforts are in place to learn how to

diversify the PC repertoire, and thus serum Ab repertoire. We have shown that the 4-valent HPV vaccine elicits a highly diverse Bmem repertoire with relatively low somatic hypermutation (SHM) that still achieves high Ab affinity/neutralization potencies[1,2]. The question remains whether the plasma cell repertoire induced by HPV vaccination has more SHM, higher affinity, and less diversity than the Bmem repertoire, as predicted? Given very new evidence that highly multi-valent antigens are less dependent on antigen affinity than antigen valency/avidity for generating GCB and PC[26], the HPV vaccine may not require as much affinity maturation to generate long-lived plasma cells and thus may generate equally diverse PC and serum Ab cell repertoires. This would be optimal and support the use of highly valent antigens in a variant pathogen vaccine design, but is untested. Thus, we propose to compare the diversity, SHM levels, gene expression profiles, and affinity of antigen-specific Bmem and PC repertoires using the HPV vaccine as a model.

4. Study Endpoints

4.1.1 Primary Endpoint

- Number of participants with a minimum four-fold increase in post-vaccination HPV-16 and HPV-18 neutralizing antibody titers 30 days after receiving the third and final vaccine dose as determined using an HPV pseudovirus neutralization assay

4.1.2 Secondary Endpoint

1. Number of HPV-specific Bmem at baseline (D0), D30, D180 (Visit 13), Visit 13 + 30±5 days, D365, D730

4.1.3 Exploratory Endpoints

1. Number of GCTfh, GCB, and HPV-specific GCB in fine needle aspirates at D-30 to D0, D14, D30, D60, Visit 8 + 14±5 days, Visit 8 + 30±5 days, D180, Visit 13 + 14±5 days, Visit 13 + 30±5 days.
2. a. Correlation of magnitude of peak GCTfh responses with magnitude and durability of HPV-specific antibody and B cell responses
   b. Gene expression profile of HPV vaccine-induced GCTfh
   c. Correlation of GCTfh gene expression profiles with magnitude and durability of HPV-specific antibody and B cell responses
3. a. Correlation of magnitude of GCB with Bmem or PC-precursor phenotype with magnitude, type, and durability of B cell memory induced by 9-valent HPV vaccination
   b. Gene expression profile of HPV vaccine-induced GCB
   c. Correlation of GCB gene expression profiles with magnitude, type, and durability of B cell memory induced by 9-valent HPV vaccination
4. Antibody repertoires, gene expression profiles, and monoclonal antibodies from GCB at D-30 to D0, D14, D30, D60, Visit 8 + 14±5 days, Visit 8 + 30±5 days, D180, Visit 13 + 14±5 days, Visit 13 + 30±5 days; Bmem at D0, D14, D30, D60, Visit 8 + 7±1 days, Visit 8 + 14±5 days, Visit 8 + 30±5 days, D180, Visit 13 + 7±1 days, Visit 13 + 14±5 days, Visit 13 + 30±5

days, D365, D730, D1095, D1460, D1825; PB at D0, D14, D30, D60, Visit 8 + 7±1 days, Visit 8 + 14±5 days, Visit 8 + 30±5 days and D180, Visit 13 + 7±1 days, Visit 13 + 14±5 days, Visit 13 + 30±5 days; and PC at D730 and D1825.

5. Gene expression changes occurring in blood post-vaccination at D1 (optional visit), D7, Visit 8 +1 day (optional visit), and Visit 8 + 7±1 days relative to baseline (D0, D60).
6. Frequency of PB at D0, D14, D30, D60, Visit 8 + 7±1 days, Visit 8 + 14±5 days, Visit 8 + 30±5 days, D180, Visit 13 + 7±1 days, Visit 13 + 14±5 days, Visit 13 + 30±5 days
7. Number, phenotype, and gene expression profiles of HPV-specific PC at D730 and D1825
8. Titers of binding HPV-specific antibodies and distribution of HPV-specific binding antibody isotypes in saliva at D0, D30, D60, Visit 8 + 30±5 days, D180, Visit 13 + 30±5 days, D365, D730
9. Frequency, phenotype, and gene expression profile of cTfh (total and HPV-specific) and their independent correlations with the magnitude of antibody and PB responses induced by 9-valent HPV vaccination
10. Frequency, function and phenotype of HPV-specific CD4 T cells at D0, D14, D30, D60, Visit 8 + 7±1 days, Visit 8 + 14±5 days, Visit 8 + 30±5 days, D180, Visit 13 + 7±1 days, Visit 13 + 14±5 days, Visit 13 + 30±5 days, D365, D730, D1095, D1460, D1825
11. HPV-specific L1 CD4 T cell epitopes
12. Titers of HPV-specific antibodies collected by microsampler at D0, D30, Visit 8 + 30±5 days, Visit 13 + 30±5 days, D365
13. Titers of binding and neutralizing HPV-specific antibodies and distribution of HPV-specific binding antibody isotypes (e.g., IgA, IgM, IgG) in serum at baseline (D0), D14, D30, D60, Visit 8 + 7±1 days, Visit 8 + 30±5 days, D180, Visit 13 + 7±1 days, Visit 13 + 30±5days, D365, D730, D1095, D1460, D1825
14. Antibody epitopes of polyclonal antibodies in blood or monoclonal antibodies cloned from B cells at any study visit.

5. Study Intervention/Investigational Agent

5.1 Description

5.1.1 The 9-valent HPV vaccine is manufactured by Merck & Co., Inc. headquartered in Kenilworth, NJ.

The 9-valent HPV vaccine, or Gardasil-9, is a non-infectious recombinant vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant Saccharomyces cerevisiae and self-assembled into VLPs. The fermentation process involves growth of S. cerevisiae on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous

Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

The 9-valent HPV vaccine, or Gardasil-9, is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 30 mcg of HPV Type 6 L1 protein, 40 mcg of HPV Type 11 L1 protein, 60 mcg of HPV Type 16 L1 protein, 40 mcg of HPV Type 18 L1 protein, 20 mcg of HPV Type 31 L1 protein, 20 mcg of HPV Type 33 L1 protein, 20 mcg of HPV Type 45 L1 protein, 20 mcg of HPV Type 52 L1 protein, and 20 mcg of HPV Type 58 L1 protein.

Each 0.5-mL dose of the vaccine also contains approximately 500 mcg of aluminum (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein, and water for injection. The product does not contain a preservative or antibiotics.

Gardasil-9 is supplied as a 0.5-mL single-dose vial or 0.5-mL single-dose prefilled Luer Lock syringe with tip cap.

After thorough agitation, GARDASIL 9 is a white, cloudy liquid.

The prospective cohort will receive all three doses of the 9-valent HPV vaccine by intramuscular injection as part of the study.

5.1.2 When indicated, 1% lidocaine, an FDA approved local anesthetic, will be injected subcutaneously to numb the area of the lymph node being sampled; whereas 1-2% lidocaine will be injected into the tissue surrounding the area where the bone marrow will be removed. In adults the recommended dose is 7 mg/kg with a maximum of 500 mg.

5.1.3 When indicated, lorazepam, an FDA-approved benzodiazepine, will be administered as an anxiolytic prior to the bone marrow aspirate procedure per the clinician performing the procedure. Lorazepam will be administered sublingually per manufacturer dosing recommendations.

5.2 Drug/Device Handling

5.2.1 After purchase of the 9-valent HPV vaccine, the Hope Clinic Investigational Drug Services will be responsible for storage and disposition of the vaccine. Only IDS staff have the code to the keypad restricting pharmacy access. Logs of receipt, temperature, maintenance, and disposal will be maintained in the study file. The pharmacist will prepare a single dose (0.5 mL) for each participant as described below.

Gardasil-9 doses should be stored refrigerated at 2 to 8°C (36 to 46°F). Doses will not be frozen. Doses that are frozen will be discarded. Doses must be protected from light. A dose should be administered as soon as possible after being removed from refrigeration. A dose can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours.

All doses will be administered as directed on the package insert (Appendix C). For persons age 15 through 45 years, Gardisil 9 should be administered as a 3-dose regimen, with one dose at 0, 2, and 6 months. The first dose will be given at the initial study visit after informed consent is obtained.

Doses should not be diluted or mixed with other vaccines. Each dose should be shaken well before use to maintain suspension of the vaccine. After thorough agitation, Gardasil-9 is a white cloudy liquid. Doses should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A dose should be discarded if particulates are present or if it appears discolored.

Each dose should be administered intramuscularly in the deltoid.

Patients should be observed for 15 minutes after administration.

For single-dose vial use, the 0.5-mL dose of vaccine should be shaken well before use, drawn from the single-dose vial using a sterile needle and syringe, and used promptly. Vial will be discarded after use.

5.2.2 Lidocaine 1% will be injected intra-dermally and subcutaneously to the margin of the lymph node to be sampled to numb the area. Lidocaine 1-2% will be injected into the tissue surrounding the area where the bone marrow will be removed to confer local anesthesia.

5.2.3 Lorazepam will be administered sublingually per manufacturer dosing recommendations.

6. Procedures Involved

Study Design

The study is designed to better understand how the 9-valent HPV vaccine elicits such potent and durable antibody responses in humans. In this study we also propose to compare the diversity, SHM levels, and affinity of antigen-specific Bmem and PC repertoires using the HPV vaccine as a model.

This is a single center, longitudinal cohort study in which participants will receive 9-valent HPV vaccine according to package insert (i.e., one dose of 9-valent HPV vaccine on day (D) 0

followed by a second dose 2 months later and a third dose 6 months later). Participants enrolled in the study will be asked to donate biological samples such as blood, saliva, and will undergo fine needle aspiration procedure for axillary lymph node and bone marrow sampling. Immune responses in the blood, saliva, bone marrow, and lymph nodes will be assessed in participants receiving the HPV vaccine.

Blood samples for immunologic testing will be collected at screening (from D-60 to D-45), on D0 (before vaccination), D1 (optional visit), D7, D14, D30, D60 (before vaccination), Visit 8 +1 day (optional visit), Visit 8 + 7±1 days, Visit 8 + 14±5 days, Visit 8 + 30±5 days, D180 (before vaccination), Visit 13 + 7±1 days, Visit 13 + 14±5 days, Visit 13 + 30±5 days, D365, D730, D1095, D1460, D1825. Saliva samples for antibody testing will be collected on D0 (before vaccination), D30, D60 (before vaccination), Visit 8 + 30±5 days, D180 (before vaccination), Visit 13 + 30±5 days, D365, and D730.

Axillary lymph node sampling by fine needle aspiration will be done 3 times per group. Group 1 will have lymph node sampling done D-30 to D0, D14, and D30. Group 2 will have lymph node sampling done D60, Visit 8 + 14±5 days, and Visit 8 + 30±5 days. Group 3 will have lymph node sampling D180, Visit 13 + 14±5 days, and Visit 13 + 30±5 days. Bone marrow sampling will be done for all groups at D730 and D1825.

The study plans to enroll 16 healthy adults between the ages of 18 to 45 years. In order to reach the sample size 16, we will enroll 32 participants to account for screen fails. However, the enrollment number may expand depending on the scientific questions being pursued at any given time. The donated samples will be stored and processed in Emory Infectious Diseases Laboratory at the Hope Clinic.

6.1 Schedule of Procedures (please see Appendix A)

6.2 Screening and Consenting

6.2.1 Participants responding to study ads will contact the Hope Clinic for a telephone screening where the research study will be explained in lay terms and eligibility criteria of the participant will be reviewed (see sections 10.1 and 10.2). If the participant is found to be eligible and continues to be interested in participating after reading the informed consent (emailed or mailed to him/her/them), an in person screening appointment will be scheduled (Day(D)-60 to D-45).

The call will last up to 30 minutes.

6.2.2 At the in person screening appointment, study staff will review the informed consent form with the participant and will answer all questions related to the study.

- Once the participant signs the informed consent, he/she/they will be assigned a unique study participation number.
- The volunteer will be asked to provide demographic information (birthdate, age, sex/gender, race and/or ethnicity) and information related to his/her/their medical history, including current medication use and vaccination history (have they ever received an HPV vaccine) and sexual history (number of partners with which they have had sexual intercourse (penetrative sex) and any history of genital warts, an abnormal pap smear, or positive HPV DNA test).
- The participant's vital signs and medical history will be recorded, including current medication use and vaccination history, and a targeted physical exam will be conducted as indicated, based on review of the participant's health status.
- All participants will have blood drawn for immunological screening tests.
- In preparation for saliva collection at the first vaccine visit, participants are notified to avoid eating for at least 30 minutes prior to sample donation. The participant should rinse their mouth after the most recent meal by drinking or gargling water. They may continue to take water up until 30 min prior to sample donation.
- Safety labs (WBC, hemoglobin, platelets, PT, PTT) will be conducted at this visit unless available by medical records.

This visit will last approximately 90-120 minutes.

The duration of participation for each participant is approximately 27 months.

6.2.3 Immunological screening test results will be available approximately two weeks after blood draw. If immunological screening tests reveal that participant has HPV 6, 11, 16, 18, 31, 33, 45, 52 or 58-specific binding antibodies (above the laboratory established cut-off value based on results from children's serum and lower limits of quantification), the participant will be screen failed. Only participants that screen pass will be contacted to continue the study. Laboratory results of the HPV binding antibody assay or other serologic assays will not be provided to the participant because the assays are not FDA-approved and "research only" test results cannot be reported out to patients as per federal CLIA regulations. Safety labs will be reviewed by a licensed clinician/co-investigator who will assess them for contraindications to planned procedures (lab result grade 2 or greater). Safety labs results will be shared with participant by phone prior to setting up the next appointment. Safety labs can be repeated at investigator discretion.

6.3 FNA Procedure (D-30 to D0 and other time points)

- Study personnel will first review the participant's current health status and note any changes in medical history since the screening visit, including medication use and vaccination history.
- The participant's vital signs will be recorded.
- For female volunteers of childbearing potential, a urine pregnancy test will be performed. Only females with a negative urine pregnancy test will get the procedure.
- Inclusion/exclusion criteria will be also verified before procedure.
- Participant will have blood drawn for immunological assays and saliva collected for antibody assays on days indicated in Schedule of Procedures (Appendix A).
- Participant will undergo lymph node sampling:
    - Group 1: Participants will undergo an FNA at D-30 to D0. Participants will repeat the procedure at D14±5 and D30±5.
    - Group 2: Participants will undergo an FNA on the same day, but prior to, the second vaccine dose (D60±5) or up to 5 days before. Participants will repeat the procedure at Visit 8 + 14±5 days and Visit 8 + 30±5 days.
    - Group 3: Participants will undergo an FNA on the same day, but prior to, the third vaccine dose (D180±5) or up to 5 days before. Participants will repeat the procedure at Visit 13 + 14±5 days and Visit 13 + 30±5 days.

Tissue sampling of an axillary lymph node will be carried out percutaneously. The FNA procedure involves performing a pre- procedure "time out" with the team and participant present to confirm identity of the participant and the nature of the procedure. Both axillae will be scanned with ultrasound to identify the most accessible node for biopsy. Once this has been identified, the skin will be sterilely prepared, and lidocaine 1%, an FDA-approved local anesthetic, will be injected intra-dermally and subcutaneously to the margin of the node in question to numb the area. A small skin incision will be made. Under real-time sonographic guidance, a 21-gauge needle will be placed. Two to four passes will be made to retrieve cytologic material. After tissue is retrieved, manual pressure will be applied to the biopsy site for 5-10 minutes. The technologist will review post-procedure instructions with the participant. The incision site will be sterilely dressed and the participant will be released after vital signs are checked.

At the end of the visit, the participant will also be instructed to promptly call the site if he/she/they develop any complication from the lymph node sampling. Participants calling the site will receive further instructions on the

proper course of action, including a return to the clinic for immediate evaluation, if appropriate.

This visit will last approximately 120 minutes.

6.4 Vaccination Visit (D0, D60±5, and D180±5)

- Study personnel will first review the participant's current health status and note any changes in medical history since the screening visit, including current medication use and vaccination history.
- The participant's temperature will be checked and recorded.
- For female volunteers of childbearing potential, a urine pregnancy test will be performed. Only females with a negative urine pregnancy test will receive the vaccine.
- Inclusion/exclusion criteria will be also verified before vaccination.
- Blood for immunological assays will be drawn and saliva for antibody assays will be collected before administration of the vaccine.
    - Saliva is obtained by asking the participant to don gloves and follow instructions of study staff to self-collect 2 saliva swabs. The device used (Oracol Plus, Malvern Medical, UK) is a soft cylindrical sponge on a plastic stick, which is used to brush the area where the external gums meet the teeth in a light, smooth brushing motion (slightly less vigorous than most people do when brushing their teeth). Once the sponge is saturated (usually ~1min, up to 2 min in some cases), the participant places the sponge side down into the original tube of the collection device (with assistance of study staff).
    - Optional procedure: On D0, approximately 40 microliters (ul) of blood will be collected by pricking the finger with a lancet (e.g., BD Microtainer Lancet) and collecting the blood with microsampler device (20 ul per device; Mitra Microsampler, Neoteryx, USA). This single-use, non-sterile device is intended to be used as a specimen collector of dried blood. It absorbs blood onto a cotton swab-like device, where the tip is covered in a hydrophilic porous material. It is non-cytotoxic, non-hemolytic, non-pyrogenic, and does not pose any sensitivity issues.
- The FDA-approved 9-valent HPV vaccine (Gardasil 9) will be administered intramuscularly in the deltoid region of the preferred arm of the participant.
- Participant's vaccination record will be updated.
- To ensure safety, each participant will be observed for a minimum of 15 minutes following vaccination, to note the occurrence of any immediate hypersensitivity reactions and because vaccinees may faint. Fainting is sometimes associated with tonic-clonic movements and other seizure-like activity and sometimes results in falling with injury. When fainting is

associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

The participant will be provided with a CDC vaccine information sheet (Refer to Appendix B).

At the end of the visit, the participant will also be instructed to promptly call 911 if signs of severe allergic reaction develop after leaving the clinic (hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, or weakness) or to call the clinic if he/she/they develop any unexpected or severe side effects from the vaccination. Participants calling the site will receive further instructions on the proper course of action, including a return to the clinic for immediate evaluation, if appropriate.

This visit will last approximately 60 minutes.

6.5 In person Follow-up Visits (D1 (optional visit), D7±1, D14±2, D30±5, Visit 8 +1 day (optional visit), Visit 8 + 7±1 days, Visit 8 + 14±5 days, Visit 8 + 30±5 days, Visit 13 + 7±1 days, Visit 13 + 14±5 days , Visit 13 + 30±5 days, D365±14, D730±14, D1095±14, D1460±14, D1825±30)

All participants will return for study-related blood draws (innate and adaptive assays) and saliva collection (antibody assays) post vaccination

- Study personnel will first review the participant's current health status and note any changes in health history since the screening visit, including current medication use and vaccination history.
- Blood for immunological assays will be drawn
- Saliva for antibody assays will be collected only on days indicated (D30±5, Visit 8 + 30±5 days, Visit 13 + 30±5 days, D365±14, D730±14)
- Optional procedure: Approximately 40 microliters of blood will be collected by finger prick and microsampler device on D30±5, Visit 8 + 30±5 days, Visit 13 + 30±5 days, and D365±5 (20 ul per device; Mitra Microsampler, Neoteryx, USA). This single-use, non-sterile device is intended to be used as a specimen collector of dried blood. It absorbs blood onto a cotton swab-like device, where the tip is covered in a hydrophilic porous material. It is non-cytotoxic, non-hemolytic, non-pyrogenic, and does not pose any sensitivity issues.

The visit will last approximately 30 minutes.

6.6 Bone marrow Procedure (D730±14 and D1825±30)

6.6.1 Up to thirty days prior to bone marrow aspiration visit, a safety labs (WBC, hemoglobin, platelets, PT, PTT) visit will be conducted unless available by medical records.

- Study personnel will first review the participant's current health status and note any changes in health history since the screening visit, including current medication use and vaccination history.
- Participant's vital signs will be recorded.
- Blood for screening assays (WBC, hemoglobin, platelets, PT, PTT) will be drawn.

The entire visit will take approximately 30 minutes.

6.6.2 Safety labs will be reviewed by a licensed clinician/co-investigator who will assess them for contraindications to the planned procedure (lab result grade 2 or greater). Safety labs can be repeated at investigator discretion.

6.6.3 The bone marrow aspirates are performed at the Winship Cancer Institute or Hope Clinic by a certified hematologist. Blood will be collected as well.

- Study personnel will first review the participant's current health status and note any changes in medical history since the screening visit (30 days prior to bone marrow aspiration visit) , including current medication use and vaccination history.
- The participant's blood pressure, pulse, respiration and temperature will be recorded. Vital signs parameters acceptable for BM aspiration procedures (if outside the following ranges, vital signs can be repeated at the investigator discretion):
    - Heart rate 55-100
    - Blood pressure systolic 90-160
    - Temperature <100.4 F
    - Respiratory rate 12-20
- For female volunteers of childbearing potential, a urine pregnancy test will be performed. Only females with a negative urine pregnancy test will undergo bone marrow aspiration.
- Blood for immunological assays will be drawn and saliva for antibody assays will be collected prior to bone marrow aspiration.
- Bone marrow aspiration:

After having the procedure explained to them, participants will be placed in the prone position on a gurney in one of the procedure rooms of the Winship Cancer Institute or Hope Clinic. The skin over the posterior iliac crest will be sterilely prepped and draped. Local anesthesia will be achieved by instillation of 1-2% lidocaine, an FDA-approved local anesthetic, into the tissue surrounding the area

where the bone marrow will be removed to numb the area. Lorazepam may be used as an anxiolytic, depending on the clinician performing the procedure. Using a sterile needle and using a sterile technique, about 40 cc of marrow will be aspirated following a single puncture of the skin and periosteum. Following completion of removing up to 40 cc of marrow, a sterile dressing will be applied using steri-strips and sterile gauze. Should less than 40 cc of marrow be removed, a second puncture will not be performed.

At the end of the visit, the participant will also be instructed to promptly call the site if he/she/they develop any complication from the bone marrow sampling. Participants calling the site will receive further instructions on the proper course of action, including a return to the clinic for immediate evaluation, if appropriate.

The entire aspiration procedure will take approximately 15 minutes. The entire visit will take approximately 60 minutes.

If a bone marrow aspiration attempt is unsuccessful in Visit 19 or 24 (a “dry tap”), the bone marrow aspiration may be re-attempted once for each visit if 1) clinician performing the procedure agrees and if 2) participant is willing. Must be within 30 days of safety labs or safety labs must also be repeated. Conducted as unscheduled visit (s).

6.6.4 Phone call (7 days after any BM aspirate ±1 days)

Seven days after any bone marrow aspirate procedure (±1 days), the study staff will call participant to assess any complications due to bone marrow procedure. If needed, participant will be asked to come to clinic for further assessment. The study staff will also administer an anonymous survey by email or text.

The call will last approximately 15 minutes.

6.7 Unscheduled Visit

6.7.1 An unscheduled visit may be conducted.

- If an unscheduled visit is conducted to evaluate an adverse event, study personnel will first review the participant's current health status and note any changes in medical history since the last visit, including current medication use and vaccination history.
- Participant’s vital signs will be recorded and a targeted physical exam will be performed.

- If indicated, blood draw for immunological assays or safety labs (WBC, hemoglobin, platelets, PT, PTT) will be drawn, but will not exceed blood draw limits.
- If prior bone marrow aspiration procedure was unsuccessful, bone marrow aspiration procedure may be re-attempted during an unscheduled visit, but only if safety labs have been conducted within 30 days and are within acceptable limits; clinician performing procedure agrees to re-attempt procedure; and participant is willing to re-attempt procedure. Participant's vital signs will be recorded and a pregnancy test performed (if indicated).

The entire visit will last 30-60 minutes.

7. Data and Specimen Banking

Participants will be asked for permission for principal investigator to keep any remaining (residual) specimens derived from venous blood, saliva swabs, or bone marrow or lymph node aspirates for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other viruses or bacteria. Future use samples/specimens will not be sold or used directly for production of any commercial product. These samples/specimens are protocol-required; thus, participants must agree to future use of these samples/specimens as a condition of their study participation.

These samples/specimens will be stored in the Emory Infectious diseases Laboratory (EIDCRL). The de-identified (all personal identifying information of the participant will be removed) Samples /Specimens will be labeled and stored in freezers at -80°C.

In keeping with NIH policy on scientific data sharing, gene expression (RNA sequencing) data and immunological assay results will be made publicly available through public database deposition and peer-reviewed publication. Participants will be fully de-identified (i.e., disseminated data will not contain direct identifiable information). Demographic data (e.g., age, race and/or ethnicity, sex/gender) associated with participants will be kept strictly separate from all experimental results, including gene expression data. This practice has become standard to protect participants' privacy.

8. Sharing of Results with Participants

Laboratory results of the HPV binding antibody assay will not be provided to the participant because the assay is not FDA-approved, and "research only" test results cannot be reported out to patients as per federal CLIA regulations.

No other immunological assay or gene expression (RNA sequencing) results will be reported back to the participant for these same reasons.

If during the lymph node FNA procedure, the ultrasound reveals an unexpected result (e.g., a mass), the attending physician will explain the nature of the finding to the

participant, provide a referral to a clinical specialist (e.g., an oncologist), and information on how to obtain health insurance to secure treatment if needed. The attending physician will also send a message to the participant's primary care physician requesting follow-up with the participant if participant authorizes and provides contact information.

Safety lab (WBC, hemoglobin, platelets, PT, PTT) results will be shared with participant by phone prior to setting up bone marrow aspiration Visit 19, bone marrow aspiration Visit V24, or bone marrow re-attempt (if safety labs repeated for re-attempt). Results can also be sent to the participant if requested.

9. Study Timelines

We anticipate that the duration of study for each participant will be approximately 1892 days or approximately 63 months in order to capture the durability of adaptive immune responses for correlation analysis with early responses and gene expression data.

We anticipate that it will take approximately 6 years to complete the laboratory analysis, for a total of approximately 8 years.

10. Inclusion and Exclusion Criteria

There will be two screening visits to determine eligibility for the study: One by phone and one in person. Participants responding to study ads will contact the recruiter or the study coordinator at the Hope Clinic for a telephone screening, where the research study will be explained in lay terms and eligibility criteria of the participant will be reviewed (see sections 10.1 and 10.2). If the participant is found to be eligible and continues to be interested in participating, the informed consent will be emailed or mailed to him/her/them to read, and an in person screening appointment will be scheduled (D-60 to D-45).

At the in person screening appointment, study staff will review the informed consent form with the participant and will answer all questions related to the study. The study activities will take place only after the informed consent has been received. The participant will sign the consent form after he/she/they confirm understanding of the study and the procedures and agrees to take part in the study. Once the participant signs the informed consent, he/she/they will be assigned a unique study participation number. Review of inclusion and exclusion criteria, medical history, including current medication use and vaccination history, and a targeted physical examination (if indicated) will be performed.

We plan to enroll 16 healthy volunteers age 18-45 years. In order to meet these enrollment goals, we may need to screen 50 participant to account for the screen fails.

Study results (i.e., publications or press releases) will be shared with all participants.

10.1 Participant Inclusion Criteria

10.1.1 Individuals aged 18-45 years old (inclusive), as the HPV vaccine is approved for this age range in adults
10.1.2 BMI $\leq$ 32.
10.1.3 Able to understand and give informed consent (provided in American English).
10.1.4 Must be in good health based on physical examination, vital signs, medical history, and the investigator's clinical judgment.
10.1.5 Must be available and willing to participate for the duration of this study
10.1.6 Must be willing to undergo lymph node fine needle aspiration and bone marrow aspiration
10.1.7 Must be willing to consent to the future use of remaining (residual) samples/specimens with IRB review

10.2 Participant Exclusion Criteria

10.2.1 Ever received a dose of an HPV vaccine
10.2.2 HPV 6, 11, 16, 18, 31, 33, 45, 52 or 58 seropositivity
10.2.3 Any history of genital warts, an abnormal pap smear, or positive HPV DNA test
10.2.4 Has known allergy or history of anaphylaxis or other serious adverse reaction to a vaccine or vaccine products
10.2.5 Has known allergy or history of anaphylaxis to yeast or products containing yeast
10.2.6 Any allergy to lidocaine.
10.2.7 Pregnancy or breast feeding.
10.2.8 Participants who believe they cannot tolerate the lymph node fine needle aspirate or bone marrow aspirate procedures without sedation
10.2.9 Any history of lymphoma involving axillary nodes, any history of breast cancer, bilateral inflammatory process of upper arms in the past 2 weeks, prior breast or axillary biopsy and/or surgery that in the opinion of the investigator would affect the immune response results.
10.2.10 Local infection, lymphadenitis, or rash in targeted area.
10.2.11 Received any vaccine from 14 days before vaccine dose until 30 days after each vaccine dose.*
*An individual who is initially excluded from study participation based on one or more of the time-limited exclusion criteria (fever, receipt of other vaccines) may be reconsidered for enrollment once the condition has resolved as long as the participant continues to meet all other entry criteria.
10.2.12 Volunteers with fever ($\geq$ 100.4 F or 38°C regardless of the route) within 3 days prior to vaccination.*
*An individual who is initially excluded from study participation based on one or more of the time-limited exclusion criteria (fever, receipt of other vaccines) may be reconsidered for enrollment once the condition has resolved as long as the participant continues to meet all other entry criteria.
10.2.13 History of or presence of severe co-morbidities as determined by the investigator, including autoimmune disease, or clinically significant cardiac,

pulmonary, gastrointestinal, hepatic, rheumatologic, renal disease, thrombocytopenia, and grade 4 hypertension*.
*Grade 4 hypertension per CTCAE criteria is defined as Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive)

10.2.14 History of a bleeding disorder or currently taking anti-coagulant products* (e.g. warfarin, direct thrombin inhibitors, heparin products, etc.), anti-platelet products, and/or NSAIDs including aspirin.
*including in the past week; however, an individual who is initially excluded from study participation based on one or more of the time-limited exclusion criteria may be reconsidered for enrollment once the condition has resolved as long as the participant continues to meet all other entry criteria

10.2.15 Has history of active malignancy other than squamous cell or basal cell skin cancer, unless there has been surgical excision that is considered to have achieved cure.

10.2.16 Current and/or expected immunosuppression due to cancer, receipt of chemotherapy, radiation therapy, and any other immunosuppressive therapies (including anti-TNF therapy).

10.2.17 Has known or suspected congenital or acquired immunodeficiency, including functional or anatomic asplenia, or recent history or current use of immunosuppressive therapy*.
*Anti-cancer chemotherapy or radiation therapy within the preceding 3 years, or long-term ($\geq$ 2 weeks within the previous 3 months) systemic corticosteroid therapy (e.g., prednisone at a dosage of $\geq$ 20 mg per day or on alternative days). Intranasal or topical prednisone (or equivalent) are allowed.

10.2.18 Known chronic infections including, but not limited to, known HIV, tuberculosis, hepatitis B or C.

10.2.19 Is post-organ, bone marrow, and/or stem cell transplant, whether or not on chronic immunosuppressive therapy.

10.2.20 Received blood products or immunoglobulin in the 3 months before study entry or planned use during this study.

10.2.21 Had major surgery (per the investigator's judgment) within 4 weeks before study entry or planned major surgery during this study.

10.2.22 Insulin-dependent diabetes* mellitus type 1 or type 2 requiring therapy
*History of isolated gestational diabetes is not an exclusion criterion.

10.2.23 Received experimental therapeutic agents within 12 months before first vaccine dose or plans to receive any experimental therapeutic agents 12 months after first vaccine dose that, in the opinion of the investigator, would interfere with the safety or objectives of the study. COVID-19 vaccines that fall under FDA EUA will be treated as approved vaccines for the purposes of this study.

10.2.24 Is currently participating or plans to participate in another clinical study which would involve receipt of an investigational product or undergo a procedure that, in the opinion of the investigator, would interfere with safety or objectives of the study.

10.2.25 Current diagnosed or self-reported alcohol abuse, drug abuse, or psychiatric conditions that in the opinion of the investigator would preclude compliance with the study.

10.2.26 Social, occupational, or any other condition that in the opinion of the investigator might interfere with compliance with the study.

11. Local Number of Participants

We anticipate we may need to enroll and screen as many as 50 participants locally to identify 16 participants that are HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 seronegative by our research assays (defined as being below the level of naturally elicited antibodies ± standard deviation with reference to international serum standards).

12. Recruitment Methods

12.1 Participants will be recruited following IRB approval

12.2 Participants will be recruited from the general population of metro Atlanta

12.3 Participants will be recruited through: posting of IRB-approved flyers in and around the Emory University campus; posting approved flyers on Emory and partner institution shuttles (e.g., Georgia Tech); use of various social media platforms such as Facebook, Twitter, Craigslist, Instagram, LinkedIn and other mobile apps; listservs (such as CDC, Emory University, Emory Vaccine Center, and Vaccine Dinner Club), and clinical trial recruitment websites such as Research Match.org; listing of clinical trials on the Emory clinical trials database (clinicaltrials.emory.edu); contacting past participants from the HIPAA-compliant clinical trials database at the Hope Clinic who have agreed to be contacted for future studies; presentations by Hope Clinic faculty at various University and community venues; and volunteer word-of-mouth (direct referrals)

12.4 Flyers and other advertising materials that will be used for recruitment purposes is attached for IRB approval

13. Withdrawal of Participants

Participants may voluntarily withdraw their consent from all future study activities including follow up at any time without penalty or loss of benefits to which they are otherwise entitled. Participants may be terminated from the study prior to study completion for reasons that might include, but are not limited to, those listed below. The investigator will inform the participant that all data acquired prior to termination will be included in the study analysis unless participant withdraws consent.

13.1 Participant no longer meets eligibility criteria (10.1 and 10.2)

13.2 The participant is considered by the PI to be “lost to follow-up” (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).

13.3 The participant dies.

13.4 The participant develops a medical condition or is started on new medication(s) that, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements, or may impact the quality of the data obtained from the study.

13.5 As deemed necessary by the PI or designee for noncompliance of any nature.

13.6 As deemed necessary by the PI after development of a grade 3 AE/SAE related to study procedure.

13.7 The participant becomes pregnant.

13.8 If the study is prematurely terminated by any regulatory authority or the investigator for any reason, the investigator will promptly inform the study participants and assure appropriate follow-up, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB.

Participants with early termination status (before D229±1 visit) are replaced as needed.

14. Risks to Participants

14.1 Risks of 9-valent HPV vaccine (Gardasil 9) as cited in Package Insert (Appendix C)

The most common ($\geq$ 10%) potential risks of receiving the FDA approved 9-valent HPV vaccine, Gardasil 9, include: local reactions such as injection-site pain (63.4% in men age 16-26 years; 89.9% in women age 16-26 years), injection site-swelling (20.2% in men age 16-26 years; 40.0% in women age 16-26 years), injection-site redness (20.7% in men age 16-26 years; 34.0% in women age 16-26 years), and systemic reactions such as headache (14.6% in women age 16-26 years)[27]. Rates of injection-site swelling and injection-site redness increased following each successive dose of Gardasil 9[27].

Since fainting has been reported following HPV vaccination, sometimes resulting in falling with injury, each participant will be observed for a minimum of 15 minutes following vaccination as recommended[27]. Fainting is sometimes associated with tonic-clonic movements and other seizure-like activity. When fainting is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. Therefore, participants who faint with tonic-clonic movements will be assisted into/maintained in these positions.

From clinical studies, four GARDASIL 9 recipients reported at least one serious adverse event that was determined to be vaccine-related. The vaccine-related serious adverse reactions were fever, allergy to vaccine, asthmatic crisis or asthma attack, and headache. There may be other unknown side effects. Across the clinical studies, no deaths were assessed as vaccine-related[27].

After 9-valent vaccination, the following events in the indicated intervals must be reported to Vaccine Adverse Event Reporting System (VAERS).

- Anaphylaxis or anaphylactic shock (7days)

- Shoulder Injury Related to Vaccine Administration (7 days)
- Vasovagal syncope (7 days)
- Any acute complication or sequelae (including death) of above events (interval - not applicable)
- Events described in manufacturer's package insert (Appendix C) as contraindications to additional doses of vaccine: hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after previous dose of Gardasil 9 or Gardasil

14.2 Risks of Study Medications

14.2.1 **Lidocaine:**

Complications of lidocaine (1% or 2%) injection used for local anesthesia are rare, mostly seen if a major vessel is inadvertently injected, the recommended dose is exceeded, or as an idiosyncratic response. The immediate side effects are related to the central nervous system (lightheadedness, confusion, tinnitus, blurred or double vision, vomiting, numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest) and cardiovascular system (decreased myocardial contractility, vasodilation, arrhythmias and cardiac arrest). Allergy to lidocaine either immediate (urticaria or anaphylaxis) or delayed (contact dermatitis) has been described. In adults, the recommended dose is 7 mg/kg with a maximum of 500 mg.

14.2.2 **Lorazepam:**

Lorazepam may be used as an anxiolytic prior to the bone marrow aspirate, depending on the clinician performing this procedure. Risks of lorazepam used for this indication are rare, but may include anterograde amnesia, drowsiness or sedation, disinhibitory reactions, respiratory depression, hypotension, or vomiting.

14.3 Risks of Study Procedures

The potential risks to participants are those associated with having blood drawn, the risks associated with lymph node fine needle aspiration, and the risks associated with bone marrow aspiration.

14.3.1 **Blood draws:**

Blood sample collection involves transient discomfort and may cause fainting, which is managed by having the participant lie down prior. The blood draw site may bruise, and this can be ameliorated by holding pressure to this site following the blood draw. The sites of blood draw are potential sites of infection, but this risk is made very unlikely by the use of sterile technique.

14.3.2 **Finger prick:**

Blood sample collection by finger prick and absorption with a microsampler device is an optional procedure that involves transient discomfort and may cause fainting, which is managed by having the participant sit or lie down prior. The blood draw site may bruise, and this can be ameliorated by holding pressure to this site following the

blood draw. The sites of blood draw are potential sites of infection, but this risk is made very unlikely by the use of sterile technique.

14.3.3 **Saliva collection:**
The procedure to obtain saliva is analogous to brushing one's teeth and there is essentially no risk involved.

14.3.4 **Fine needle aspiration (FNA) of the lymph node:**
Fine needle aspirates are generally tolerated very well, with most (n = 8/13) experiencing no discomfort to mild discomfort[28]. The potential risks for fine needle aspiration are rare. They include, but are not limited to: tenderness around aspiration site, bruising, bleeding and hematoma formation, as well as much rarer complications: infection, vagal reaction, numbness caused by accidental nerve damage, and pneumothorax (for axillary lymphadenopathy sampling).[29-31]

14.3.5 **Bone marrow aspiration:**
The physical risks of undergoing a bone marrow aspiration are pain and bruising that may last 1 to 3 days. Very rarely more serious side effects could occur including damage to normal blood vessels, veins or bone structures or rarely localized infection at the area where the marrow is removed. The removal of 40 ml or less of marrow produces a temporary and mild transient anemia[32]. A small number of participants experience vaso-vagal response including, lightheadedness, nausea, and transient hypotension.

14.4 Loss of Confidentiality:
All clinical data, including birthdate and demographics, are stored on a HIPAA compliant clinical management database and HIPAA compliant Emory RedCap database and/ or a password protected Excel file at Hope Clinic, only trained Hope Clinic personnel will have access to the databases. Hard copy clinical data forms, for example source or protocol-specific CRFs, are stored at Hope Clinic in a locked filed cabinet that only staff have access to. A file linking the participant identity, i.e., name, to their unique study participant ID (PTID) is maintained at the Hope Clinic in a separate locked file cabinet and in a HIPAA compliant clinical management database. All samples are de-identified and stored using only the study number, PTID, date of visit, and visit number. All samples shipped to collaborators are sent without PTID (CDC) or assigned a non-linked identifier (EPFL).

However, total confidentiality cannot be guaranteed.

Any publications from this study will not use information that will identify participants by name. A description of this trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This web site will not include information that can identify participants. At most, this web site will include a summary of the results.

14.5 Risks of Gene Expression (RNA Sequencing) Analysis

Any RNA sequencing data generated will be kept separated from data that could identify specific participants. There may be a risk that information resulting from research RNA sequencing could be misused for discriminatory purposes. However, state and federal laws provide protections against genetic discrimination.

14.6 Risk of Concomitant Medications, Prophylactic Medications and Rescue Medications

14.6.1 Concomitant Medications

In accordance with exclusion criteria, participants expected to receive prohibited medications (please see **Section 10.2**) will be considered ineligible for the study. All medications, therapies, or vaccines administered to study participants after study entry will be documented at each visit.

All medications and vaccines received by study participants after administration of study vaccine should be reported to the study staff and recorded. This includes, but is not limited to, the following:

- blood products, chemotherapy, immunosuppressive therapy (including anti-TNF therapy), and radiation therapy (administered at any time after study vaccination).
- Any non-study vaccine (administered 60 days before the first vaccination (D0) until 60 days after the last vaccination (D240)).

Any of the above medications could affect the innate or adaptive assay results and should not be used unless medically indicated.

14.6.2 Prophylactic Medications

Prophylactic medications will not be administered before vaccination or any other study procedures, but are allowed.

14.6.3 Rescue Medications

We do not anticipate the use of any other medication; however, should anaphylactic or hypersensitivity reactions occur, epinephrine (1:1000) and diphenhydramine injections are readily available.

- Epinephrine injection can be associated with high blood pressure, arrhythmia, lightheadedness, nervousness, restlessness, tremor, shortness of breath and diaphoresis. The frequency of these side effects is not defined.

- Diphenhydramine injection may be required to treat possible allergic reactions and its use can be associated with low blood pressure, arrhythmia, confusion, dizziness, sedation, restlessness, diarrhea, nausea

and urinary retention. The frequency of these side effects is also not defined.

When facing a medical emergency, the clinic staff will follow the institutional SOP by calling 911 first (Hope Clinic) or a code to the hospital on call team (Winship Cancer Institute). If needed, the participant will be transferred to Emory University Emergency Department for further care.

Participants are allowed to use acetaminophen if they experience a moderate to severe local or systemic side effects after vaccine administration. Participants are allowed to use acetaminophen if they experience a moderate to severe local or systemic side effects after lymph node FNA or bone marrow aspiration.

15. Potential Benefits to Participants

Participants will benefit by receiving the 9-valent HPV vaccine, Gardasil 9, free of charge. The 9-valent HPV vaccine was approved in 2018. It prevents infection by HPV types that cause 90% of cancer cases (HPV 16, 18, 31, 33, 45, 52, and 58)[6] and 90% of genital warts cases (HPV 6 and 11)[7]. The 9-valent HPV vaccine was >96% effective at preventing high-grade cervical, vulvar, or vaginal disease in 16-26 year old women who did not have evidence of ongoing or prior infection (i.e., seronegative and PCR negative)[9] and the 4-valent HPV vaccine was >74% effective at preventing high-grade anal disease in 16-26 year old men without evidence of ongoing or prior infection[10]. Both of these study populations were similar to the target population of this study (i.e., seronegative adults age 18-26 years). Importantly, the 9-valent vaccine was shown to induce highly durable antibody responses above the antibody levels induced by natural infection in boys and girls for 7.5 years,[14] and the 4-valent vaccine was shown to induce antibody responses above the antibody levels induced by natural infection in adult women age 16-23 years for 14 years[11]. As antibodies are thought to be mediate protection by this vaccine[33], this data indicates that participants of this study may be protected against HPV disease caused by the vaccine types for at least this long.

16. Compensation to Participants

As compensation for expenses/travel and time, participants will receive $50 in the form of a gift debit/credit card (ClinCard) for each visit that involves a blood draw or saliva collection (11-15 total), as well as for any unscheduled visit without bone marrow aspiration; $200 in the form of a gift debit/credit card (ClinCard) for each visit that involves a lymph node fine needle aspirate (3 total); and $350 in the form of a gift debit/credit card (ClinCard) for visits that involve bone marrow aspirates (2 total, with a maximum of 1 re-attempt for Visit 19 and 1 re-attempt for Visit 24, which will be conducted as unscheduled visits). The 9-valent HPV vaccine will be provided free of charge. If a participant completes all visits, he/she/they will receive a total of

$2,000 to $3,000. In the event gift, debit/credit cards (ClinCard) is unavailable, cash reimbursement maybe done.

17. Data Management and Confidentiality

17.1 Data analysis plan

This is an exploratory, non-placebo controlled analysis of immune responses obtained from blood, lymph node aspirates, and bone marrow aspirates. This will provide us with descriptive data to analyze immune responses.

17.2 Steps taken to secure data

17.2.1 All faculty and staff at the Hope Clinic receive HIPAA, human participants, and EHSO (e.g., bloodborne pathogens) training as part of their onboarding and continuing training.

17.2.2 Each participant will be assigned a unique study participant identification number (PTID) and these numbers rather than names will be used to collect and store participant information, including gene expression (RNA sequencing) data.

17.2.3 Investigators and study personnel will keep accurate records to ensure that the conduct of the study is fully documented. Clinical data from this study, including participant birthdate and demographics, will be associated with the PTID, maintained on a HIPAA compliant clinical management database and a HIPAA compliant RedCap database and/ or password protected Excel file, respectively at Hope Clinic accessible to investigators and study personnel only. Hard copy clinical data forms, for example source or protocol-specific CRFs, associated with the PTID will be stored at Hope Clinic in a locked filed cabinet and accessible to investigators and clinical staff only. A file linking the participant PII (i.e., their name and contact information) to their PTID will be maintained at the Hope Clinic in a separate locked file cabinet and HIPAA compliant clinical management database accessible to investigators and clinical staff only. Study personnel will only send documents containing personal PII via fax or encrypted email in accordance with HIPAA regulations (e.g., to send/receive safety lab data and medical records request to/from primary care physician).

17.3 Procedures for quality control of collected data

The Principal Investigator (or designee) will keep accurate records to ensure that the conduct of the study is fully documented. The investigator will ensure that all CRFs and participant study files are legible and complete for every participant. The Principal Investigator (or designee), through the use of an internal Quality Management Plan, appropriate site quality control, and quality assurance monitoring staff, will be responsible for the regular review of the conduct of the study for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data and accuracy of source documentation verification. The first five volunteers enrolled will receive a 100% review. Monthly reviews will consist of a random selection of 10% of study research

records. The reports of the internal site monitor will be submitted to the Principal Investigator (or designee).

The RedCap data entry system will include checks for data that are outside feasible limits (e.g., dates that are in the future) or skipped answers.

17.4 How data and specimens will be handled

17.4.1 All de-identified samples will be stored at Emory Infectious Diseases Research Laboratory (EIDRL) at Hope Clinic by laboratory staff using only the study number, PTID, date of visit, and visit number, with the following exceptions: Dried blood samples collected by microsampler device and paired serum samples, as well as a serum aliquot from Visit 1 will be temporarily stored at EIDRL and then shipped to collaborators at Centers for Disease Control and Prevention using only a specimen ID, date of visit, and visit number. De-identified serum will be shipped to collaborators at EPFL using only a non-linked identifier and visit number. The data from immunological assays and gene expression analysis (RNA sequencing) will be linked to PTID, maintained by the laboratory, and accessible to investigators and laboratory staff. Laboratory data and demographic data may be linked by PTID for statistical analysis by investigators or collaborators (e.g., to control for age); however, PTID will not be published nor will the gene expression (RNA sequencing) data be linked to demographic data in order to protect participant privacy and prevent the discovery of participant identity.

17.4.2 Specimens and demographic data linked by PTID will be stored indefinitely, but all personal identifiable information (PII) and PII/PTID links will be destroyed once the laboratory analysis associated with this protocol is complete and the last manuscript associated with this protocol has been published.

17.4.3 Study investigators and personnel will maintain the highest degree of confidentiality for the clinical and research information obtained from the participants. Medical and research records will be maintained in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of a clinical study, investigators will permit authorized representatives of regulatory authorities to examine (and when required by applicable law, to copy) clinical records for the purpose of quality assurance reviews and evaluations of study safety and progress. Unless required by laws that permit copying of records, only the PTID associated with documents or with other participant data may be copied (and all personally identifying information will be removed). Authorized representatives described above are bound to maintain the strict confidentiality of medical and research information that is linked to identify individuals.

17.4.4 The blood tubes will be labeled at the Hope Clinic with a unique identifier and will be transported to the lab at the Hope Clinic in EHSO-approved transport containers. Fresh lymph node fine needle aspirate samples labeled with PTID and visit number performed at the Winship Cancer Institute or Hope Clinic will be transported to the Hope Clinic or Scherer laboratory in a timely fashion in EHSO-approved transport containers. Fresh bone marrow aspirate samples labeled with PTID and visit number performed at the Winship site or Hope Clinic will be transported to the Hope Clinic

or Scherer laboratory in a timely fashion in EHSO-approved transport containers. The dried blood microsamplers and paired serum samples, as well as serum samples from Visit 1 will be labeled at the Hope Clinic with a unique identifier and shipped to the collaborators at the Centers for Disease Control and Prevention. De-identified serum will be labeled with a unique identifier and shipped to collaborators at EPFL.

18. Provisions to Monitor the Data to Ensure the Safety of Participants

- The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether participants remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor. Description of plan for notifying the IRB of reportable events; whether the sponsor requires reporting above and beyond the Emory IRB reporting requirements, and if so, a description of the requirements and plan for meeting them. See http://irb.emory.edu/documents/DSMB-DSMPGuidance.pdf for guidance.
- What data are reviewed, including safety data, untoward events, and efficacy data.
- How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).
- The frequency of data collection, including when safety data collection starts.
- Who will review the data.
- The frequency or periodicity of review of cumulative data.
- The statistical tests for analyzing the safety data to determine whether harm is occurring.
- Any conditions that trigger an immediate suspension of the research.

18.1 Study Oversight

The Principal Investigator and the research team (co-Investigators, research nurses, study coordinators, and data managers) are responsible for identifying adverse events. Adverse events will be reviewed regularly by the research team.

18.2 Adverse Events

This section defines the types of adverse events that may occur, and outlines the procedures for appropriate adverse event collecting, grading, recording, and reporting.

Information in this section complies with 21CFR 312; ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and Good Clinical Practice; and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events Version 5.0 [Published: November 27, 2017; http://evs.nci.nih.gov/ftp1/CTCAE/About.html]

These criteria have been reviewed by the study investigators and have been determined to be appropriate for this study population.

18.2.1 **Safety Reporting**

- **Adverse Events (AE)**

  Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

  An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the procedure, without any judgment about causality.

  After 9-valent vaccination, the following adverse events in the indicated intervals must be reported to Vaccine Adverse Event Reporting System (VAERS).
  - Anaphylaxis or anaphylactic shock (7 days)
  - Shoulder Injury Related to Vaccine Administration (7 days)
  - Vasovagal syncope (7 days)
  - Any acute complication or sequelae (including death) of above events (interval - not applicable)
  - Events described in manufacturer's package insert (Appendix C) as contraindications to additional doses of vaccine: hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after previous dose of Gardasil 9 or Gardasil

  Any grade 3 or higher adverse event (up to 7 days after phlebotomy, lymph node FNA, or bone marrow aspiration) will be recorded and reported within a week to Independent Safety Monitor (ISM).

- **Suspected Adverse Reaction (SAR)**

  Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug or procedure caused the adverse event.

  Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

  SARs after vaccine administration may include:
  - Local reactions: injection site redness, injection site swelling, pain at the site of injection, itching of the skin at the injection site.
  - Systemic reactions: headache, fever, nausea, dizziness.

  SARs after phlebotomy may include:

- Local reactions: pain at the site of venipuncture, bruising at the site of venipuncture, infection at the site of venipuncture
- Systemic reactions: lightheadedness or fainting

SARS after lymph node FNA procedure may include:

- Local reactions: pain at the site of aspiration, bruising of the skin at the site of aspiration, bleeding and hematoma formation at the sight of reaction, , infection at site of aspiration, numbness caused by accidental nerve damage, pneumothorax (collapsed lung)
- Systemic reactions: Vaso-vagal response (lightheadedness or fainting) or allergic reaction to anesthetic

SARSs after bone marrow aspiration may include:

- Local reactions: pain at the site of aspiration, bruising at the site of aspiration, infection at the site of aspiration
- Systemic reactions: mild transient anemia, lightheadedness, nausea, transient low blood pressure, or allergic reaction to anesthetic

Any SAR of Code 3 or higher related to phlebotomy, lymph node FNA, or bone marrow aspiration up to 7 days after the procedure will be recorded and reported within 7 days to ISM.

- **Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction**

An adverse event or suspected adverse reaction is considered ‘‘serious’’ if, in the view of the investigator, it results in any of the following outcomes:

- **Death.**
- **A life-threatening adverse event.**
- **Inpatient hospitalization or prolongation of existing hospitalization.**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.**
- **A congenital anomaly/birth defect.**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Serious adverse events will be recorded for the entire duration of the study and reported within 24 hours to ISM, and also to IRB if study related.

An adverse event or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of the investigator, its occurrence places the patient or participant

at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- **Unexpected Adverse Event or Unexpected Suspected Adverse Reaction**

  An adverse event or suspected adverse reaction is considered ‘‘unexpected’’ if it is not listed in the Summary of Product Characteristics or is not listed at the specificity or severity that has been observed; or, if the Summary of Product Characteristics is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

  For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents.

  ‘‘Unexpected,’’ as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Summary of Product Characteristics as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

  Any unexpected adverse event grade 3 or higher related to phlebotomy, lymph node FNA, or bone marrow aspiration up to 7 days after the procedure will be recorded and reported within 7 days to ISM.

- **Independent Safety Monitoring**

  The ISM is a physician with relevant expertise in clinical studies whose primary responsibility will be to provide independent safety monitoring in a timely fashion and to provide recommendations regarding the safe continuation of this study.

  The ISM will evaluate safety data generated from study participants against the known safety profile of the study product or study procedure to assess for possible changes to the overall risk of the study.

  The ISM will communicate with the Principal Investigator as needed. The study has provisions for a back-up ISM to ensure that independent safety monitoring happens at all times during the study.

18.2.2 Collecting and Recording Adverse Events and Pregnancy

Adverse events may be identified during this study through any of these methods:

- Examination of the participant during study visits.
- Questioning the participant during study visits.
- Receiving a safety contact from the participant at any time during the study

Note: participants will be asked to call the site if they develop any of the following:

- Illness or treatment from a physician or emergency department the entire duration of the study;
- Any adverse event that limits self-care activities of daily living (e.g. bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bed ridden) even if he/she decides not to seek medical care
- Local AEs and/or systemic AEs of grade 3 or higher related to phlebotomy, lymph node FNA, or bone marrow aspiration up to 7 days after the procedure will be recorded and reported within 7 days to ISM.
- Any SAEs for duration of study
- Any SARs of Code 3 or higher related to phlebotomy, lymph node FNA, or bone marrow aspiration up to 7 days after the procedure will be recorded and reported within 7 days to ISM.
- Any unexpected adverse events grade 3 or higher related to phlebotomy, lymph node FNA, or bone marrow aspiration up to 7 days after the procedure will be recorded and reported within 7 days to ISM.
- Anaphylaxis or anaphylactic shock up to 7 days after receiving vaccine dose and any acute complication or sequelae (including death) of anaphylaxis (interval - not applicable)
- Shoulder Injury Related to Vaccine Administration up to 7 days after receiving vaccine dose and any acute complication or sequelae (including death) of shoulder injury (interval - not applicable)
- Vasovagal syncope up to 7 days after receiving vaccine dose and any acute complication or sequelae (including death) of vasovagal syncope (interval - not applicable)
- Events described in manufacturer's package insert (Appendix C) as contraindications to additional doses of vaccine: hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after previous dose of Gardasil 9 or Gardasil

A complete recording of safety events in the CRF will include event term; date(s) of onset and resolution/stabilization; assessment of severity; relationship to procedures/intervention(s) such as phlebotomy, FNA, or bone marrow aspiration;

expectedness; determination of whether the AE qualifies as serious or non-serious; treatment required; action taken with study participation; and outcome. AEs qualifying as serious also require a narrative of the event. Updates in safety events will be recorded as additional information becomes available.

Information on pregnancies will be collected from the time a participant signs the consent until the participant completes study participation.

If a participant becomes pregnant after study entry, the investigator will discuss with the participant and/or the treating physician the known possible risks to the fetus.

Participants becoming pregnant after study entry will be withdrawn from the study and followed until the end of the pregnancy. A pregnancy resulting in congenital anomaly/birth defect will be considered a SAE. Any premature termination of the pregnancy will also be reported and assessed as an SAE as needed.

18.3 Grading and Attribution of Adverse Events

18.3.1 Grading Criteria

Adverse events will be graded according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 5.0 [November 27, 2017; http://evs.nci.nih.gov/ftp1/CTCAE/About.html]

This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.
All adverse events whether or not listed in the NCI-CTCAE will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual (A semi-colon indicates 'or' within the description of the grade):

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

*Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care Activities of Daily Living (ADL) refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Not all Grades are appropriate for all AEs; therefore, some AEs are listed with fewer than five options for Grade selection.

Anaphylaxis is a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.

Severity grading of anaphylaxis as per the NCI-CTCAE manual is as follows:

- Grade 1= not applicable
- Grade 2= not applicable
- Grade 3= Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
- Grade 4= Life-threatening consequences; urgent intervention indicated
- Grade 5= Death

Severity grading of AEs of laboratory abnormalities will be assessed as per the NCI-CTCAE manual.

18.3.2 Definition of Attribution

The site investigator will initially determine the relationship of an adverse event grade 3 and above to study procedures.

The relationship of an AE to study participation will be determined using definitions in the table below:

Code	Descriptor	Definition (guidelines)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related to study. The event is completely related to an etiology other than the study product or study intervention (the alternative etiology must be documented in the study participant's medical record)
2	Unlikely	The adverse event is doubtfully related to study and likely to be related to factors other than study product or study intervention.
RELATED CATEGORIES		

3	Possible	The adverse event may be related to study. There is an association between the event and the administration of study product or between the event and a study procedure and there is a plausible mechanism for the event to be related to the study product or procedure. There may be also an alternative etiology, such as characteristics of the participant's clinical status and/or underlying disease
4	Probable	The adverse event is likely related to study. There is (1) an association between the event and the administration of study product or study intervention, (2) a plausible mechanism for the event to be related to the study product or study procedure, and (3) the event could not be reasonably explained by known characteristics of the participant's clinical status and or an alternative etiology is not apparent
5	Definite	The adverse event is clearly related to study. There is (1) an association between the event and the administration of the study product or study intervention, (2) a plausible mechanism for the event to be related to the related to the study product or study procedure, and (3) causes other than the study product have been ruled out and/or the event re-appeared on re-exposure to the study product

18.3.3 **Reporting Timelines**

- **Reporting Serious Adverse Events to the Independent Safety Monitor**

  The Principal Investigator will notify the ISM by email of any SAE within 24 hours of becoming aware of the event. The ISM may request further information if necessary and possibly request changes to the protocol or consent form as a consequence of the adverse event.

- **Notifying Institutional Review Board**

  The Principal Investigator will ensure the timely dissemination of SAE information, including SAEs requiring expedited review by the ISM and to the IRB in accordance with IRB regulations and guidelines. Serious adverse events that are unanticipated, related to study participation, and involving risk to participant or others will be reported to the IRB promptly per IRB guidelines.

18.4 Stopping Rules

18.4.1 **Study Stopping Rules:**

Study procedures will be suspended pending expedited review of all pertinent data by the institutional review board and the ISM if Gardasil 9, lidocaine, or lorazepam were recalled by the manufacturer.

Also, procedures will be suspended pending review of all pertinent data by the PI and the ISM after the occurrence of any of the following:

- 1 case of infection at the site of lymph node sampling.
- 2 cases of hematomas at the site of lymph node sampling.
- 1 case of pneumothorax from lymph node sampling.
- 1 case of persistent (>4 weeks) paresthesia or numbness in upper extremity due to lymph node sampling.
- 1 case of persistent (>4 weeks) decreased range of motion due to lymph node sampling.
- Bone marrow aspiration-related grade 3 AE or SAE

18.4.2 **Individual Participant Stopping Rules:**

Early study termination will occur in participants due to any of the following circumstances detailed in **Section 14**.

18.4.3 **Early Termination From Study Procedures with Continued Study Participation/Follow-up:**

Please refer to **Section 14**.

18.4.4 **Follow-up After Early Study Termination:**

Participants who are prematurely terminated from the study due to an AE will be followed until resolution of the AE or until 28 days after a participant terminates from the study, or 7 days after a participant undergoes lymph node or bone marrow sampling, whichever comes later. Resolution of an AE is defined as the return to baseline status or as stabilization of the condition with the expectation that it will remain chronic.

After assessing terminated participants for safety under the provisions stated above, the participant will be seen in clinic, if necessary.

18.4.5 **Participant Replacement**

In the case of premature termination (before D229±1 visit), extra participants may be recruited, at the discretion of the Principal Investigator, to maintain the target sample size.

18.5 Protocol Deviations

Deviations occur when the investigators, study staff, or participants fail to adhere to protocol requirements or when there is non-adherence to GCP guidelines.

Upon determination that a protocol deviation has occurred, the study staff will notify the Principal Investigator promptly. Substantive protocol deviations from the protocol that affect rights, safety or welfare of participants, their willingness to continue in the study or impact the integrity of the research data will be reported promptly to the IRB per IRB regulations.

19. Provisions to Protect the Privacy Interests of Participants

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique patient identification number (PTID) and these numbers rather than names will be used to collect and store participant information and samples. All samples shipped to collaborators are sent without PTID (CDC) or assigned a non-linked identifier (EPFL). A file linking the participant identity, i.e., name, to their unique study participant ID (PTID) is maintained at the Hope Clinic in a separate locked file cabinet and on a HIPAA compliant clinical management database. Screening, consenting, and study visits will take place in private clinic rooms.

Any publications from this study will not use information that will identify participants by name or PTID. A description of this trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This web site will not include information that can identify participants. At most, this web site will include a summary of the results. Site personnel will only transmit documents containing personal identifiable information (PII) using encrypted email or fax in accordance with HIPAA regulations (e.g., to send/receive safety lab data and medical records to/from primary care physician).

20. Economic Burden to Participants

There is no cost to participants for the research tests, procedures, or study product while taking part in this study. If the study procedures result in any medical complications, the cost of treatment for those complications may be charged to you or your insurance. Participants may be compensated for their participation in this study. Compensation will be in accordance with the local IRB's policies and procedures, and participant to IRB approval.

If it is determined by the principal investigator that an injury occurred to a participant as a direct result of the tests, procedures or treatments that are done for this study, then referrals to appropriate health care facilities will be provided to the participant. Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating site. No financial

compensation will be provided to the participant for any injury suffered due to participation in this study.

21. Consent Process

21.1 Statement of Compliance

This study was designed to ensure the protection of participants according to the ethical principles of the Declaration of Helsinki and amendments concerning medical research in human participants. This clinical study will be conducted using current good clinical practice and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by IRB, as well as any other appropriate health authorities. Any amendments to the protocol or to the consent materials will also be approved by the appropriate bodies listed above prior to implementation.

21.2 Informed Consent Process

The informed consent form will provide information about the study to a prospective participant to allow for an informed decision about participation in the study. Prospective participant must be given ample opportunity to review the informed consent and inquire about the results of the study. The consent form will be provided electronically to the participant during the first screening phone call (prior to D-60). A copy of the informed consent form will again be provided to a prospective participant for review prior to any study procedure during the in person screening visit (D-60 to D-45). The Principal Investigator or an approved designee will discuss the consent with the prospective participant and answer questions. Study staff will read through the consent form with potential participants and answer any questions. Participants will be allowed sufficient time to consider participation in the study, after having the nature and risks of the trial explained to them and have the opportunity to discuss the trial with their family, friends. The prospective participant will be told that being in the study is voluntary and that he or she may withdraw from the study at any time, for any reason. The consenting process will take place in private exam rooms at the Hope Clinic. We anticipate that the consent process will take about 20 minutes.

All participants must read, sign, and date a consent form before undergoing any study procedures. Consent materials will be provided in the American English language. A copy of the signed consent form will be given to the participant.

The informed consent form will be revised and receive IRB approval whenever important new safety information is available, whenever the protocol is

amended, and/or whenever any new information becomes available that may affect participation in the study.

Participants will be compensated for their time and travel. The informed consent form will specify the amount of compensation for each participant.

22. Setting

Participants will be recruited and screened from the general population of metro Atlanta. Participants will be enrolled at the Hope Clinic, Decatur, Georgia and will undergo lymph node FNA at the Breast Center at Winship Cancer Institute or Hope Clinic and bone marrow aspiration by a certified hematologist at the Winship Cancer Institute or Hope Clinic.

22.1 Independent Safety Monitoring

The ISM is a physician with relevant expertise in vaccine trials whose primary will be to provide independent safety monitoring in a timely fashion and to provide recommendations regarding the safe continuation of this study.

The ISM will evaluate safety data generated from study participants including all SAEs against the known safety profile of the study vaccine to assess for possible changes to the overall risk of the study.

The ISM will communicate with the PI as needed to discuss any safety events of special interest developing during the study and when conducting the review of the monthly reports of cumulative safety data. The study has provisions for a back-up ISM to ensure that independent safety monitoring happens at all times during the study

23. Resources Available

The Hope Clinic has a database of more than 5000 previous volunteers who can be considered for the currently proposed work. The Hope Clinic also has a website and the ability to reach out to potential participants through advertising around Emory University campus. We anticipate enrolling 3-4 participants weekly, with all participants enrolled in approximately 1 year.

23.1 Facilities

The Hope Clinic is a community-based vaccine research clinic and is the clinical arm of the Emory Vaccine Center at Emory University. The Winship Cancer Institute is the only National Cancer Institute–Designated Comprehensive Cancer Center in Georgia and one of only 50 in the country.

23.2 Participant Support

Referrals to appropriate medical or psychological health care facilities will be provided by the investigators to the participant as needed due to the anticipated consequences of human research. Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating site (Hope or Winship).

23.3 Study Personnel Training

All faculty and staff at the Hope Clinic receive HIPAA, human participants, and EHSO (e.g., bloodborne pathogens) training as part of their onboarding and continuing training. In addition, all study personnel will complete ongoing approved protocol review and provide documentation of this training to study quality management personnel.

24. Multi-Site Research when Emory is the Lead Site

N/A

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26. Appendix A

	-60 to -45*	-30 to 0	0	1	7±1	14±5	30±5	60±5#	V8 + 1 day	V8 + 7±1 days	V8 + 14±5 days
	Visit (V) 1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Informed consent	x										
Demographics, medical history	x										
Targeted physical exam	x										
Vital signs/temperature	x	x	x			(x)	(x)	x			(x)
Blood draw for screening	x										
Pregnancy test		(x)	(x)			(x)	(x)	(x)			(x)
Vaccination			x					x			
Blood draw for serology assays			x			x	x	x		x	
Optional: Microsampler for serology assays			x				x				
Saliva collection for antibody assays			x				x	x			
Blood draw for cellular assays			x			x	x	x		x	x
Blood draw for transcriptomics			x	(x)	x			x	(x)	x	
FNA lymph node sampling (Group 1)		x				x	x				
FNA lymph node sampling (Group 2)								x			x
FNA lymph node sampling (Group 3)											
Blood draw for immunological screening and safety labs	(x)										

	V8 + 30±5 days	180±5#	V13 + 7±1 days	V13 + 14±5 days	V13 + 30±5 days	365±14	V19 - 15±14 days	730±14	7±1 days from V19^
	V12	V13	V14	V15	V16	V17	V18	V19	V20
Vital signs/temperature	(x)	x		(x)	(x)			x	
Pregnancy test	(x)	(x)		(x)	(x)			(x)	
Vaccination		x							

Blood draw for serology assays	x	x	x		x	x		x	
Optional: Microsampler for serology assays	x				x	x			
Saliva collection for antibody assays	x	x			x	x		x	
Blood draw for cellular assays	x	x	x	x	x	x		x	
FNA lymph node sampling (Group 1)									
FNA lymph node sampling (Group 2)	x								
FNA lymph node sampling (Group 3)		x		x	x				
Safety labs for bone marrow aspiration							(x)		
Bone marrow aspiration								x	
phone call (BM follow up) and survey									x

*Conducting a visit outside window is allowed if approved by investigator

^One week +/- one day from the actual date of Visit 19

#FNA and pregnancy test to occur on the same day, but prior to, the second vaccine dose (Visit 8, D60±5) or up to 5 days before. If FNA occurs prior to Visit 8, a pregnancy test will again be administered prior to vaccination on Visit 8.

+FNA and pregnancy test to occur on the same day, but prior to, the second vaccine dose (Visit 13, D180±5) or up to 5 days before. If FNA occurs prior to Visit 13, a pregnancy test will again be administered prior to vaccination on Visit 13.

An unscheduled visit may be conducted; this may include a blood draw, if indicated, but will not exceed blood draw limits; this may include bone marrow aspiration procedure if safety labs have been conducted within 30 days and are within acceptable limits, clinician performing procedure agrees, and participant is willing. If unscheduled visit is conducted to perform a bone marrow aspiration, vital signs and pregnancy test (if indicated) will be performed. If an unscheduled visit is conducted to evaluate an adverse event, vital signs and a targeted physical exam will be performed.

	1095±14	**1460±14**	**V24 - 15±14 days**	**1825±30 days**	**7±1 days from V24^^**
	V21	**V22**	**V23**	**V24**	**V25**
Vital signs/temperature				x	
Pregnancy test				(x)	

Blood draw for serology assays	x	x		x	
Blood draw for cellular assays	x	x		x	
Safety labs for bone marrow aspiration			(x)		
Bone marrow aspiration				x	
phone call (BM follow up) and survey					x

^^One week +/- one day from the actual date of Visit 24

Appendix B

EMORY UNIVERSITY CLINICAL QUALITY MANAGEMENT PLAN VERSION 8.0, 11-DEC 2020

1.0 SITE IDENTIFICATION

1.1 SITE IDENTIFICATION:

THE HOPE CLINIC OF THE EMORY VACCINE CENTER, 500 IRVIN COURT, SUITE 200, DECATUR, GA 30030

THE HOPE CLINIC OF THE EMORY VACCINE CENTER, 484 IRVIN COURT, SUITE 230, DECATUR, GA 30030

EMORY CHILDREN'S CENTER VACCINE RESEARCH CLINIC (ECC-VRC), 2015 UPPERGATE DR, ATLANTA, GA 30322

EMORY UNIVERSITY HOSPITAL, 1364 CLIFTON RD NE, ATLANTA, GA 30322

EMORY UNIVERSITY HOSPITAL-MIDTOWN, 550 PEACHTREE ST NE, ATLANTA, GA 30308 EMORY SAINT JOSEPH HOSPITAL, 5665 PEACHTREE DUNWOODY RD, ATLANTA, GA 30342 EMORY DECATUR HOSPITAL, 2701 N DECATUR RD, DECATUR, GA 30033
GRADY MEMORIAL HOSPITAL, 80 JESSE HILL JR. DRIVE SE, ATLANTA, GA 30303

THE ATLANTA VETERANS AFFAIRS (VA) MEDICAL CENTER, 1670 CLAIRMONT ROAD, DECATUR, GA 30033

1.2 WHEN VTEU/IDCRC STUDIES ARE CONDUCTED AT THE SITES LISTED ABOVE OUR CQMP PLAN WILL BE FOLLOWED.

2.0 SCOPE AND RESPONSIBILITY

THE QUALITY MANAGERS AT THE HOPE CLINIC AND EMORY CHILDREN'S CENTER VACCINE RESEARCH CLINIC (ECC-VRC) AT EMORY UNIVERSITY HAVE BEEN DESIGNATED BY THE PRINCIPAL INVESTIGATOR, NADINE ROUPHAEL, MD AND EVAN ANDERSON, MD TO DEVELOP, IMPLEMENT, AND OVERSEE ALL FUNCTIONS OF THIS QUALITY MANAGEMENT PLAN FOR FEDERALLY FUNDED AND HUMAN SUBJECTS RESEARCH/CLINICAL TRIALS. PER INTERNATIONAL COUNCIL FOR HARMONIZATION (ICH) GCP E6 (R2) THE INVESTIGATOR IS RESPONSIBLE FOR SUPERVISING ANY INDIVIDUAL OR PARTY TO WHOM THE INVESTIGATOR DELEGATES STUDY TASKS CONDUCTED AT THE TRIAL SITE.

NADINE ROUPHAEL, MD IS RESPONSIBLE FOR THE QUALITY MANAGEMENT PLAN AT THE HOPE CLINIC AND EVAN ANDERSON, MD, AT THE ECC-VRC.

THE QUALITY MANAGER ENSURES DELEGATED STAFF AND RESPECTIVE FUNCTIONS ARE DOCUMENTED ON THE STUDY PERSONNEL/SITE RESPONSIBILITY-SIGNATURE LOG OR EQUIVALENT DELEGATION OF RESPONSIBILITY LOG VIA

QUALITY ASSURANCE (QA) REVIEW OF EACH INSTITUTIONAL REVIEW BOARD (IRB) APPROVED STUDY PRIOR TO INITIATION OF ENROLLMENT AND IMMEDIATELY PRIOR TO STUDY TERMINATION.

3.0 CLINICAL QUALITY MANAGEMENT PROCESS DESCRIPTION

3.1 PER ICH E6 (R2), INVESTIGATOR SECTION 4.9 RECORDS AND REPORTS, THE INVESTIGATOR SHOULD MAINTAIN ADEQUATE AND ACCURATE SOURCE DOCUMENTS (SD) AND TRIAL RECORDS THAT INCLUDE ALL PERTINENT OBSERVATIONS ON EACH OF THE SITE'S TRIAL SUBJECTS. SOURCE DATA SHOULD FOLLOW A.L.C.O.A.C. PRINCIPLES (ATTRIBUTABLE, LEGIBLE, CONTEMPORANEOUS, ORIGINAL, ACCURATE, AND COMPLETE). CHANGES TO SOURCE DATA SHOULD BE TRACEABLE, SHOULD NOT OBSCURE THE ORIGINAL ENTRY AND SHOULD BE EXPLAINED, IF NECESSARY, (E.G, VIA AN AUDIT TRAIL). THESE GUIDELINES/PRINCIPLES WILL BE APPLIED TO ALL FEDERALLY FUNDED ACTIVITIES, AS WELL AS ALL HUMAN SUBJECT RESEARCH STUDIES AND CLINICAL TRIALS PREFORMED AT THE HOPE CLINIC AND THE ECC-VRC. ALL RECORDS WILL BE KEPT IN AUDIT READY PREPAREDNESS WITH EMPHASIS ON WRITTEN PROCESSES (STANDARD OPERATING PROCEDURES (SOPS), SOURCE DOCUMENTS, CORRECTIVE AND PREVENTIVE ACTION PLANS (CAPA) AND HOW THEY WERE CARRIED OUT AND/OR EVALUATED.

3.2 QUALITY CONTROL (QC) ACTIVITIES: QUALITY CONTROL IS DEFINED AS THE REAL TIME, "DAY-TO-DAY", OBSERVATION AND DOCUMENTATION OF THE SITES' WORK PROCESSES TO ENSURE THAT ACCEPTED PROCEDURES ARE FOLLOWED.

3.2.1 APPLICABLE SITE STANDARD OPERATING PROCEDURES WILL BE FOLLOWED SUCH AS:

- INFORMED CONSENT PROCESS

- REPORTING OF ABNORMAL LABORATORY RESULTS
- SOURCE DOCUMENTATION GUIDELINES
- DIRECT DATA ENTRY (DDE) GUIDELINES (SEE DIRECT DATA ENTRY (DDE) SOP)

3.2.2 ROLES/RESPONSIBILITIES: AT EACH CLINIC VISIT THE CLINICAL STAFF RECORD DATA ON APPROPRIATE SOURCE DOCUMENTS. THE QM MANAGER, OR DESIGNEE, IS RESPONSIBLE FOR CONDUCTING QUALITY CONTROL REVIEW OF CASE REPORT FORMS (CRFS) AND SDS FOR COMPLETENESS AND CORRECTNESS. A QM MANAGER, OR DESIGNEE, WILL NOT REVIEW HIS/HER OWN DOCUMENTATION.

3.2.2.1 QUALITY MANAGER, OR DESIGNEE, WILL REVIEW 100% OF INFORMED CONSENT DOCUMENTS (ICFS) AND CASE REPORT FORMS (CRFS) FOR ACCURACY, COMPLETENESS, AND TO ENSURE PROPER DATING AND SIGNING. THE A.L.C.O.A.C. PRINCIPLES FOR APPROPRIATE DOCUMENTATION WILL BE EMPLOYED IN OUR QC ACTIVITIES. CRFS WILL BE SUBMITTED TO THE SPONSOR WITHIN THE TIMEFRAME REQUESTED BY THE SPONSOR, 3 BUSINESS DAYS.

3.2.2.2 ERRORS WILL BE QUANTIFIED AND PRESENTED AS THE NUMBER OF ERRORS/100 SOURCE DOCUMENT PAGES REVIEWED. DIRECT DATA ENTRY ERRORS WILL BE QUANTIFIED BY DATA SYSTEM CHARACTERISTICS AND ESTABLISHED AT STUDY ONSET.

3.2.2.3 IDENTIFIED ERRORS WILL BE BROUGHT TO THE ATTENTION OF THE APPROPRIATE STAFF MEMBER FOR CORRECTION ON THE SOURCE AND/OR ELECTRONIC DATA CAPTURE (EDC) DOCUMENT WITHIN 3 BUSINESS DAYS OF THE ERROR(S) BEING IDENTIFIED.

3.2.2.4 THE QUALITY CONTROL REVIEW TOOL (APPENDIX C) WILL BE COMPLETED BY THE QM MANAGER OR DESIGNEE. THIS LOG IDENTIFIES AND TRACKS CATEGORIES OF ICF AND CRF ERRORS. THIS INFORMATION WILL BE AGGREGATED AND REPORTED TO THE SITE STAFF, USING THE MONTHLY QC ERROR REPORT (APPENDIX D) AT THE MONTHLY QM MEETING.

3.2.2.4.1.1 INFORMATION COLLECTED AND DOCUMENTED ON APPENDIX D INCLUDE:
3.2.2.4.1.1.1 REVIEWER INITIALS (PERFORMED BY QM MANAGER OR DESIGNEE.
3.2.2.4.1.1.2 REVIEWER DATE.
3.2.2.4.1.1.3 PARTICIPANT IDENTIFICATION NUMBERS (PID) REVIEWED.
3.2.2.4.1.1.4 SPECIFIC INDICATORS REVIEWED. 3.2.2.4.1.1.5 FINDINGS/RESULTS OF REVIEW.
3.2.2.4.1.1.6 DATE ERRORS/FINDINGS WERE CORRECTED.

3.2.2.5 CLINICAL QUERY REQUESTS WILL BE REVIEWED AND ANSWERED BY THE STUDY COORDINATOR, OR A DESIGNEE, OR REFERRED TO THE ATTENTION OF THE APPROPRIATE STAFF MEMBER FOR A RESPONSE. THE STUDY COORDINATOR, OR DESIGNEE, WILL PROVIDE THE RESPONSE TO THE SPONSOR WITHIN THE REQUIRED TIME-FRAME INDICATED BY THE

SPONSOR. THE STUDY COORDINATOR, OR DESIGNEE, WILL MAINTAIN COPIES OF QUERY RESPONSES IN THE STUDY FILES.

3.2.2.6 THE ABOVE TOOLS WILL BE USED TO IDENTIFY TRENDS AND/OR ISSUES OF CONCERN. THESE TRENDS WILL BE PRESENTED AND DISCUSSED WITH THE STAFF MEMBERS AT THE MONTHLY QM MEETING OR SOONER IF INDICATED.

3.2.2.7 CORRECTIVE ACTION WILL BE TAKEN AS NEEDED TO ADDRESS AREAS OF CONCERN. SEE SECTION 9.5 CORRECTIVE AND PREVENTIVE ACTIONS.

3.2.2.8 EVALUATION OF THE CAPA WILL TAKE PLACE AS PART OF THE ONGOING QM PROCESS. SEE SECTION 9.5 CORRECTIVE AND PREVENTIVE ACTIONS.

3.2.3 RECORD SELECTION: METHODS FOR RECORD SELECTION FOR REVIEW ARE AS FOLLOWS:

3.2.3.1 NEW PROTOCOLS: RECORDS (E.G., ICFS, CRFS – PAPER AND/OR ELECTRONIC, CLINICAL LABORATORY REPORTS, SPECIMEN LOGS, CLINIC NOTES, VOLUNTEER CHARTS, AND OTHER SOURCE DOCUMENTS) OF THE FIRST FIVE VOLUNTEERS ENROLLED IN EACH PROTOCOL WILL RECEIVE A 100% REVIEW. NEW PROTOCOLS WILL BE GIVEN PRIORITY OVER OPEN PROTOCOLS FOR REVIEW.

3.2.3.2 PROTOCOLS INVOLVING STUDY PRODUCT AND/OR A PROCEDURE: QUALITY MANAGER, OR DESIGNEE, WILL REVIEW, IN REAL-TIME, 100% OF INFORMED CONSENT DOCUMENTS (ICFS) AND CASE REPORT FORMS (CRFS) FOR ACCURACY, COMPLETENESS, AND TO ENSURE PROPER DATING AND SIGNING. THE A.L.C.O.A.C. PRINCIPLES FOR APPROPRIATE DOCUMENTATION WILL BE EMPLOYED IN OUR QC ACTIVITIES.

3.2.3.3 NEW CLINICAL RESEARCH STAFF: 100%, BUT NOT LESS THAN FIVE, OF ALL VISITS COMPLETED BY A NEW MEMBER, WILL RECEIVE A PROMPT, “REAL-TIME”, REVIEW UNTIL COMPETENCY IS DETERMINED.

3.2.3.4 HIGH RISK EMERGENT PROTOCOLS: PROTOCOLS THAT ARE CONSIDERED TO BE HIGH RISK OR CONDUCTED UNDER EMERGENT CONDITIONS WILL FOLLOW THE SAME PROCEDURE OF “REAL-TIME” REVIEW AND WILL BE REVIEWED WITHIN ONE (1 BUSINESS DAY OF THE VISIT. 100% OF ALL ICFS AND CRFS WILL BE REVIEWED,

3.2.3.5 HIGH ACCRUING PROTOCOLS: BASED ON THE RECOMMENDATIONS OF THE PI AND/OR STUDY COORDINATOR, HIGH ENROLLING PROTOCOLS MAY BE TARGETED FOR AN EARLY “REAL-TIME” OR MORE THOROUGH REVIEW. 100% OF ALL ICFS AND CRFS WILL BE REVIEWED.

3.2.3.6 SCREEN FAILURE/CONSENT WITHDRAWAL: ALL SCREEN FAILURES/CONSENT WITHDRAWAL RECORDS WILL BE REVIEWED, IN “REAL-TIME”, TO ASSURE APPROPRIATE

INFORMED CONSENT PROCESS AND DOCUMENTATION OF THE REASON FOR SCREEN FAILURE OR CONSENT WITHDRAWAL.

3.2.4 QUALITY CONTROL TOOLS (TOOLS, CHECKLISTS AND REMINDERS) THE TOOLS FOR QC ARE ATTACHED.
3.2.4.1 INTERNAL (SITE-SPECIFIC) SOURCES:
3.2.4.1.1 THE EMORY UNIVERSITY QUALITY CONTROL REVIEW TOOL (APPENDIX C). INFORMATION REGARDING STUDY VISIT SCHEDULE/PROCEDURES, ELIGIBILITY CHECKLIST, AND INFORMED CONSENT ARE REVIEWED USING THIS TOOL.
3.2.4.1.2 THE EMORY UNIVERSITY MONTHLY QC ERROR REPORT (APPENDIX D). INTERNAL QA/QC FINDINGS, SUMMARY REPORTS ARE REVIEWED AND REPORTED USING THIS TOOL.
3.2.4.1.3 THE EMORY UNIVERSITY ANNUAL QUALITY MANAGEMENT REPORT (APPENDIX F)
3.2.4.1.4 THE EMORY VTEU SUMMARY REPORT LOG (APPENDIX G)

3.2.4.2 EXTERNAL SOURCES:
3.2.4.2.1 DATA ENTRY, QUERY/ERROR, OR TRANSMISSION REPORTS FROM THE DATA MANAGEMENT CENTER
3.2.4.2.2 CLINICAL SITE MONITORING REPORTS

3.3 QUALITY ASSURANCE (QA) ACTIVITIES:

QA IS DEFINED AS THE PERIODIC, SYSTEMATIC, OBJECTIVE, AND COMPREHENSIVE EXAMINATION OF THE TOTAL WORK EFFORT TO DETERMINE THE LEVEL OF COMPLIANCE WITH GOOD CLINICAL PRACTICE (GCP) STANDARDS. QA ACTIVITIES SHOULD ALSO BE PERFORMED. THE HOPE CLINIC AND ECC-VRC WILL PARTICIPATE IN QUALITY ASSURANCE ACTIVITIES IDENTIFIED BY THE INFECTIOUS DISEASES CLINICAL RESEARCH CONSORTIUM (IDCRC).

AT EACH CLINIC VISIT THE CLINICAL STAFF RECORD DATA ON APPROPRIATE SOURCE DOCUMENTS. THE QUALITY MANAGER, OR DESIGNEE, IS RESPONSIBLE FOR CONDUCTING QA REVIEWS OF THE SOURCE DOCUMENTS TO ENSURE THE ADHERENCE TO POLICIES AND PROCEDURES, THE STUDY PROTOCOL, AND THE ACCURACY OF RESEARCH RECORDS. A QM MANAGER, OR DESIGNEE, WILL NOT REVIEW HIS/HER OWN DOCUMENTATION.

THE FOLLOWING ONGOING ACTIVITIES WILL BE CONDUCTED AT THE SITE AS PART OF THE QA PROCESS:

3.3.1 ROLES/RESPONSIBILITIES: AT EACH CLINIC VISIT THE CLINICAL STAFF RECORD DATA ON APPROPRIATE SOURCE DOCUMENTS. THE QM MANAGER, OR DESIGNEE, IS RESPONSIBLE FOR CONDUCTING QUALITY ASSURANCE REVIEWS OF THE SOURCE DOCUMENTS FOR THE FIRST FIVE PARTICIPANTS ENROLLED IN A STUDY TO ENSURE THE ADHERENCE TO POLICIES AND PROCEDURES, THE STUDY PROTOCOL, AND THE ACCURACY OF THE RESEARCH RECORDS. THE QM MANAGER, OR DESIGNEE, WILL ALSO PERFORM REVIEW(S), REAL-TIME, PERIODIC, , AND ON A RANDOM BASIS, DURING THE COURSE OF THE STUDY. THE QM MANAGER, OR DESIGNEE,

IS RESPONSIBLE FOR CONDUCTING QUALITY ASSURANCE REVIEW OF CRFS AND SDS. A QM MANAGER, OR DESIGNEE, WILL NOT REVIEW HIS/HER OWN DOCUMENTATION.

3.3.2 RECORD SELECTION: SD DATA ENTRIES WILL BE REVIEWED BY THE QM MANAGER, OR DESIGNEE, USING QA REVIEW TOOL (APPENDIX A). THE QA REVIEW TOOL INCLUDES THE KEY INDICATORS FOR QA AS LISTED IN SECTION 4.0.

3.3.2.1 METHODS OF RECORD SELECTION FOR QA REVIEW ARE AS FOLLOWS:
3.3.2.1.1 SAMPLE SIZE (MINIMUM PERCENTAGE) MONTHLY QA REVIEWS WILL CONSIST OF A RANDOM SELECTION OF 10%, AT A MINIMUM, OF CLINIC RECORDS (E.G. CASE REPORT FORMS – PAPER AND/OR ELECTRONIC, CLINICAL LABORATORY REPORTS, SPECIMEN LOGS, CLINIC NOTES, VOLUNTEER CHARTS, AND OTHER SOURCE DOCUMENTS), ALTERNATING EXISTING OPEN PROTOCOLS TO ASSURE REVIEW OF ALL ACTIVE PROTOCOLS OVER THE COURSE OF THE CALENDAR YEAR. THIS PERCENTAGE MAY INCREASE BASED ON FINDINGS AND/OR PROBLEMS WITH PROTOCOL(S).
3.3.2.1.2 HIGH RISK PROTOCOLS – PROTOCOLS THAT ARE CONSIDERED TO BE HIGH RISK WILL BE TARGETED FOR AN EARLY AND MORE THOROUGH REVIEW THAN THE SAMPLE SIZE DESCRIBED ABOVE.
3.3.2.1.3 HIGHER ACCRUING PROTOCOLS – BASED ON THE RECOMMENDATIONS OF THE PI AND/OR STUDY COORDINATOR, HIGH ENROLLING PROTOCOLS MAY BE TARGETED FOR AN EARLY OR MORE THOROUGH REVIEW.

3.3.2.1.4 INITIAL ENROLLMENT IN NEW PROTOCOLS – THE FIRST FIVE (5) ENROLLED PARTICIPANT RECORDS FOR EACH NEW PROTOCOL WILL RECEIVE A 100% QA AUDIT.
3.3.2.1.5 NEW CLINICAL RESEARCH STAFF – 100%, BUT NOT LESS THAN 5, OF ALL VISITS COMPLETED BY A NEW STAFF MEMBER WILL RECEIVE A PROMPT QA AUDIT UNTIL COMPETENCY IS DETERMINED.
3.3.2.1.6 SCREEN FAILURE/CONSENT WITHDRAWAL – ALL SCREEN FAILURES/CONSENT WITHDRAWAL RECORDS WILL BE REVIEWED TO ASSURE APPROPRIATE INFORMED CONSENT PROCESS AND DOCUMENTATION OF THE REASON FOR SCREEN FAILURE OR CONSENT WITHDRAWAL.

3.3.3 QA TOOLS

3.3.3.1 INTERNAL (SITE) SOURCES:
3.3.3.1.1 DMID CLINICAL QUALITY MANAGEMENT (CQMP): EMORY UNIVERSITY QUALITY ASSURANCE (QA) REVIEW TOOL (APPENDIX C). CHART REVIEW CHECKLISTS/WORKSHEETS ARE REVIEWED USING THIS TOOL.

3.3.3.1.1.1 INFORMATION COLLECTED AND DOCUMENTED ON APPENDIX D INCLUDE:
3.3.3.1.1.1.1 REVIEWER INITIALS
3.3.3.1.1.1.2 REVIEWER'S ROLE
3.3.3.1.1.1.3 REVIEWER DATE

3.3.3.1.1.1.4 PARTICIPANT IDENTIFICATION NUMBERS (PID) REVIEWED
3.3.3.1.1.1.5 SPECIFIC INDICATORS REVIEWED 3.3.3.1.1.1.6 FINDINGS/RESULTS OF REVIEW
3.3.3.1.1.1.7 PROTOCOL REGULATORY DOCUMENTS REVIEWED 3.3.3.1.1.1.8 TIME PERIOD COVERED BY THE REVIEW.

3.3.3.1.2 THE EMORY UNIVERSITY MONTHLY QC ERROR REPORT (APPENDIX D). INTERNAL QA/QC FINDINGS, SUMMARY REPORTS ARE REVIEWED AND REPORTED USING THIS TOOL.
3.3.3.1.3 THE EMORY UNIVERSITY REGULATORY FILE REVIEW TOOL (APPENDIX E) REVIEWED AND REPORTED USING THIS TOOL.
3.3.3.1.4 THE EMORY UNIVERSITY ANNUAL QUALITY MANAGEMENT REPORT (APPENDIX F)
3.3.3.1.5 THE EMORY UNIVERSITY VTEU SUMMARY REPORT LOG (APPENDIX G)

3.3.3.2 EXTERNAL SOURCES:
3.3.3.2.1 DATA ENTRY, QUERY/ERROR, OR TRANSMISSION REPORTS FROM THE DATA MANAGEMENT CENTER
3.3.3.2.2 CLINICAL SITE MONITORING REPORTS

THE ABOVE TOOLS WILL BE USED TO IDENTIFY TRENDS AND/OR AREAS OF CONCERN. THESE TRENDS WILL BE PRESENTED AND DISCUSSED WITH THE STAFF MEMBERS AT THE MONTHLY QM MEETINGS OR SOONER AS INDICATED. QUALITY SUMMARY REPORTS ARE REVIEWED BY THE SITE PI ON A MONTHLY BASIS. THE SIGNED REPORTS ARE KEPT IN A BINDER AND MADE AVAILABLE TO THE SITE MONITOR(S) UPON REQUEST.

3.3.4 THE MONTHLY QUALITY ASSURANCE REPORT (APPENDIX B) PROVIDES SITE-SPECIFIC SUMMARIES OF QM ACTIVITIES. THE RESULTS OF THESE ACTIVITIES ARE SHARED WITH THE SITE STAFF AT THE MONTHLY QM MEETING.

3.3.5 SITE MONITORING REPORTS, AS RECEIVED FROM EXTERNAL MONITORING GROUPS WILL ALSO BE UTILIZED AS A QA TOOL. THIS WILL ALLOW FOR THE REVIEW OF ANY TRENDS OR PROBLEMS IDENTIFIED BY THE EXTERNAL MONITOR. THESE REPORTS WILL BE GIVEN TO THE SITE STAFF UPON RECEIPT AND REVIEWED AND DISCUSSED AT THE MONTHLY QM MEETINGS AS INDICATED.

3.3.6 CORRECTIVE ACTION WILL BE TAKEN AS NEEDED TO ADDRESS AREAS OF CONCERN. SEE SECTION 9.5 CORRECTIVE AND PREVENTIVE ACTIONS

3.3.7 EVALUATION OF THE CORRECTIVE ACTION WILL TAKE PLACE AS PART OF THE ONGOING QA PROCESS. SEE SECTION 9.5 CORRECTIVE AND PREVENTIVE ACTIONS.

3.4 QUALITY ASSURANCE REPORTING REQUIREMENTS
3.4.1 QA FINDINGS WILL BE REPORTED USING THE EMORY UNIVERSITY QUALITY ASSURANCE (QA) REVIEW TOOL (APPENDIX A).

3.4.2 THE QA SUMMARY REPORT WILL INCLUDE IDENTIFICATION OF PROBLEMS, IDENTIFICATION OF POSSIBLE CAUSES, AND ANY CORRECTIVE AND PREVENTATIVE ACTIONS TAKEN.
3.4.3 IF AN UNREPORTED SAE IS IDENTIFIED DURING THE QM ACTIVITIES, THE EVENT WILL BE REPORTED PER PROTOCOL, DMID POLICY AND INSTITUTIONAL REQUIREMENTS

3.5 PROTOCOL-SPECIFIC CQMP:
3.5.1 A PROTOCOL-SPECIFIC CQMP WILL BE DEVELOPED FOR APPLICABLE PROTOCOLS PER PI DIRECTION.
3.5.2 A PROTOCOL-SPECIFIC CQMP MAY BE DEVELOPED AND IMPLEMENTED FOR PROTOCOLS BEING CONDUCTED AT MULTIPLE SITES WITHIN THE EMORY NETWORK, OR FOR EMORY SUBCONTRACTOR SITES INCLUDING DOMESTIC AND INTERNATIONAL LOCATIONS.
3.5.3 THE PROTOCOL-SPECIFIC CQMP TEMPLATE, AVAILABLE ON THE DMID CROMS WEBSITE, WILL BE UTILIZED AND WILL BE MODIFIED TO DEFINE AND PROVIDE DATA FOR PROTOCOL- DRIVEN PARAMETERS FOR QC AND QA RECORDING AND REPORTING.
3.5.4 QUALITY MANAGERS AT THE HOPE CLINIC AND/OR ECC WILL OVERSEE IMPLEMENTATION THE PROTOCOL-SPECIFIC CQMP AND WILL ENSURE THAT SITE STAFF ARE TRAINED IN PROPER CQMP USE AND PROCESS.

3.6 RETENTION OF QUALITY MANAGEMENT (QM) DOCUMENTS

3.6.1 THE CQMP WILL BE SIGNED AND DATED BY THE PI AND KEPT ON FILE.

3.6.2 COMPLETED QA SUMMARY REPORTS, CHART REVIEW TOOLS AND REGULATORY FILE REVIEW TOOLS WILL BE KEPT ON FILE AND ACCESSIBLE UPON DMID REQUEST.

3.7 OVERSIGHT OF SUBCONTRACTOR SITE(S), IF APPLICABLE:
3.7.1 SUBCONTRACTOR SITES WILL BE REQUIRED TO DEVELOP AND IMPLEMENT AN EMORY APPROVED CQMP UTILIZING A CONSISTENT CQMP FORMAT DEFINED BY EMORY.
3.7.2 THE PI, WITH THE ASSISTANCE OF THE QUALITY MANAGER, WILL WORK WITH THE SUBCONTRACTOR SITE TO DRAFT A PROTOCOL-SPECIFIC CQMP.
3.7.3 THE CQMP WILL BE COMPLETED BY THE EMORY SUBCONTRACTOR/PERFORMANCE SITES CONDUCTING DMID-FUNDED PROTOCOLS, AND WILL BE CONSISTENT WITH A PARTICULAR PROTOCOL.
3.7.4 IF QC AND QA TOOLS (AS DESCRIBED IN SECTIONS 3.2.4 AND 3.3.3) ARE USED BY SUBCONTRACTOR/PERFORMANCE SITES FOR DOCUMENTING QUALITY REVIEWS, PROCESSES AND INSTRUCTIONS WILL ENSURE CONSISTENT APPLICATION/IMPLEMENTATION ACROSS SITES.
3.7.5 IN THE CASE OF MULTI-SITE PROTOCOLS, A SINGLE CQMP MIGHT BE GENERATED FOR CONSISTENCY, AS DIRECTED BY THE DMID CPM.
3.7.6 THE CQMP WILL BE DEVELOPED, FINALIZED AND APPROVED BY EMORY, AND DMID AS APPLICABLE, PRIOR TO INITIATION OF THE PROTOCOL.
3.7.7 MONTHLY SUBCONTRACTOR REPORTS WILL BE SUBMITTED TO THE PRIME CONTRACT SITE BY THE SPECIFIED DUE DATE. REPORTS WILL INCLUDE: DOCUMENTATION OF

ONGOING CQMP ACTIVITIES, DESCRIPTION OF PROBLEMS IDENTIFIED, CORRECTIVE ACTION PLANS, IF REQUIRED, AND OTHER SPONSOR REQUIREMENTS/CONTRACTUAL OBLIGATIONS.

4.0 KEY QUALITY INDICATORS

THE KEY INDICATORS THAT WILL BE AUDITED IN EACH VOLUNTEER RECORD SELECTED FOR INTERNAL QA REVIEW ARE:

4.1 INFORMED CONSENT FORM AND PROCESS

4.2 ASSESSMENT OF UNDERSTANDING AS APPLICABLE

4.3 ELIGIBILITY CRITERIA AND PROCESS

4.4 STUDY PRODUCT MANAGEMENT: RECEIPT, STORAGE, PREPARATION, TRANSPORT, ADMINISTRATION, AND ACCOUNTABILITY (IF APPLICABLE) – PHARMACY QM HANDLED BY EU PHARMACY AND RECORDS ARE ON FILE.

4.4.1 REVIEW AND COMPARISON OF THE STUDY PRODUCT ACCOUNTABILITY LOGS, SHIPPING RECORDS, AND THE STUDY PRODUCT INVENTORY

4.4.2 MASKING PROCEDURES (MAINTENANCE OF STUDY BLIND, STUDY PERSONNEL RESTRICTIONS)

4.4.3 RANDOMIZATION CODE LIST AND DECODING PROCEDURES

4.4.4 STUDY PRODUCT STORAGE, HANDLING, AND LABELING PROCEDURES

4.4.5 VACCINE OR OTHER STUDY PRODUCT PREPARATION PROCEDURES

4.4.6 STUDY PRODUCT ADMINISTRATION PROCESSES

4.5 ADVERSE EVENTS (AE), SERIOUS ADVERSE EVENTS (SAE) IDENTIFICATION AND REPORTING AS APPLICABLE

4.6 PROTOCOL VISITS (EVALUATE FOR MISSED VISITS, OUT OF WINDOW VISITS, LOST TO FOLLOW-UP, ETC.)

4.7 PROTOCOL-SPECIFIC PROCEDURES (ALL INCLUSIVE)

4.8 INTERVENTION/STUDY DISCONTINUATION

4.9 REACTOGENICITY (IF APPLICABLE)

4.10 SPECIMENS -

4.10.1 PROCESSING SPECIMENS AS PER PROTOCOL AND/OR MANUAL OF OPERATIONAL PROCEDURES – QM HANDLED BY LABORATORY MANAGER

4.10.2 STORAGE OF SPECIMENS (REQUIRED CONDITIONS, LOCATION, LENGTH OF STORAGE) – QM HANDLED BY LABORATORY MANAGER.

4.10.3 DOCUMENTATION (SHIPPING LOGS, TEMPERATURE DEVIATION REPORTING, ACCREDITATIONS, EQUIPMENT CALIBRATION, COMMUNICATIONS TO STUDY TEAM/PI) – QM HANDLED BY LABORATORY MANAGER.

4.11 CONCOMITANT/PROHIBITED MEDICATIONS

4.12 PROTOCOL DEFINE ENDPOINT IDENTIFICATION AND REPORTABLE AS APPLICABLE

4.13 SOURCE DOCUMENTS, SIGNATURES, INITIALS, DATE(S) (SEE APPENDIX E: THE EMORY UNIVERSITY REGULATORY FILE REVIEW TOOL)

4.14 INVESTIGATOR FILE REVIEW DEFICIENCIES (SEE APPENDIX E: THE EMORY UNIVERSITY REGULATORY FILE REVIEW TOOL)

4.15 ADDITIONAL PROTOCOL-SPECIFIC INDICATORS, AS APPLICABLE.

4.16 LABORATORY AND PHARMACY FOLLOW THEIR OWN QM PROCEDURES. THESE PROCEDURES HAVE BEEN REVIEWED INTERNALLY AND MONITORED DURING SITE VISITS AS WELL AS FEDERAL AUDITS WITH NO CONCERNS/ISSUES.

5.0 REGULATORY FILE REVIEW

THE REGULATORY FILE REVIEW WILL ENSURE DOCUMENTS AS LISTED IN THE INTERNATIONAL CONFERENCE ON HARMONIZATION (ICH) GUIDELINES FOR GOOD CLINICAL PRACTICE (GCP); E6 (R2), SECTION 8, ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL ARE PRESENT. THE RESULTS OF THE REGULATORY FILE REVIEW WILL BE DISCUSSED AT THE MONTHLY QM MEETING OR SOONER AS INDICATED.

5.1 FREQUENCY OF REVIEW: THE REGULATORY FILE WILL BE REVIEWED AT THE BEGINNING OF A STUDY (PRIOR TO THE FIRST MONITORING VISIT) AND IMMEDIATELY PRIOR TO STUDY TERMINATION (PRIOR TO THE CLOSE OUT VISIT).

5.2 ONGOING REGULATORY REVIEW IS CONDUCTED DURING WEEKLY VTEU OPERATIONS MEETINGS WHERE ALL PENDING/APPROVED AMENDMENTS, CONTINUING REVIEWS AND REPORTABLE EVENTS ARE DISCUSSED AND STATUS UPDATES ARE GIVEN. REGULATORY CORE MEETINGS ARE ALSO HELD ON A WEEKLY BASIS AND PENDING AMENDMENTS, CRS AND REPORTABLE EVENTS ARE DISCUSSED AS WELL AS ANY PENDING ISSUES OR IRB QUESTIONS, ETC. WHEN IRB APPROVAL IS GIVEN, THE REGULATORY COORDINATOR SENDS AN EMAIL OUT TO ALL STUDY TEAM MEMBERS CONFIRMING THAT ALL REGULATORY DOCUMENTS HAVE BEEN FILED APPROPRIATELY, INFORMING THEM OF CHANGES TO THE STUDY AND WHETHER OR NOT PARTICIPANTS NEED RE-CONSENT. THE REGULATORY FILE MAY ALSO BE REVIEWED DURING THE COURSE OF THE STUDY OR WHEN A PROTOCOL IS REVISED, PER PI DISCRETION.

5.3 ESSENTIAL REGULATORY DOCUMENTS WILL BE UPLOADED TO THE SITE ESSENTIAL REGULATORY DOCUMENTS (SERD) PORTAL WITHIN THE NIAID CLINICAL RESEARCH MANAGEMENT SYSTEM (CRMS) AS REQUESTED, AS WELL AS THE REGULATORY FILE LOCATED ON THE EMORY UNIVERSITY SHARE DRIVE.

5.4 THE EMORY UNIVERSITY REGULATORY FILE REVIEW TOOL (APPENDIX E).

5.5 IDENTIFIED ERRORS WILL BE BROUGHT TO THE ATTENTION OF THE APPROPRIATE STAFF MEMBER FOR CORRECTION WITHIN 3 BUSINESS DAYS OF THE ERROR(S) BEING IDENTIFIED.

6.0 TOOLS AND CHECKLISTS

6.1 INTERNAL (SITE) SOURCES:
6.1.1 THE EMORY UNIVERSITY QUALITY ASSURANCE (QA) REVIEW TOOL (APPENDIX A)
6.1.2 THE EMORY UNIVERSITY QUALITY ASSURANCE (QA) SUMMARY REPORT (APPENDIX B)
6.1.3 THE EMORY UNIVERSITY QUALITY CONTROL REVIEW TOOL (APPENDIX C)
6.1.4 THE EMORY UNIVERSITY MONTHLY QUALITY CONTROL (QC) ERROR REPORT (APPENDIX D)
6.1.5 THE EMORY UNIVERSITY REGULATORY FILE REVIEW TOOL (APPENDIX E)
6.1.6 THE EMORY UNIVERSITY ANNUAL QUALITY MANAGEMENT REPORT (APPENDIX F)
6.1.7 THE EMORY UNIVERSITY STANDARD OPERATING PROCEDURES (SOP)
6.2 EXTERNAL SOURCES:
6.2.1 DATA ENTRY, QUERY/ERROR, OR TRANSMISSION REPORTS FROM THE DATA MANAGEMENT CENTER
6.2.2 CLINICAL SITE MONITORING REPORTS

7.0 STAFF TRAINING / QUALIFICATIONS

EMORY UNIVERSITY HAS AN ON-BOARDING AND GENERAL TRAINING PROCEDURE THAT HAS BEEN OUTLINED IN THE SOP . THE REGULATORY COORDINATOR MAINTAINS DOCUMENTATION OF ALL STAFF TRAINING AND ESSENTIAL DOCUMENTS. DOCUMENTS ARE REVIEWED BY THE QM MANAGER, OR DESIGNEE, AS PART OF THE REGULATORY DEPARTMENT AUDITS TO ENSURE STAFF IS QUALIFIED AND HAVE DEMONSTRATED COMPETENCY PER EMORY AND SPONSOR REQUIREMENTS.

7.1 INSTITUTION-SPECIFIC TRAINING:
7.1.1 HUMAN SUBJECTS PROTECTION (CITI)- EVERY THREE (3) YEARS
7.1.2 GOOD CLINICAL PRACTICE (CITI) – EVERY THREE (3) YEARS
7.1.3 KEY CONCEPTS FOR INVESTIGATORS COURSE (INVESTIGATORS ONLY)
7.1.4 INTRODUCTION TO CLINICAL RESEARCH AT EMORY (COORDINATORS ONLY) – REQUIRED OF STAFF WITH LESS THAN 5 YEARS RESEARCH EXPERIENCE
7.1.5 HIPAA TRAINING – EVERY THREE (3) YEARS
7.1.6 BLOOD BORNE PATHOGENS TRAINING – ANNUALLY

7.1.7 BIOSAFETY TRAINING – EVERY THREE (3) YEARS
7.1.8 CPR CERTIFICATION (CLINICAL STAFF) – EVERY TWO (2) YEARS
7.1.9 LABORATORY SAFETY TRAINING – ANNUALLY
7. 2.0 A.L.C.O.A.C PRINCIPLES (WHEN AND HOW APPLIED TO SOURCE DOCUMENT(S)) OVERVIEW – BI- ANNUALLY DURING NETWORK OPERATIONS MEETINGS.

7.2 PROTOCOL-SPECIFIC TRAINING:
7.2.1 AS DESIGNATED BY THE SPONSOR

7.3 DMID-SPECIFIC TRAINING:
7.3.1 HUMAN SUBJECTS PROTECTION – EVERY THREE (3) YEARS
7.3.2 GOOD CLINICAL PRACTICE – EVERY THREE (3) YEARS

7.3.3 DMID REGULATORY FILE DOCUMENT GUIDELINES - EVERY THREE (3) YEARS
7.3.4 DMID SOURCE DOCUMENTATION STANDARDS - EVERY THREE (3) YEARS
7.3.5 INVESTIGATOR RESPONSIBILITIES - EVERY THREE (3) YEARS
7.3.6 DMID STUDY PRODUCT MANAGEMENT - EVERY THREE (3) YEARS
7.3.7 NIH COMPUTER SECURITY AWARENESS - ANNUALLY

8.0 IMPLEMENTATION AND CONDUCT

8.1 PROTOCOL IMPLEMENTATION

THE EMORY VTEU AIMS AT IMPLEMENTING THE PROTOCOL IN A TIMELY MANNER WITH TYPICALLY 90 DAYS BETWEEN PROTOCOL DISTRIBUTION TO SITE-SPECIFIC PROTOCOL ACTIVATION.

8.2 ACTIVATION TO FIRST ENROLLMENT

THE EMORY VTEU AIMS AT ENROLLING SUBJECTS IN A TIMELY MANNER. TYPICALLY, THE FIRST SUBJECT WILL BE ENROLLED IN EARLY PHASE TRIALS WITHIN 2 WEEKS OF SITE PROTOCOL ACTIVATION AND PRODUCT AVAILABILITY AT THE SITE.

8.3 ENROLLMENT

THE EMORY VTEU AIMS AT REACHING ENROLLMENT TARGETS WITH >90% ENROLLED WITHIN THE ASSIGNED PERIOD IN EARLY PHASE TRIALS.

8.4 VISIT COMPLETION

THE EMORY VTEU AIMS AT ACHIEVING HIGH RETENTION RATES WITH >90% VISITS COMPLETED WITHIN THE ASSIGNED PERIOD IN EARLY PHASE TRIALS.

9.0 CLINICAL QUALITY MANAGEMENT REPORTING

9.1 THE HOPE CLINIC AND ECC-VRC, WILL MAKE AVAILABLE STUDY-SPECIFIC QUALITY REPORTS TO THE IDCRC UPON REQUEST.

9.2 TOOLS/FORMS USED TO DOCUMENT / SUMMARIZE QUALITY REVIEWS: THE EMORY UNIVERSITY QUALITY CONTROL REVIEW TOOL (APPENDIX C) WILL BE COMPLETED BY THE QM MANAGER OR DESIGNEE. THIS LOG IDENTIFIES AND TRACKS CATEGORIES OF CASE REPORT FORM (CRF) ERRORS.

9.3 IDENTIFICATION OF PROBLEM AREAS: INFORMATION GATHERED VIA APPENDIX C WILL BE AGGREGATED AND REPORTED TO THE SITE STAFF, USING THE MONTHLY QC ERROR REPORT (APPENDIX D) AT THE MONTHLY QM MEETING. THIS TOOL WILL ALSO BE USED TO IDENTIFY TRENDS AS WELL.

9.4 TREND ANALYSIS: CLINICAL QUERY REQUESTS WILL BE REVIEWED AND ANSWERED BY THE STUDY COORDINATOR, OR A DESIGNEE, OR REFERRED TO THE ATTENTION OF THE APPROPRIATE STAFF MEMBER FOR A RESPONSE. THE STUDY COORDINATOR, OR DESIGNEE, WILL PROVIDE A RESPONSE TO THE SPONSOR WITHIN THE REQUIRED TIMEFRAME INDICATED BY THE SPONSOR. THE STUDY COORDINATOR, OR DESIGNEE, WILL MAINTAIN COPIES OF QUERY RESPONSES IN THE STUDY FILES.

9.5 CORRECTIVE AND PREVENTIVE ACTION PLAN(S): A ROOT CAUSE ANALYSIS WILL BE COMPLETED BY THE PI/STUDY STAFF ALONG WITH INPUT FROM THE QM MANAGER. A CORRECTIVE AND PREVENTIVE ACTION (CAPA) PLAN WILL BE DEVELOPED TO MITIGATE THE ISSUE AND PREVENT FUTURE OCCURRENCES. THE ACTION PLAN WILL BE DETERMINED, IMPLEMENTED AND MONITORED BY THE PI FOR EFFECTIVENESS AND PROBLEM/ISSUE RESOLUTION. THESE ACTIONS MAY INCLUDE, BUT ARE NOT LIMITED TO, CHANGING A PROCESS OR FORM, TRAINING, OR REASSIGNING A TASK. ANY ADVERSE TREND WILL BE RE-EVALUATED TO ASSESS THE EFFECTIVENESS OF THE CORRECTIVE ACTION. TIMELINES FOR IMPLEMENTATION AND RE-EVALUATION WILL BE SET BASED ON THE TYPE/ACUITY OF PROBLEM. THE PLAN AND RESULTS OF RE-EVALUATION WILL ALSO BE COMMUNICATED TO THE STUDY STAFF AT THE MONTHLY QM MEETING AND DOCUMENTED IN THE MONTHLY QM MEETING MINUTES. THE HOPE CLINIC AND ECC-VRC WILL RESPOND TO FEEDBACK FROM THE IDCRC ABOUT QUALITY ISSUES REPORTED TO THE SITE (E.G. THROUGH CROMS MONITORING OR FROM OTHER OVERSIGHT ACTIVITIES). SUCH RESPONSES MAY INCLUDE THE NEED TO PRODUCE FORMAL CAPAS.

9.6 REVISION TO THE CQMP: REVIEW AND/OR REVISION TO THE CQMP WILL BE PERFORMED BY THE VTEU CONTACT PI, VTEU PROJECT MANAGER AND QM STAFF ON AN ANNUAL BASIS OR SOONER IF INDICATED.

10.0 SITE EVALUATION OF THE CLINICAL QUALITY MANAGEMENT PLAN

10.1 CQMP REVIEW: THE EMORY UNIVERSITY QUALITY MANAGEMENT PLAN IS REVIEWED ANNUALLY. THE VTEU CONTACT PI, VTEU PROJECT MANAGER, AND THE QUALITY MANAGER, WITH INPUT FROM THE CLINICAL STAFF, WILL DETERMINE IF ANY REVISIONS ARE TO BE MADE TO THE QM PLAN. IF REVISIONS ARE MADE, ALL STAFF WILL BE TRAINED IN THE NEW PROCEDURE AND SUCH TRAINING WILL BE DOCUMENTED IN THE QM MEETING MINUTES.

10.2 ADMINISTRATIVE CHANGES TO THE CQMP, WHICH DO NOT IMPACT THE EFFECTIVENESS OF THE CQMP, WILL NOT REQUIRE A RE-REVIEW BY THE DMID-CROMS REVIEW TEAM. HOWEVER, THE SITE WILL PROVIDE REVISED DOCUMENTS TO THE DMID-CROMS CQMP REVIEW TEAM.

10.3. THE EMORY VTEU SUMMARY REPORT LOG (APPENDIX G) WILL BE KEPT IN A BINDER AND MADE AVAILABLE TO THE SITE MONITOR(S)