GARDASIL 9: 3-Dose vs. 2-Dose with Delayed 3rd-Dose

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CPRIT Funding ID # RP190022

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SIGNATURE PAGE

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

Site Investigator:*

Signed: _____ Date: _____

Name, Title

** The protocol should be signed by the local investigator who is responsible for the study implementation at his/her specific site; i.e., if Investigational New Drug study, the individual who signs the Form FDA 1572.*

1.0 Background

The human papillomavirus (HPV) causes most cases of cervical, anal, vaginal, oropharyngeal, and penile cancers, and many vulvar cancers.[1] Overall, 40% of women and 45% of men in the US have a genital HPV infection at any given time and more than 38,000 people in the US are diagnosed with an HPV-related cancer each year.[2,3] Effective vaccines to prevent infection are available and widespread uptake could have dramatic effects. A systematic review determined that if 80% of girls and boys in high-income countries such as the US were vaccinated, then transmission of oncogenic HPV types could actually be eliminated.[4] To achieve this, the Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination against HPV of all adolescents at 11–12 years of age.[5]

However, only 34% of 13–17 year-old males and females in the US completed all required doses by 2016.[6] For those not vaccinated at a younger age, catch-up vaccination can still occur through age 26.[5] Few unvaccinated individuals over 17 years of age, however, seek out and obtain all required doses of the HPV vaccine. This low completion rate among older adolescents and young adults is concerning as they could derive substantial benefit from the vaccine even if they have already initiated sexual activity. This is a critical group to immunize as increasing vaccination rates among older adolescents and young adults will decrease the amount of time required to achieve herd immunity in the US.[7]

One possible reason for the low completion rate among older adolescents and young adults is that finishing the series requires an additional dose if the first dose happens after age 14. When the HPV vaccine was first introduced 12 years ago, 3 doses were recommended for everyone. After a study demonstrated that a 2-dose schedule of Gardasil 9 elicited a sufficient antibody response in 9–14 year olds, the recommendation was changed to only 2 doses for adolescents who began before 15 years old.[5,8,9] However, 3 doses are still recommended for older patients as immunogenicity data are not available for a 2-dose schedule in this population.[5]

To explore the immunogenicity of a 2-dose schedule in 15–26 year olds, the PI has already requested and obtained an exemption from the Food and Drug Administration's Investigational New Drug requirements. On May 9, 2017 she was informed she could conduct the study. She has arranged for a laboratory at the Centers for Disease Control and Prevention (CDC) to perform all assays (see letter from CDC.) Third, she has obtained permission from the president of UTMB to conduct the trial in UTMB clinics (see letter from Dr. David Callender of UTMB).

This study is testing an alternative dosing schedule of a vaccine currently given as standard of care. Actually, it is not uncommon for patients to receive one or more doses later than the recommended dosing schedule due to transportation issues, missed appointments, scheduling issues, etc. In these instances, it is recommended that patients of all ages and dosing schedules receive the vaccine at the next available opportunity as part of standard of care. Thus, this study is similar to standard care and presents minimal risks to participants.

2.0 Rationale and Specific Aims

Hypothesis: A 2-dose schedule of the HPV vaccine administered at 0 and 6 months to males and females 15–26 years old will elicit a non-inferior immune response compared to 3 doses administered at 0, 2, and 6 months to females and males 15–26 years old.

Aim 1: Determine if a 2-dose schedule of Gardasil 9 administered at 0 and 6 months to females 15–26 years old elicits a non-inferior type-specific antibody response to that generated in females 15–26 years old who receive the currently recommended 3-dose schedule.

Aim 2: Determine if a 2-dose schedule of Gardasil 9 administered at 0 and 6 months to males 15–26 years old elicits a non-inferior type-specific antibody response to that generated in males 15–26 years old who receive the currently recommended 3-dose schedule.

Aim 3: Evaluate the persistence of the immune response by comparing antibody levels 6 months after the last dose in (a) females 15–26 years of age receiving 2 vs. 3 doses and (b) males 15–26 years of age receiving 2 vs. 3 doses.

3.0 Inclusion/Exclusion Criteria

Inclusion criteria:

1) Males and females 15–26 years old.
2) Ability to give informed consent. All participants under 18 years of age must have the informed consent of a parent and must assent to participation.
3) Has not received any prior doses of the HPV vaccine. We will ask the patient and his/her parent (if <18) about prior vaccination and check the state registry (Immtrac), as well as the UTMB electronic medical record (if previously seen at UTMB), We will check with their primary care provider, if feasible, for patients who are not a previously established UTMB patient.
4) Identified source of funding for vaccine which may include Texas Vaccines for Children (VFC) program, Medicaid, the Children's Health Insurance Plan (CHIP), Texas Healthy Women program, Merck Patient Assistance Program, or other public or private health insurance.
5) Reliable telephone access.
6) Participant and parent/ guardian (if <18) can read and speak either English or Spanish.

Exclusion criteria:

1) For females, currently pregnant or plans to become pregnant or donate eggs in next 12 months. Sexually active females must report that they use regular birth control. All female subjects will be required to take a urine pregnancy test before each Gardasil 9 dose, unless it can be verified that she gave birth within the last week. Any subjects with positive tests at the initial visit will be disqualified from the study and advised to seek prenatal care. If a subject is pregnant when her follow-up visit window closes, she will be removed from the study.
2) History of 6 or more lifetime sexual partners.
3) History of any immunodeficiencies (HIV+, chemotherapy treatment, status splenectomy) or autoimmune disorders (lupus, thyroid disorder, psoriasis).
4) History of bleeding or platelet disorders such as hemophilia.
5) Currently taking medication which can suppress immune function including systemic corticosteroids, radiation therapy, cyclophosphamide, azathioprine, methotrexate, cyclosporine, leflunomid, TNF-alpha antagonists, monoclonal antibody therapies, or intravenous immunoglobulin treatment.
6) Known allergies to any components of the vaccine, including aluminum, yeast or Benzonase.
7) Febrile at ≥100°F in the 24 hours prior to vaccination. This will be reviewed before each Gardasil 9 dose.

8) Received any non-study inactive vaccines within the past 14 days or any live vaccines within the past 30 days. Those excluded for this reason will be re-screened under the same study number at a later date.
9) Plan to move out of the Galveston/Houston area in the 13 months following study entry.

4.0 Enrollment/Randomization

Recruitment:

800 males and females 15–26 years of age will be recruited to participate. We will collaborate with physicians in pediatric, family medicine, and women's health clinics/hospitals within the UTMB Health System and ask them if they will allow us to directly recruit their patients. Directly recruiting in the clinics will give us a place to properly store vaccine doses, vaccinate patients, draw blood, and prepare serum samples. Signs will be posted in the clinic informing patients about the study and how to enroll. Clinical personnel (eg, nurses, physicians, patient navigators) will also assist by asking eligible patients and parents whose medical record indicates they or their child are unvaccinated if they are interested in participating. If they agree, they will be screened using a standardized form to determine if they meet all inclusion and exclusion criteria. Permission will be obtained from parents to query minors in private about their sexual history. We will also place flyers and announcements at UTMB and advertise at non-UTMB college/university campuses. If necessary, we will expand our advertising to newspapers and social media. Flyers will be displayed in public areas in the community, including but not limited to schools, churches, community centers/events, and local retail establishments. Flyers will be sent by mail to patients whose providers have given us permission to contact them, and postcards or flyers will be mailed to local residents using a commercially available mailing list. Flyers will also be emailed/mailed to School of Nursing (SON) students at UTMB so as to inform them of the study and to provide contact information should they desire additional information or wish to enroll. Participants recruited in this way will be able to attend one of our recruitment clinics for study procedures. This combination of recruitment sources is needed to ensure that we will meet our goal of 800 participants.

EPIC will also be used to identify eligible patients who previously indicated their interest in (and consent to be contacted about) participating in research projects at UTMB.

For those who agree to participate and meet all inclusion and exclusion criteria, written informed consent will be obtained. For those <18 years of age, a parent/guardian will provide written consent and the adolescent will provide written assent. Screening and recruiting procedures will occur in a private space whenever available. We will devote adequate time to explain the study to participants and parents of minors using terminology they can understand in English or Spanish, when needed. Potential participants who do not meet study criteria will be directed to their physician or a facility that can provide the HPV vaccine to them. To increase efficiency and decrease patient burden, the patient record numbers of those who decline will be recorded so that they are not approached again in future visits.

To clarify, a) permission to contact patients to participate was obtained from their individual providers and b) a waiver of consent was requested in order to pre-review patient medical records for eligibility to participate in this study.

Randomization:

After obtaining informed consent, enrolled participants will be randomized in a 1:1 ratio to either the 2-dose study group or the 3-dose standard care group. The UTMB Office of Biostatistics

(OBIOS) will generate the randomization scheme. The scheme will be centralized on a secure website to facilitate access to study personnel and eliminate selection bias. At the time that a participant has signed informed consent and met all eligibility criteria, study personnel will utilize REDCap, which has been programmed to randomize patients as described above, to obtain the study allocation information. Study personnel will be required to enter information including the protocol number, the site number, and participant's age and sex to receive the participant identification number and study assignment for the 2-dose study group or the 3-dose standard care group. The PI has previously used these techniques in randomized trials conducted in UTMB clinics with excellent success.

5.0 Study Procedures

Baseline visit:

Project staff will follow standardized instructions to ensure unbiased and systematic data collection. At the baseline visit, all participants will have their blood drawn (B_1; see Figure 1), which will be processed and later sent to the CDC lab to determine their baseline levels of antibodies for the 9-valent HPV types. After the blood draw, participants will be randomized to either the 3-dose standard care group or the 2-dose experimental group. All participants will receive the first dose of the HPV vaccine (V_1) at this time (T_0). They will be observed for up to 15 minutes after the injection to ensure they do not have any adverse reactions to the vaccine. Participants will be scheduled for their next visit before leaving the clinic.

Demographics (i.e., date of birth, age, ethnicity, race, marital status) and other information (i.e., height, weight, coverage, and clinic site) will be collected by project staff (via the EMR and subjects' self-reports) utilizing internal-use documents previously approved by the IRB.

An appointment reminder handout will be distributed to all subjects. It will specify when they are scheduled to receive follow up doses and state that they are in a clinical trial and thus should not receive the HPV vaccine at a regular clinic visit.

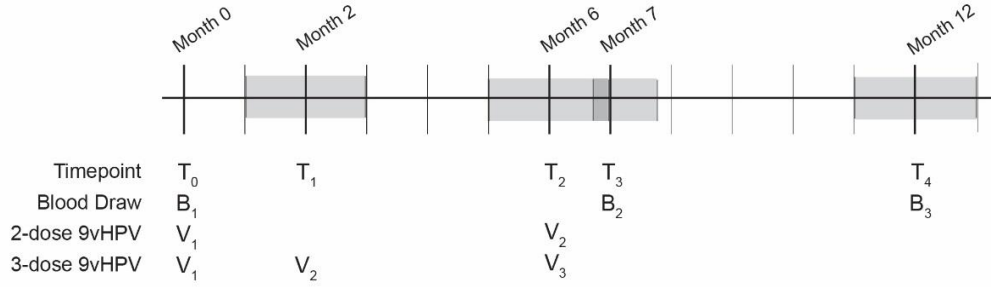

Figure 1: Dosing and Sampling Schedule: Gray boxes indicate windows of time during which a participant can return for a follow-up vaccination or blood draw. The windows of time for the Month 6 vaccination (T_2) and second blood draw (B_2) overlap in the figure; however, per participant, the window for B_2 will be set by T_2. See text for details.

Follow-up visits:

Participants will be screened during each follow-up vaccination visit to ensure they continue to meet those inclusion and exclusion criteria required for safe vaccination, including whether they have developed any new allergies to the vaccine's components. Febrile patients or those who received another vaccine will be rescheduled, if possible, to do so within the allowed window for vaccination (±4 weeks). Study personnel may call participants who miss a scheduled visit (due to transportation issues or scheduling conflicts) prior to withdrawing them from the study. These participants will be offered a home visit to receive the time-sensitive follow up study procedure (i.e., vaccination, urine pregnancy test, or blood draw) that they need to stay within their allowed window and remain in the study.

Participants will also be screened to determine if they received the vaccine at another location. Those who receive HPV vaccination doses outside the study or do not meet the study parameters will be excluded. In an effort to prevent doses being administered by clinic personnel outside of the study, the project manager will post notices at the clinic prompting nurses to check the FYI flags in EPIC and/or will attend one or more of the clinics' in-service events to remind them in person. Which option to be utilized will be determined by each clinic manager's preference.

Participants who are pregnant when their follow-up visit window closes will be removed from the study.

At T_1, only participants in the standard 3-dose arm of the study will need to return to the clinic. Two months ±4 weeks after T_0, 3-dose arm participants will receive a second dose of the HPV vaccine (V_2) (Figure 1). The window of time for vaccination is similar to that used in the 2-dose study in 9–14 year olds by Iveresen et al.[8] Participants in the experimental group will not receive a vaccine dose at 2 months and therefore will not need to attend clinic at T_1.

Six months after enrollment (T_2), the third dose of Gardasil 9 (V_3) will be administered to the standard 3-dose group and the second dose (V_2) will be administered to the experimental 2-dose group. Participants will have a window of 6 months ±4 weeks after T_0 to receive their final dose

The second blood (B_2) draw will be done at T_3, which will be timed to 3–7 weeks after T_2 when the final HPV dose was administered. The third and final blood draw (B_3) will be done at T_4, 6 months ±4 weeks after T_2. Participants will be reimbursed for their time and effort at the time of each blood draw: \$50 for B_1 and B_2 and \$75 for B_3. After the B_3 blood draw, we will administer the 3rd dose to participants in the 2-dose arm with their consent.

We considered collecting blood specimens at more or less frequent intervals. Timing of collection of blood specimens was carefully considered, and we chose a sampling scheme that would limit the number of blood draws while still allowing us to achieve the aims of the study. We also considered collecting all information via self-report, such as vaccination history. However, the literature demonstrates that patients often forget whether they were vaccinated, and therefore, accessing past vaccination records to improve reliability of vaccination history is necessary.

Handling of blood samples:

Study personnel will verify the participant's identity before drawing the blood sample. Five mL of whole blood will be collected by venipuncture and will be collected in a red-top Vacutainer tube using standard procedures.

Home Visits

Licensed phlebotomists or medical assistants on the study staff will transport the vaccine in a cooler with icepacks to keep it at 0°C and 2°C. Vaccine syringes will be prepared during the home visit. Female participants will need a urine pregnancy test prior to vaccination; a specimen cup will be provided. Study staff will also bring a caddy that contains additional supplies needed (alcohol wipes, gauze, bandages, butterfly needles, red top tubes, small test tube rack, gloves, biohazard disposable bin, tourniquet, absorbent pads, thermometer, etc.). A transportable table and chair will also be utilized.

With each shipment/delivery of serum aliquots to the Galveston UTMB campus, a data file with the Sample IDs, sample locations in the box, collection dates, and other relevant information will be sent to the Project Manager via e-mail. Each sample will be checked against the worksheet for correct sample label ID when it arrives at UTMB Galveston. Samples will not be labeled with participant name or identifying information in order to protect confidentiality of participants and to mask the study group of the participants from lab personnel. One aliquot of serum per participant per blood draw will be sent to the CDC for analysis. The CDC lab will record serology results in an Excel spreadsheet. Data will be transferred to the PI at completion of testing and quality control validation of results. Methods for this immunoassay have been developed by the CDC.[10] Assays will be performed at CDC laboratory facilities.

6.0 Study Product Description

Gardasil 9 is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Gardasil 9 is a vaccine indicated in girls, boys, women and men 9 through 45 years of age.

Gardasil 9 is a sterile suspension for intramuscular administration. The dosage form is a 0.5-mL suspension for injection as a single-dose vial and prefilled syringe. Gardasil 9 should be administered as soon as possible after being removed from refrigeration. Gardasil 9 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. These are not, however, recommendations for storage. After thorough agitation, Gardasil 9 is a white, cloudy liquid.

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of Gardasil 9 or Gardasil (4, 11), is a contraindication to the receipt of vaccine.

Modification of Study Intervention/Investigational Product for a Participant

The individual dose will not be modified, just the dosing schedule. If patient has a contraindication, no dose will be administered.

Accountability Procedures for the Study Intervention/Investigational Product(s)

As the intervention under study is a change in the dosing regime of an existing, recommended vaccine, standard procedures for distribution and storage of doses are already in place.

Assessment of Subject Compliance with Study Intervention/Investigational Product

Study personnel will review the medical records of every participant prior to each dose administration to check for exclusion criteria including: history of immunodeficiency or autoimmune disorder, medication that can suppress immune function, allergies to vaccine components, recent receipt of non-study vaccines (within 14 days for inactive vaccines and within 30 days for live vaccines).

The oral or tympanic temperature of all patients will be determined before each dose of Gardasil 9 is administered. All female subjects will be required to take a urine pregnancy test before each Gardasil 9 dose, unless it can be verified that she has given birth within the last week. Any subjects with positive tests will be disqualified from the study and advised to seek prenatal care.

Compliance will be determined by and limited to receipt of all required doses of Gardasil 9.

Concomitant Medications/Treatments

All drugs and/or treatments are permitted except:

1. Medications that suppress immune function including systemic corticosteroids, radiation therapy, cyclophosphamide, azathioprine, methotrexate, cyclosporine, leflunomid, TNF-alpha antagonists, monoclonal antibody therapies, or intravenous immunoglobulin treatment.
2. Non-study inactive vaccines within past 14 days or live vaccines within past 30 days.

7.0 Adverse Events/Unanticipated Problems involving Risk

The risks of this study are similar to those currently experienced in the general population, as the vaccine has already been approved by the FDA and is administered as a routine vaccine in males and females 9–26 years old. We will not be administering the vaccine to any age or sex groups for which it is not approved or recommended.

Syncope has been reported, but is not common for the HPV vaccine. It has been reported in 8 out of 100,000 doses of Gardasil.[11] Observation for up to 15 minutes after administration is recommended. Anaphylactic reactions occur in approximately 1 in 1,000,000 doses following administration of Gardasil.[12] Appropriate medical treatment and supervision will be available in case this unlikely event occurs.

Injection-site reactions (pain, swelling, and erythema) and oral temperature recorded for five days after each injection of Gardasil 9 among females 16–26 years of age during the clinical studies showed that any pain was reported by up to 89.9% after any dose although severe pain was reported by only 4.3%.[13] Any swelling was reported by 40.0% with severe swelling by 3.8%. Any injection-site redness was reported by 34% with severe erythema by 1.6%. Fever greater than or equal to 102◦F was reported by 1.0%. Injection-site pruritus was reported by 5.5%. Headache occurred in 14.6%, pyrexia in 5.0%, nausea in 4.4% dizziness in 3.0% and fatigue in 2.3%, diarrhea in 1.2%, oropharyngeal pain in 1.0%, myalgia in 1.0%, upper abdominal pain in 0.7%, and upper respiratory tract infection in 0.1%.
Among males 16–26 years of age receiving Gardasil 9 in clinical studies, any injection-site pain was reported by up to 63.4% after any dose; severe pain was reported by only 0.6%.[13] Any swelling was reported by 20.2% with severe swelling by 1.1%. Any injection-site redness was reported by 20.7% with severe erythema by 0.4%. Fever greater than or equal to 102◦F was

reported by 0.6%. Injection-site pruritus was reported by 1.0%, headache by 7.3%, pyrexia by 2.4%, nausea by 1.0%, dizziness by 1.0%, fatigue by 1.4%, and nausea by 1.0%.

Across clinical studies of Gardasil 9, no deaths occurred that were assessed as vaccine-related.[13]

In all of the clinical trials with Gardasil 9 subjects were evaluated for new medical conditions potentially indicative of a systemic autoimmune disorder. In total, 2.2% (351/15,703) of Gardasil 9 recipients reported new medical conditions potentially indicative of systemic autoimmune disorders, which were similar to rates reported following saline placebo in historical clinical trials.

Serious Adverse Event (SAE):

An SAE is defined as an AE that meets one of the following conditions that occur within six weeks of vaccination and is possibly related to the vaccine:

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

All SAEs will be:

- recorded on the UTMB External SAE Reporting log followed through resolution by a study clinician
- reviewed and evaluated by a study clinician
- reported to the PI, IRB, and the Vaccine Adverse Event Reporting System (VAERS)

Serious Adverse Events

Any AE which occurs within 6 weeks of vaccination considered serious by the PI or Sub investigator or which meets the aforementioned criteria must be submitted on the SAE form to the IRB in accordance with IRB policies and procedures. SAEs will also be reported to VAERS if possibly related to the study procedures.

All SAEs will be followed until satisfactory resolution or until the PI,Sub investigator, or patient's physician deems the event to be chronic or the patient to be stable.

Procedures to be followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

This study does not include any physical exams or safety laboratory tests.

Reporting Procedures

The most common adverse reactions to Gardasil 9 are injection-site pain, injection-site swelling, erythema, and headaches. Study personnel will counsel subjects to report adverse reactions to their health care provider. All serious adverse events will be reported to the VAERS system (www.vaers.hhs.gov).

8.0 Study Withdrawal/Discontinuation

Reasons for Withdrawal

A study subject will be discontinued from participation in the study if any of the following occur:

- Inability of study personnel to contact subjects for follow-up vaccinations
- Excessive appointment cancellations (> 6) by the subject
- Subject withdrawals consent to continue in the research for any reason
- An unanticipated/unacceptable toxicity or adverse event (AE)

Handling of Withdrawals

There is minimal risk involved in this study. As the intervention under investigation is a reduced schedule of a currently used vaccine, patients who choose to withdraw will not be under any additional risk beyond that of normal patient care. Patients who choose to withdraw will not be contacted any further after notifying study staff. However, the data that they have provided up to the point of withdrawal will be retained and possibly used for research purposes.

Termination of Study

This is a minimal risk study with no foreseeable reasons for potential termination.

9.0 Statistical Considerations

Data Analysis: We will compare the immunogenicity of the 2-dose experimental group to the 3-dose standard care group for the corresponding sex. Participants will be required to 1) have received all injections of the vaccine within the predetermined time ranges, 2) have an adequate serum sample collected at the appropriate time intervals, and 3) be seronegative at T_0 for the HPV type that will be analyzed. Results of this experiment will be analyzed using intention-to-treat analyses, as these are the standard for non-inferiority trials.

> **Aim 1. Determine if a 2-dose schedule of the HPV vaccine administered at 0 and 6 months to females 15–26 years old elicits a non-inferior type-specific antibody response to that generated in females 15–26 years old who receive the currently recommended 3-dose schedule.**
>
> H_a: Two-dose 9-valent HPV vaccination immunogenicity levels among females are non-inferior to 3-dose 9-valent HPV vaccination immunogenicity levels among females.
>
> H_0: Two-dose 9-valent HPV vaccination immunogenicity levels are inferior to 3-dose 9-valent HPV vaccination immunogenicity levels among females.

Non-inferiority of antibody GMTs at 1 month after the last dose is administered will be tested by developing 2-sided 95% confidence intervals for the ratio of GMTs drawn at T_3, as is consistent with the power analyses of non-inferiority trials in the literature.[8] This will be equivalent to the lower bound of a 1-sided 97.5% confidence interval (1-sided test, α=0.025). The ratio will be developed using antibody GMTs in 15–26 year old females in the 2-dose study group relative to antibody GMTs among 16–26-year-old females in the 3-dose standard care group. In order to reject the null hypothesis, the lower bound of the ratio of antibody GMTs in females who received 2 doses should be 0.5 or greater for each of the 9 vaccine types.[17-26] If inferior immunogenicity is noted for any of the 9 vaccine types for the 2-dose experimental group, then H_0 will not be rejected.

Aim 2. Determine if a 2-dose schedule of the HPV vaccine administered at 0 and 6 month to males 15–26 years old elicits a non-inferior type-specific antibody response to that generated in males 15–26 years old who receive the currently recommended 3-dose schedule.

H_a: Two-dose Gardasil 9 immunogenicity levels among males are non-inferior to 3-dose 9-valent HPV vaccine immunogenicity levels among males.

H_0: Two-dose Gardasil 9 immunogenicity levels among males are inferior to 3-dose 9-valent HPV vaccine immunogenicity levels among males.

Non-inferiority of antibody GMTs at 1 month after the last dose is administered will be tested similar to the analysis plan presented for Aim 1. Two-sided 95% confidence intervals for the ratio of antibody GMTs drawn at T_3 will be developed. The ratio will consist of antibody

GMTs in 15–26-year-old males as compared to 15–26-year-old males in the 3-dose standard care group. In order to reject the null hypothesis, the lower bound of the 95% confidence interval for the ratio of antibody GMTs in males should be 0.5 or greater for each of the 9 vaccine-type HPVs. If inferior immunogenicity is noted for any of the 9 vaccine types, then H_0 will not be rejected.

Secondary analyses: We will also compare immunogenicity of the experimental 2-dose group in males with the immunogenicity of the 3-dose standard care group in females. This will allow us to compare the immunogenicity of the 2-dose schedule in males to that of the standard schedule in females, the population originally studied in efficacy trials.[14,15] Non-inferiority at T_3 will be tested by constructing 2-sided 95% confidence intervals for the ratio of antibody GMTs among the 2-dose 15–26-year-old male experimental group as compared to the 3-dose 15–26-year-old female group. To determine non-inferiority between the 2 groups, the lower bound of the ratio of antibody GMTs in males should be 0.5 or greater for each of the 9 vaccine types. We will also determine whether the level of immunogenicity for each type is above naturally-acquired immunity among males at T_3.

Aim 3: Evaluate the persistence of the immune response by comparing antibody levels 6 months after the last dose in (a) females 15–26 years of age receiving 2 vs 3 doses and (b) males 15–26 years of age receiving 2 vs 3 doses.

H_a: Two-dose Gardasil 9 immunogenicity levels are non-inferior to 3-dose 9-valent HPV vaccine immunogenicity among females and males at 6 months after the last dose.

H_0: Two-dose Gardasil 9 immunogenicity levels are inferior to 3-dose 9-valent HPV vaccine immunogenicity among females and males at 6 months after the last dose.

Non-inferiority of antibody GMTs at 6 months after T_2 will be tested by constructing two-sided 95% confidence intervals for the ratio of antibody GMTs drawn at T_4. The ratios will consist of antibody GMTs in 15–26-year–old females in the 2-dose group as compared to 15–26-year-old females in the 3-dose standard care group. Likewise, ratios of antibody GMTs in 15–26-year-old males in the 2-dose experimental group as compared to 15–26-year-old males in the 3-dose standard care group will be constructed. In order to reject the null hypothesis, the lower bound of the 95% confidence interval for the ratio of antibody GMTs in both comparisons should be 0.5 or greater for each of the Gardasil 9 types. If inferior immunogenicity is noted for any HPV type for either sex, then H_0 will not be rejected.

Sample Size Justification:

The sample size determined for this study takes into account the need to recruit a sufficient number of participants who 1) could be included in assessments for the 9 HPV types that the vaccine protects against, considering that some may have been exposed before baseline, and 2) to account for loss to follow-up. Power analysis calculations were performed using estimates from published clinical trials and HPV prevalence rates in the age groups that will be included in this study. It was estimated that up to 15% of study participants will be seropositive for 1 or more vaccine types.[16] We then assumed an attrition rate of 15% at the 12-month follow-up point.

We calculated the sample size for the hypothesis: H_a: Antibody response to 2 doses will be non-inferior to the antibody response to 3 doses of Gardasil 9 for females (Aim 1) and males (Aim 2). The GMTs will be non-inferior if the true ratio between each study group (female 2-dose and male 2-dose) and the 3-dose standard care groups (female 3-dose and male 3-dose) are equal to 1.2, with a standard deviation of 1.2 consistent with the power analyses conducted by a previous clinical trial.[8] The inferiority margin was set at 0.5, which is the standard in HPV vaccine clinical trials[17-26]. The statistical criterion for non-inferiority will be determined to be null when the lower bound of the 97.5% confidence interval for the GMT is 0.5 or greater for any of the vaccine types. A sample size of 91 in each group who are naïve to at least 1 of the vaccine types is required to reach 90% power to detect non-inferiority of the 2-dose compared to the 3-dose regimen at T_3. Based on estimates of 15% of the baseline samples testing seropositive for at least one of the types, a sample size of 108 is required in each group for comparisons of T_3 antibody titers.

We also calculated the sample size for the hypothesis: H_a: Two-dose 9-valent HPV vaccine immunogenicity levels are non-inferior to 3-dose Gardasil 9 immunogenicity among females and males at 6 months after the last dose. Between T_0 and T_4, we assumed an attrition rate of 15%. Therefore, each comparison group requires a total sample size of 128 per group to achieve at least 90% power to determine non-inferiority of the 2-dose experimental groups compared to the 3-dose standard care groups at T_4. The total sample size required is 800. All calculations were made using statistical software PASS, version 15.

10.0 Ethics and the Protection of Human Subjects

Discussion of risks and possible benefits of Gardasil 9 will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks will be given to the subject and written documentation of informed consent obtained prior to administering Gardasil 9. Consent forms will be IRB-approved and the subject will be

asked to read and review the document. Upon reviewing the document, study personnel will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subject may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

Privacy/Confidentiality Issues

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal investigator.

Individuals authorized to view study records will be identified to the study subject on the informed consent but may include a study monitor or other authorized representatives of agencies that regulate research including representatives from the Office of Human Research Protections or the Institutional Review Board. Study records may also be made available for internal compliance reviews and quality assurance representatives.

These individuals may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

In accordance with the Food and Drug Administration Amendment Act of 2007 (FDAAA) and The International Committee of Medical Journal Editors (ICMJE) member journals trials-registration policy as a condition for publication, this study will be registered in the public trials registry ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Results will be published to ClinicalsTrial.gov when available but will not identify individual subjects.

11.0 Record Retention

The investigator shall retain records required to be maintained under 21 CFR 312.62 for a period of 3 years following the date the investigation is discontinued. There will be no marketing application for a new drug as a result of this study as the intervention of study uses an FDA-approved vaccine.

Consent forms that include the HIPAA Authorization will be retained for a minimum of 3 years from the date of the authorization.

For pediatric subjects, records shall be maintained until 3 years after completion of the research.

Research records will be maintained in accordance with the current version of the Texas Health Records Table 17-III Record Retention Schedule, Human Subject Research Records and Documents.

12.0 References

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