COVER PAGE

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A prospective, single-arm, open-label, non-randomized, phase IIA trial of a nonavalent prophylactic HPV vaccine to assess immunogenicity of a prime and deferred-booster dosing schedule among 9-11 year-old girls and boys

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SCHEMA

A prospective, single-arm, open-label, non-randomized, phase IIA trial of a nonavalent prophylactic HPV vaccine to assess immunogenicity of a prime and deferred-booster dosing schedule among 9-11 year-old girls and boys

Healthy, medically well girls and boys ages 9-11 years old

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Prestudy Screening Evaluation

Informed consent from legal representative(s) of participants and assent of participants,
Medical history (including age at menarche), Concomitant medications,
Weight, height, vital signs,
Review of baseline signs and symptoms, and
Basic socioeconomic status

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Baseline Visit

(may be combined with the screening visit)
Weight, height, vital signs, adverse events, concomitant medications, and menarche and urine pregnancy test, if applicable,
Blood collection (for serologic analysis),
Priming HPV vaccine injection
(Weight, height, and vital signs are not required if this visit occurs within 30 days of the screening visit)

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Months 6, 12, 18 Visits

Adverse events, concomitant medications, and menarche, if applicable,
Weight and height at Month 12,
Blood collection (for serologic analysis)

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Months 24 and 30 Visits

Vital signs, adverse events, concomitant medications, and menarche and urine pregnancy test, if applicable,
Weight and height at Month 24,
Blood collection (for serologic analysis),
Booster HPV vaccine injection at Month 24. At the Month 30 visit, an optional booster injection will be offered. Vital signs and urine pregnancy test will not be required at the Month 30 visit for participants who opt to not receive the 3rd vaccine injection.

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Follow-up

Safety follow-up for 2 weeks after the last HPV vaccine injection

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1. OBJECTIVES

The overall objective of this prospective, single-arm, open-label, non-randomized, Phase IIA trial is to determine the immunogenicity of a prime and deferred-booster dosing schedule (prime dose at baseline and deferred-booster dosing at 24 months and optional booster at 30 months) of a nonavalent prophylactic HPV vaccine (GARDASIL 9) among 9-11 year-old girls and boys.

1.1 Primary Objectives

- To determine the persistence and stability of serologic geometric mean titer (GMT) of HPV 16/18 between 6, 12, 18, and 24 months after the prime dose and prior to the administration of the second dose.

1.2 Secondary Objectives

- To determine the persistence and stability of serologic GMT of HPV types 6/11/31/33/45/52/58 between 6, 12, 18, and 24 months after prime dose and prior to the administration of the second dose and
- To assess safety and reactogenicity to each vaccine dose.

2. BACKGROUND

2.1 HPV infection

Persistent infection with human papillomavirus (HPV) can cause cervical cancer in women as well as genital warts, anogenital and oropharyngeal cancers in both women and men. More than 150 HPV types have been identified. High-risk types (e.g., types 16 and 18) can cause low-grade cervical cell abnormalities, high-grade cervical cell abnormalities that are precancerous to cancer, and cervical cancers [1]. Essentially all cervical cancers are attributable to high-risk HPV types [2], and approximately 70% of cervical cancer cases worldwide are caused by types 16 and 18 [3]. In addition to cervical cancer, HPV infection can lead to some other anogenital cancers as well as cancer of the oropharynx [4, 5]. Low-risk types (e.g., types 6 and 11) can cause benign or low-grade cervical cell changes, genital warts, and recurrent respiratory papillomatosis [6].

2.2 HPV vaccine

Three HPV vaccines are licensed for use in the U.S. including the bivalent vaccine that protects against HPV types 16 and 18, quadrivalent vaccine that protects against HPV types 6, 11, 16, and 18, and the recently approved nonavalent vaccine that protects against HPV types 6/11/16/18/31/33/45/52/58. The available HPV vaccines provide an opportunity to decrease the burden of HPV-attributable cancers and genital warts.

The HPV vaccines have been given as a series of three injections over 6 months (consisting of a priming injection followed by booster injections at 2 and 6 months after the priming injection). In addition to the currently approved 3-dose schedule, a 2-dose schedule has recently been recommended by the U.S. Centers for Disease Control and Prevention (CDC) for 9-14 year-old. The U.S. Food and Drug Administration (FDA) has also recently approved adding a 2-dose schedule (consisting of a priming injection followed by 1 booster injection 6-12 months later) for the nonavalent HPV vaccine for children ages 9 through 14 years. At present, the cost of these regimens and logistical difficulties associated with administering 2-3 doses over 6-12 months make it impractical to vaccinate preadolescent and young women in developing countries [7]. In the U.S., recent CDC data suggests that only 37% of the target-age adolescents complete the recommended 3-dose vaccine series [8] with most receiving vaccine doses outside of the recommended windows of the prescribing schedule.

2.3 Rationale

Recent data showed that serologic responses following two doses of the quadrivalent and bivalent HPV vaccine are non-inferior to those following three doses of the respective vaccines [9, 10]. Consequently, the Strategic Advisory Group of Experts on immunization for the World Health Organization recommended a two-dose regimen for girls aged <15 years in 2014 (http://www.who.int/immunization/sage/meetings/2014/april/report_summary_april_2014/en/). This was followed by the recent (October 2016) FDA approval and CDC's recommendation of the 2-dose schedule for children ages 9 through 14 years (https://www.cdc.gov/media/releases/2016/p1020-hpv-shots.html). Furthermore, studies suggest that HPV vaccine may have the potential to achieve efficacy with only one dose because the HPV vaccines employ virus-like particles, which induce strong immunogenicity secondary to repetitive antigen display [11]. Kreimer et al. [12] evaluated the vaccine efficacy of fewer than three doses of the bivalent HPV vaccine in women randomized in a Phase III clinical trial in Costa Rica and showed that the vaccine efficacy against 12-month persistent HPV16/18 infection was similarly high among women who received, one, two, or the recommended three doses of the vaccine. A follow-up study investigated the magnitude and durability of serologic response to the bivalent vaccine [13] in four vaccinated groups: one dose, two-doses separated by one month, two-doses separated by six months, and three scheduled doses. The analysis showed that at four years, 100% of the women in all dose groups remained seropositive for HPV16/18. HPV16/18 geometric mean titers (GMT) were at least 24 and 14 times higher in the two-dose group and 9 and 5 times higher in the one-dose group in comparison with those in women with the natural infection. In addition, the antibody levels following one dose remained stable from month 6 through month 48. These data suggest that one dose of HPV vaccine may induce long-term protection.

Data comparing immunogenicity of 1 vs. 2 vs. 3 doses of the quadrivalent HPV vaccine (Gardasil) in a trial among ~17,000 girls ages 10-18 years in India suggests that single dose recipients had HPV 16/18/6/11 antibody titers higher than the seropositivity cut-off levels of titers defined for natural infection, and that these titers in single-dose recipients were stable and persistent up to 36 months post-vaccination [14]. The antibody avidity responses in single dose recipients of the HPV vaccine were non-inferior to similar responses in 2-dose and 3-dose recipients up to 36 months post-vaccination. Furthermore, as an early indicator of efficacy by dosing groups, in the subset of sexually active participants for whom cervical DNA was available for testing, the frequency of incident HPV infections were similar across the different dose groups, and no persistent HPV16 or HPV18 infections were reported in any of the dose groups.

It is not known whether a single dose of the nonavalent HPV vaccine will exert persistent immunogenicity similar to the bivalent or quadrivalent HPV vaccines. Because vaccination with a single vaccine dose could simplify the logistics and reduce costs of vaccination in the US and the developing world, it is important to determine the persistence of the immune titers of a single dose of nonavalent vaccine. In addition, it is anticipated that the vaccination pattern of the nonavalent HPV vaccine will be similar to the previous generations of the HPV vaccines. Therefore, it is also important to understand the immunogenicity of the nonavalent HPV vaccine to determine whether immunization occurring outside the recommended window would induce protection similar to the recommended schedule.

Here, we propose a prospective, single-arm, open-label, non-randomized, Phase IIA trial of a nonavalent prophylactic HPV vaccine (GARDASIL 9) to assess the immunogenicity of an alternative schedule (prime dose at baseline and deferred-booster dosing at 24 months, with an optional booster to be offered at 30 months) among 9-11-year-old girls and boys. The booster at 30 months is now optional because after this study began, CDC changed their recommendation for HPV vaccination from 3 to 2 doses for people starting their series before the 15th birthday

(https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a5.htm; https://www.cdc.gov/hpv/hcp/2-dose/clinician-faq.html). Participants from the youngest of the licensed age groups (9-11 years) are selected for this proof-of-principle study given the potential for younger age children to mount higher immune titers [15], and the fact that immune responses to a single dose or two doses of the HPV vaccines among girls aged 9-14 years appear to be comparable to antibody responses of 3 doses in young women 15-25 years old [9]. The study hypothesis is that a single dose of the nonavalent HPV vaccine will induce persistent and stable serological responses for up to 24 months to all 9 vaccine HPV types in girls and boys 9-11 years of age.

3. SUMMARY OF STUDY PLAN

This is a prospective, single-arm, open-label, non-randomized, Phase IIA trial of a nonavalent prophylactic HPV vaccine (Gardasil 9) to assess the immunogenicity of a deferred-booster schedule (prime dose at baseline and deferred-booster dosing at 24 months and optional booster at 30 months) among 9-11 year-old girls and boys.

Healthy young, medically well girls and boys ranging from 9-11 years of age referred by their practitioners for HPV vaccination will be recruited from institution pediatric clinics and collaborating clinics. Detailed inclusion and exclusion criteria are described in sections 4.1 and 4.2.

Participants will undergo a pre-study screening evaluation. The legal representative(s) of the participants will be required to sign the informed consent form and medical records release form. Participants will be asked to sign the assent form. Participants and their legal representative(s) will be interviewed for past medical history (including age of menarche) and concomitant medication use. Participants will be assessed for height, weight, and vital signs (temperature, pulse, and blood pressure). Participants will be evaluated for baseline signs and symptoms. Urine pregnancy test will be performed on female participants who have started menstrual periods. The legal representative(s) will complete a questionnaire to collect information on the participant's parental education attainment and household income.

Eligible participants and their legal representative(s) will return to the clinic for a baseline visit. This visit may be combined with the prestudy screening evaluation visit. If the baseline visit occurs more than 30 days from the screening visit, participants will be reassessed for weight and vital signs. Adverse events and concomitant medications will be reviewed and age at menarche and urine pregnancy test, if applicable, will be reassessed at the baseline visit unless it occurs on the same day as the screening visit. If the participant is pregnant, she will be considered off-study and not undergo additional study procedures, including vaccination. A blood sample will be collected from the participants and serum separated and stored at -80°C. Participants will be offered topical anesthetic cream to be applied to the blood collection site prior to the collection. Following the blood collection, participants will receive the priming injection of Gardasil 9 and be observed in the clinic for at least 15 minutes.

Participants and legal representatives will be instructed to record adverse events for two weeks following each injection which will then be mailed back to the study office in a pre-stamped and addressed envelope.

Participants and their legal representatives will return to the clinic at 6, 12, 18, 24, and 30 months after the priming injection of Gardasil 9. These study visits will occur +/- 2 weeks of the scheduled times unless significant scheduling problems arise.

For the months 6, 12, and 18 visits, participants will be assessed for adverse events, concomitant medications, menarche, if applicable. Weight and height will be assessed at the month 12 visit. A blood sample will be collected from the participants at each visit and serum separated and stored at -80°C.

Similarly, participants will be offered topical anesthetic cream to be applied to the blood collection site prior to the collection.

For the months 24 and 30 visits, participants will be assessed for vital signs, adverse events, concomitant medications, and menarche and urine pregnancy test, if applicable. If the participant is pregnant, she will be considered off-study and not undergo additional study procedures, including vaccination. Weight and height will be assessed at the month 24 visit. A blood sample will be collected from the participants at each visit and serum separated and stored at -80°C. Similarly, participants will be offered topical anesthetic cream to be applied to the blood collection site prior to the collection. Following the blood collection at the month 24 visit, participants will receive the booster injection of Gardasil 9 and be observed in the clinic for at least 15 minutes. The booster injection of Gardasil 9 at the month 30 visit will be offered but is optional based on the latest CDC recommendation. Vital signs and urine pregnancy test will not be required for participants who do not receive the 3rd vaccine injection at the Month 30 visit.

Participants and their legal representatives will be contacted once a month and also within two weeks prior to each visit in their preferred method of contact to promote participant retention. They will be reminded during each contact that the subject should not receive the HPV vaccine from any provider outside the study. Additionally, we will provide subjects/legal representatives with wallet cards to indicate that the subject is participating in a research study and include the dates the HPV vaccine injection was given. We will also send a letter to the subject's primary care provider.

Participants will be followed for 2 weeks after completion of the last Gardasil 9 injection for safety evaluation.

We plan to accrue a total of 143 girls and 57 boys. With an estimated attrition rate of 30%, we anticipate having at least 100 girls and 39 boys completing the 30 month visit.

In addition, participants and their legal representatives may be contacted in the future if they have consented to allow for the possibility of re-consenting for additional serologic testing after the trial is completed.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Healthy, medically well girls and boys

4.1.2 Ages 9-11 at enrollment (on/after the 9th birthday but before the 12th birthday at enrollment)

4.1.3 Ability to understand and the willingness to sign a written informed consent document by the legal representative(s) of the participant

4.1.4 Ability to understand and the willingness to sign a written assent document by the participant

4.2 Exclusion Criteria

4.2.1 Previous vaccination against HPV

4.2.2 The use of any investigational agent within 30 days preceding the first dose of the study vaccine or subsequent participation in another clinical trial at any time during the study period, in which the subject will be exposed to an investigational product

4.2.3 Chronic administration of immunosuppressive agents or other immune-modifying drugs or chemotherapeutic agents within six months prior to the first vaccine dose. Use of inhaled steroids, nasal sprays, and topical creams for small body areas is allowed

4.2.4 Receiving active treatment for cancer or an autoimmune condition

4.2.5 Confirmed or suspected immunosuppressive or immunodeficient condition

4.2.6 Known bleeding disorders that preclude intramuscular injection (e.g., on anticoagulants or thrombocytopenia)

4.2.7 Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal dysfunction, which in the opinion of the investigator precludes administration of the study vaccine

4.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition of GARDASIL 9, including yeast allergy

4.2.9 Are pregnant

4.3 Inclusion of Women and Minorities

HPV vaccines have been approved for use in both girls and women as well as in boys and men between 9 and 26 years of age. This study focuses on the youngest of the licensed age groups (9-11 years), including both girls and boys, because of the potential for younger age children to mount higher immune titers. Members of all races and ethnic groups are eligible for this trial.

4.4 Recruitment and Retention Plan

For University of Arizona, study participants will be primarily recruited from the University of Arizona pediatric clinics and Pima County Health Department Clinics. For University of California Los Angeles, study participants will be primarily recruited from outpatient offices of the UCLA Community Physician Network.

Additional recruitment methods include community physician referrals, the institutional websites postings, community outreach activities, advertisement from different media outlets, and outreach to local schools. Recruitment materials such as brochures or flyers may be developed to help recruit study participants.

The study team will provide a friendly and comfortable study setting for participants and their legal representative(s) from initial contact through the completion of the study. Demands upon the subjects will be minimized to foster comfort while preserving the research goals. Wherever possible, flexibility will be built into the study schedule to promote compliance. Participants and their legal representatives will be contacted once a month and also within two weeks prior to each visit in their preferred method of contact to promote participant retention.

5. AGENT ADMINISTRATION

Agent will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

- The study agent is Gardasil 9.
- Participants will receive the priming injection at baseline, a booster injection at 24 months and an optional booster injection at 30 months after the priming injection.

5.2 Gardasil 9 Administration

- Shake well before use.
- Administer the entire dose of Gardasil 9 (0.5 ml) intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.
- Participants should be seated or lying down during administration.
- Participants should be observed in the clinic for at least 15 minutes following the administration of Gardasil 9.

5.3 Run-in Procedures

Not applicable.

5.4 Contraindications

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL.

5.5 Concomitant Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include: 1) start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g.*, biopsy) should also be included. Participants and their legal representatives will be reminded to refrain from non-study HPV vaccination during their study participation. If a subject receives an HPV vaccine outside the context of the study, he/she will be taken off study. This information will be captured in the source document and on the Concomitant Medication CRF and a comment addressing this will be added to the Agent Interruption CRF. Other vaccines received by the participants will be considered to be concomitant medications and will also be captured on the Concomitant Medications CRF.

5.6 Dose Modification

At the discretion of the study physician, the vaccine injection may be delayed because of a current or recent febrile illness. Low-grade fever itself (temperature <= 100.4) and mild upper respiratory infection are not generally contraindications to vaccination.

Participants who develop anaphylactic reactions following the first injection will permanently discontinue Gardasil 9.

5.7 Adherence/Compliance

5.7.1 Participants are considered compliant for statistical analysis if they have received all doses of the vaccine.

5.7.2 The compliance will be measured by the number of vaccines administered.

6. PHARMACEUTICAL INFORMATION

6.1 GARDASIL 9 (IND exempt by FDA 8/12/15)

This clinical study investigating the chemopreventive efficacy of recombinant human papillomavirus (HPV) nonavalent vaccine, Gardasil 9, has been deemed IND exempt per FDA letter received on 8/12/15. Gardasil 9 is indicated for prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, and for the prevention of genital warts caused by HPV types 6 or 11 in females 9–26 years of age and males 9–15 years of age. Gardasil 9 adds protection against five additional HPV types—31, 33, 45, 52, and 58—which cause approximately 20% of cervical cancers and are not covered by previous FDA-approved HPV vaccines.

Gardasil 9 is manufactured by Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (Whitehouse Station, New Jersey). It is supplied in 0.5 mL single-dose vials as a sterile suspension for intramuscular administration. Each 0.5 mL dose contains approximately 30 µg HPV Type 6 L1 protein, 40 µg HPV Type 11 L1 protein, 60 µg HPV Type 16 L1 protein, 40 µg HPV Type 18 L1 protein, 20 µg HPV Type 31 L1 protein, 20 µg HPV Type 33 L1 protein, 20 µg HPV Type 45 L1 protein, 20 µg HPV Type 52 L1 protein, and 20 µg HPV Type 58 L1 protein. Each 0.5 mL dose of the vaccine also contains approximately 500 µg aluminum (provided as amorphous aluminum hydroxyphosphate sulfate [AAHS]), 9.56 mg sodium chloride, 0.78 mg L-histidine, 50 µg polysorbate 80, 35 µg sodium borate, <7 µg yeast protein, and water for injection. The product does not contain a preservative or antibiotics. After thorough agitation, Gardasil 9 is a white cloudy liquid.

6.2 Reported Adverse Events and Potential Risks

The manufacturer evaluated the safety of Gardasil 9 in six clinical studies that included 13,234 individuals who received at least one dose and had safety follow-up. The vaccine was administered on the day of enrollment, with subsequent doses administered approximately two and six months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of Gardasil 9. The individuals who were monitored using VRC-aided surveillance included 8,022 women 16–26 years of age and 5,212 girls and boys 9–15 years of age (3,436 girls and 1,776 boys) at enrollment.

Injection site reactions (pain, swelling, and erythema) and oral temperature were solicited using VRC-aided surveillance for five days after each injection of Gardasil 9 during the clinical studies. The rates of injection site pain were approximately equal across the three reporting time periods; the rates of injection site swelling and injection site erythema increased following each successive dose of Gardasil 9. Unsolicited injection site and systemic adverse reactions were assessed as vaccine-related by the investigator. Few individuals discontinued study participation due to adverse experiences after receiving the vaccine.

The most common (≥10%) local and systemic adverse reactions in females 16–26 years of age who received Gardasil 9 were injection site pain (89.9%), injection site swelling (40.0%), injection site erythema (34.0%), and headache (14.6%). The most common (≥10%) local and systemic reactions in girls 9–15 years of age who received Gardasil 9 were injection site pain (89.3%), injection site swelling (47.8%), injection site erythema (34.1%), and headache (11.4%). The most common (≥10%) local and systemic reactions in boys aged 9–15 years who received Gardasil 9 were injection site pain (71.5%), injection site swelling (26.9%), and injection site erythema (24.9%).

Serious adverse events (SAEs) were collected throughout the entire study period (range one to 48 months post-last dose) for the six integrated clinical studies with Gardasil 9. Of the 13,236 individuals who were administered Gardasil 9 and had safety follow-up, 305 reported an SAE, representing 2.3% of the population. Five reported at least one SAE that was determined to be vaccine-related: pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis. There were no vaccine-related deaths among individuals administered Gardasil 9 in the clinical studies.

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, 2.4% (321/13,234) of Gardasil 9 recipients reported new medical conditions potentially indicative of systemic autoimmune disorders, which were similar to rates reported following Gardasil, AAHS control, or saline placebo in historical clinical trials.

The safety of Gardasil 9 when administered concomitantly with Menactra (Meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate Vaccine) and Adacel (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed [Tdap]) was evaluated in a randomized study of 1,241 boys (n = 620) and girls (n = 621) with a mean age of 12.2 years. Of the 1,237 boys and girls vaccinated, 1,220 had safety follow-up for injection site adverse reactions. The rates of injection site adverse reactions were similar between the concomitant group and nonconcomitant group (vaccination with Gardasil 9 separated from vaccination with Menactra and Adacel by one month) with the exception of an increased rate of swelling reported at the injection site for Gardasil 9 in the concomitant group (14.4%) compared to the non-concomitant group (9.4%). The majority of injection site swelling adverse reactions were reported as mild to moderate in intensity.

Reproductive studies performed in female rats at a dose approximately 240 times the human dose on a mg/kg basis revealed no evidence of impaired female fertility or harm to the fetus due to Gardasil 9. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, Gardasil 9 should be used during pregnancy only if clearly needed. It is not known whether Gardasil 9 is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Gardasil 9 is administered to a nursing woman.

The safety and effectiveness of Gardasil 9 have not been established in pediatric patients below nine years of age.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to Gardasil 9.

6.3 Availability

Gardasil 9 will be purchased by each study site according to the institutional practice.

6.4 Agent Distribution

The study site may not dispense study agent until a complete regulatory package, including IRB approval, is provided to DCP and a drug shipment authorization email is received by the site.

6.5 Agent Accountability

Careful records of the inventory and disposition of all agents will be maintained by the pharmacist or designee at each site according to the institutional policy.

6.6 Packaging and Labeling

Not applicable.

6.7 Storage

Gardasil 9 is supplied in single-dose vials and should be stored in a secure location protected from light at temperatures between 2°C and 8°C (36°F and 46°F).

6.8 Registration/Randomization

Participants will be considered registered on the date they sign the assent form and their legal representative(s) sign the approved informed consent document with a member of the study staff. This study does not involve randomization.

6.9 Blinding and Unblinding Methods

Not applicable.

6.10 Agent Destruction/Disposal

Institutional policy will be followed for agent destruction/disposable.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Evaluation/ Procedure	Prestudy Evaluation	Baseline Visit[1]	Months 1-6	Month 6 Visit[4]	Months 7-12	Month 12 Visit[4]	Months 13-18	Month 18 Visit[4]	Months 19-24	Month 24 Visit[4]	Months 24-30	Month 30 Visit[4]	Follow-up[2]
Informed Consent/Assent	X												
Parental/Household Questionnaire	X												
Assess Eligibility	X												
Medical History	X												
Age of Menarche, if applicable	X	X		X		X		X		X		X	
Urine Pregnancy Test[5]	X	X								X		X[7]	
Baseline signs and symptoms	X												
Vital Signs	X	X[6]								X		X[7]	
Weight, Height	X	X[6]				X				X			
Concomitant Medications	X	X		X		X		X		X		X	
Blood Collection		X		X		X		X		X		X	
Priming Vaccine Injection		X											
Booster Injection										X		X[7]	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
Telephone/email/text Contact[3]			X		X		X		X		X		X

[1]Baseline visit should occur within 90 days of enrollment and can be combined with the prestudy evaluation.
[2]Participants will be followed for 2 weeks after completing the last Gardasil 9 injection.
[3]Participants and their legal representative(s) will be contacted once a month to remind them to refrain from non-study HPV vaccination during the study period and also within two weeks prior to each study visit to remind them of their upcoming visit.
[4]Study visits will occur +/- 2 weeks of the scheduled times unless significant scheduling problems arise.
[5]For girls who have started their periods.
[6]Not required, if the baseline visit occurs within one month of the prestudy evaluation
[7]The booster injection is optional at the Month 30 visit. Urine pregnancy test and vital signs are not required at this visit for participants who do not receive the 3rd injection.

7.2 Baseline Testing/Prestudy Evaluation

Participants will undergo a pre-study screening evaluation. The legal representative(s) of the participants will be required to sign the informed consent form and medical records release form. Participants will be asked to sign the assent form. Participants and their legal representative(s) will be interviewed for past medical history (including age of menarche) and concomitant medication use. Participants will be assessed for height, weight, and vital signs (temperature, pulse, and blood pressure). Participants will be evaluated for baseline signs and symptoms. Urine pregnancy test will be performed on participants who have started menstrual periods. The legal represnetative(s) will complete a questionnaire to collect information on the participant's parental education attainment and household income.

Eligible participants and their legal representative(s) will return to the clinic for a baseline visit. This visit may be combined with the prestudy screening evaluation visit. If the baseline visit occurs more than 30 days from the screening visit, participants will be reassessed for weight and vital signs. Adverse events and concomitant medications will be reviewed and age at menarche and urine pregnancy test, if applicable, will be reassessed at the baseline visit unless it occurs on the same day as the screening visit. If the participant is pregnant, she will be considered off-study and not undergo additional study procedures, including vaccination. A blood sample will be collected from the participants and serum separated and stored at -80°C. Participants will be offered topical anesthetic cream to be applied to the blood collection site prior to the collection. Following the blood collection, participants will receive the priming injection of Gardasil 9. Participants should be seated or lying down during vaccine administration. Participants will be required to sit or lie down for 15 minutes after the vaccine injection to help prevent fainting and injuries caused by falls and be observed in the clinic for at least 15 minutes. Topical anesthetic cream may be distributed to participants to apply at home prior to study visits requiring blood draws. This may be done either by giving the cream to the participant's parent/guardian while in the clinic or by mailing the cream to the participant's address.

7.3 Evaluation During Study

Participants and legal representatives will be instructed to record adverse events for two weeks following each injection which will then be mailed back to the study office in a pre-stamped and addressed envelope.

Participants and their legal representatives will return to the clinic at 6, 12, 18, 24, and 30 months after the priming injection of Gardasil 9. These study visits will occur +/- 2 weeks of the scheduled times unless significant scheduling problems arise.

For the months 6, 12, and 18 visits, participants will be assessed for adverse events, concomitant medications, menarche, if applicable. Weight and height will be assessed at the month 12 visit. A blood sample will be collected from the participants at each visit and serum separated and stored at -80°C. Similarly, participants will be offered topical anesthetic cream to be applied to the blood collection site prior to the collection.

For the months 24 and 30 visits, participants will be assessed for vital signs, adverse events, concomitant medications, and menarche and urine pregnancy test, if applicable. If the participant is pregnant, she will be considered off-study and not undergo additional study procedures, including vaccination. Weight and height will be assessed at the month 24 visit. A blood sample will be collected from the participants at each visit and serum separated and stored at -80°C. Similarly, participants will be offered topical anesthetic cream to be applied to the blood collection site prior to the collection. Following the blood collection at the month 24 visit participants will receive the booster injection of Gardasil 9. At the month 30 visit, a 3rd vaccine injection will be offered but is optional. Vital signs and urine pregnancy test are not

required for participants who do not receive the 3rd vaccine injection at the Month 30 visit. Participants should be seated or lying down during vaccine administration. Participants will be required to sit or lie down for 15 minutes after the vaccine injection to help prevent fainting and injuries caused by falls and be observed in the clinic for at least 15 minutes.

Participants and their legal representatives will be contacted monthly and within two weeks prior to each visit using their preferred method of contact to promote participant retention. Participants and their legal representatives will be reminded to refrain from non-study HPV vaccination during the study period. If a subject receives an HPV vaccine booster injection outside the context of the study, that subject will be taken off study. This information will be captured in the source document and on the Concomitant Medication CRF and a comment addressing this will be added to the Agent Interruption CRF.

7.4 Evaluation at Completion of Study

As described in section 7.3, the study ends at the month 30 visit.

7.5 Follow-up Period

Participants will keep a diary of any illness or injury for 2 weeks after the last Gardasil 9 injection and mail the diary back to the study office in a pre-stamped envelope provided by the study office.

In addition, participants and their legal representatives may be contacted in the future if they have consented to allow for the possibility of re-consenting for additional serologic testing after the trial is completed.

7.6 Methods for Clinical Procedures

Not applicable.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

The primary endpoint is the persistence and stability of serologic GMT of HPV16/18 between 6, 12, 18 and 24 months after the prime dose/prior to administration of the second dose.

8.2 Secondary Endpoints

The secondary endpoints include

- Determination of the persistence and stability of serologic GMT of other carcinogenic HPV types 31/33/45/52/58 and non-carcinogenic HPV 6/11 between 6, 12, 18, and 24 months.
- Assessment of safety and reactogenicity to each vaccine dose.

8.3 Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed procedures, adverse event or serious adverse event, received an HPV vaccine outside the context of the study, inadequate agent supply, noncompliance, concomitant medications, and medical contraindication. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. Participants who have received HPV vaccine outside the context of the study will be taken off study,

8.4 Off-Study Criteria

Participants may go 'off-study' for the following reasons: the protocol procedures and any protocol-required follow-up period is completed, adverse event/serious adverse event, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, death, determination of ineligibility (including screen failure), pregnancy, or have received HPV vaccine outside the context of the study.

8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

HPV16 and HPV18 serology will be determined by VLP ELISA assays as previously described [16-18]. This ELISA assay is a standard measure of immunogenicity, measures total levels of HPV16 and 18 specific IgG antibodies, both neutralizing and non-neutralizing, and is amenable for use in large epidemiologic and clinical studies.

Serology of HPV types 6/11/31/33/45/52/58 will be determined using CLIA/ELISA assays when the assays are developed and made available.

9.2 Comparable Methods

The VLP ELISA assays have been used previously to measure HPV16/18 serology in prior HPV vaccine trials [19-22]. We will be able to compare the serology data from this study to the serology data from prior trials.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

HPV16 and HPV18 serology will be analyzed in the HPV Immunology Laboratory of the National Cancer Institute led by Dr. Ligia Pinto.

10.2 Collection and Handling Procedures

Approximately 5 ml of blood will be drawn into a SST or tiger top Vacutainer tube at baseline and at months 6, 12, 18, 24, and 30 visits. The SST tube will be held at room temperature for 30 min and then centrifuged. One hundred (100) µl of serum will be aliquoted into each cryovial, filling as many cryovials as possible, and stored at -80°C. The cryovials will be labeled with study ID, subject ID, and visit date.

10.3 Shipping Instructions

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations. Current shipper and institutional procedures must be followed. Biologic specimens (Category B, UN3373) will be in leak-proof primary and secondary receptacles with puncture

resistant packaging and absorbent material. Shipments are to be preceded with phone contact to the receiving lab to assure the shipment will be met and processed promptly.

Frozen serum cryovials will be shipped in batches overnight on dry ice to DCP Repository Contractor at the Frederick National Laboratory for Cancer Research (Leidos Biomedical Research, Inc.) for centralized storage and distribution for serological measurements.

10.4 Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in §6.2, Pharmaceutical Information, as well as the Investigator Brochure or package insert.

11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRF (paper and/or electronic) including whether or not they are related to study agent.

11.1.2 AE Data Elements:

The following data elements are required for adverse event reporting.

- AE verbatim term
- System Organ Class (SOC)
- Common Terminology Criteria for Adverse Events v4.0 (CTCAE) AE term
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a serious adverse event (SAE)
- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the CTCAE version 4.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each adverse event listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

CTCAE v4.0 general severity guidelines:

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

ADL

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the adverse event is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Fed. Reg. 75, Sept. 29, 2010 defines SAEs as those events, occurring at any dose, which meet any of the following criteria:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions

- A congenital abnormality or birth defect
- Important medical events that may not be immediately life-threatening or result in death or require hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE form found at at http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia.

11.2.2.2 Contact the DCP Medical Monitor by phone within 24 hours of knowledge of the event.

DCP Medical Monitor:
Eva Szabo, MD
Chief, Lung & Upper Aerodigestive Cancer Research Group
Division of Cancer Prevention
National Cancer Institute
9609 Medical Center Drive, Room 5E-102, MSC 9781
Bethesda, MD 20892-9781 (For FedEx, use Rockville, MD 20850)
Telephone: (240) 276-7011
Fax: (240) 276-7848
Email: szaboe@mail.nih.gov

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug

11.2.2.3 The Lead Organization and all Participating Organizations will email written SAE reports to DCP's Regulatory Contractor, CCS Associates, Inc. (CCSA phone: 650-691-4400) safety@ccsainc.com within 48 hours of learning of the event using the fillable PDF SAE Report Form.

11.2.2.4 The DCP Medical Monitor and regulatory staff will determine which SAEs require FDA submission.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE form in the appropriate format. Follow-up information should be sent to DCP as soon as available. SAE related to the study agent will be followed until resolved, or deemed unlikely to further resolved by the Protocol Chair, or until the subject withdraws

consent for further follow-up. SAE unrelated or unlikely to be related to study agent will be followed for at least 30 days after the last dose of study agent.

12. STUDY MONITORING

12.1 Data Management

This study will report clinical data using the OnCore application from Forte Research Systems, Inc., as stated in the Master Data Management Plan. All users of the database will have appropriate education, training and experience to perform assigned tasks. The data collection and management will be done according to the Consortia 2012 DMP.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF) developed from the standard set of DCP Chemoprevention CRF Templates and utilizing NCI-approved Common Data Elements (CDE). The approved CRFs will be used to create the electronic CRF (e-CRF) screens in the OnCore application. Consortia site staff will enter data into the e-CRF for transmission to DCP according to pre-established DCP standards and procedures. Amended CRF will be submitted to the DCP Protocol Information Office for review and approval. Approved changes will be programmed into the OnCore database by the Consortium Data Management staff.

CRF Submission Information:
University of Arizona Early Phase Chemoprevention Consortium Office
Attn: Bonita Weible
1430 E. Fort Lowell, Suite 304
Tucson, AZ 85719
Phone: (520) 318-7178
Fax: (520) 514-6015
Email: UACC-CPRE@UACC.arizona.edu

12.3 Source Documents

Source documentation for this trial will consist of protocol-specific source documents as well as clinical and research laboratory reports. In the event of a Serious Adverse Event, medical records related to the event will be sought for source documentation of the event and its treatment, if any.

12.4 Data and Safety Monitoring Plan

The University of Arizona Cancer Center (UACC) Data and Safety Monitoring Board (DSMB) will provide oversight for subject safety for all UA Consortium clinical trials consistent with the National Institutes of Health Policy for Data and Safety Monitoring dated June 10, 1998; further guidance statement issued by the NIH on June 5, 2000, and the policy for Data and Safety Monitoring by Data and Safety Monitoring Boards. The UACC DSMB meets quarterly.

Regular monthly meetings of the UA Consortium, are used as a forum to review accrual rates, problematic issues relating to accrual and protocol implementation, adverse events occurrence, follow-up, and reporting; submission of all required study reports; and progress and outcomes of laboratory analyses.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

Not applicable.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

This is a single-arm, open-label, non-randomized, phase IIA trial to determine the immunogenicity of a prime and deferred-booster dosing schedule of a nonavalent prophylactic HPV vaccine (GARDASIL 9) among 9-11 year-old girls and boys. The primary endpoint analysis will be evaluating persistence and stability of serologic geometric mean titers (GMT) of HPV16/18 between 6, 12, 18, and 24 months after the prime dose/prior to administration of the second dose. If the HPV 16/18 antibody level at 12/18/24 months is not inferior to the HPV 16/18/24 antibody level at 6/12/18 months at a non-inferiority margin of 0.35 standard deviation, then the serologic GMT is considered as persistent and stable.

13.2 Randomization/Stratification

This is a single-arm, open-label and non-randomized trial so no randomization, stratification or blocking will be performed. Also, no formal interim analysis is planned.

13.3 Accrual and Feasibility

We plan to accrue 143 eligible girls and 57 eligible boys to receive the deferred-booster schedule of the Gardasil 9. With an anticipated attrition rate of 30%, we expect to have at least 100 girls and 39 boys to complete the 30-month visit. We anticipate to enroll 6-8 participants/per month for each study site and estimate that it will take approximately 12-17 months to complete accrual.

13.4 Primary Objective, Endpoint(s), Analysis Plan

The primary objective of this study is to determine the persistence and stability of serologic geometric mean titer (GMT) of HPV 16/18 between 6, 12, 18, and 24 months after the prime dose and prior to the

administration of the second dose. The primary endpoints are the HPV 16/18 antibody levels at 6, 12 18, and 24 months. To address the primary objective, the primary endpoint analysis will be evaluating persistence and stability of serologic geometric mean titers (GMT) of HPV16/18 between 6, 12, 18, and 24 months after the prime dose/prior to administration of the second dose. We first propose to perform a one-sided paired t test to compare the difference in the mean of the log-transformed antibody levels between 6 and 12 months, between12 and 18 months, and between 18 and 24 months respectively, to evaluate whether the GMT at 12/18/24 months, respectively, is not inferior to the GMT at 6/12/18 months. Comparing the difference in the mean of the log-transformed antibody levels is equivalent to comparing the logarithm of the ratio of GMTs since GMT is equal to the exponentiation of log-transformed mean. Bonferroni correction will be used to correct for multiple comparisons (6 vs.12, 12 vs. 18 and 18 vs. 24).

The protocol was originally designed to assess the serologic response in girls. Amendment 4 includes the addition of a cohort of boys. Due to limits in the study completion timeline and available study budget, a smaller number of boys than girls will be included in the study to generate pilot data on the serologic response in boys. Boys have been shown to mount a higher serologic response than girls. Therefore, we expect boys and girls to have different responses to the vaccine and will perform the primary analyses for girls and boys separately. For girls, with a sample size of 100 and an overall significance level of 5% (based on Bonferroni correction, i.e. a 1.67% significance level for each test), there will be at least 90% power to detect a non-inferiority margin no greater than 0.35 standard deviations [23]. For boys, with a sample size of 39 and an overall significance level of 5%, there will be at least 80% power to detect a non-inferiority margin no greater than 0.50 standard deviations. In addition, similar to the analysis performed by Safaeian et al. [13], we will also evaluate the stability by categorizing the changes in antibody level from 6 months to 12 months. Specifically, a participant's antibody level at 12 months either remains within two-fold of the level at 6 months (considered as stable) or decreases/increases more than two-fold of the level at 6 months (same for the changes from 12 months to 18 months and from 18 months to 24 months). Percentage of participants whose type-specific antibody levels decrease, increase, or remain stable between the 6 and 12 month study visits, between the 12 and 18 month study visits and between the18 month and 24 month study visits will be reported along with the associated 95% confidence interval. For girls, a sample size of 100 will produce a two-sided 95% confidence interval with a width ≤ 0.203 based on the exact method approach. For boys, a sample size of 39 will produce a two-sided 95% confidence interval with a width ≤ 0.328 based on the exact method approach.

13.5 Secondary Objectives, Endpoints, Analysis Plans

The secondary objectives include to determine the persistence and stability of serologic GMT of HPV types 6/11/31/33/45/52/58 between 6, 12, 18, and 24 months after prime dose and prior to the administration of the second dose and to assess safety and reactogenicity to each vaccine dose. The secondary endpoints are the antibody levels at 6, 12 18, and 24 months for each HPV type. Similarly to the primary endpoint analysis, for evaluating persistence and stability of serologic GMT of each HPV type we propose to perform a one-sided paired t test to evaluate the difference in the mean of log-transformed antibody level between 6 and 12 months, between 12 and 18 months and between 18 and 24 months, respectively, to evaluate whether the GMT at 12/18/24 months is not inferior to the GMT at 6/12/18 months. In addition, percentage of participants whose type-specific antibody levels decrease, increase, or remain stable between the 6 and 12 month study visits, between the 12 and 18 month study visits and between the 18 and 24 month study visits will be reported along with the associated 95% confidence interval. A linear mixed effects model with BMI, time and the interaction between BMI and time as the covariates will be performed on antibody level data measured at 6, 12, 18, and 24 months to evaluate whether BMI affects the changes in each specific antibody level.

Similar to the primary analyses, we will perform all of the secondary and exploratory analyses separately for girls and boys. In addition, for all of the secondary and exploratory analyses, adjustment for multiple comparisons will not be performed. However, the number of comparisons will be reported and we will also cautiously interpret the findings. For both primary and secondary endpoints, if the normality assumption is violated, potential transformation will be sought or nonparametric methods such as signed rank test will be performed.

We will try to reduce the fraction of participants with missing outcomes as much as possible. The covariates (e.g. BMI, BSA, and sociodemographics) that are predictive of missing-ness for each outcome at each visit (i.e. 6, 12, 18 and 24 months) will be identified through use of logistic regression for each missing indicator and then incorporated into multiple imputation procedures to handle missing data while performing the statistical analysis for both primary and secondary endpoints.

13.6 Reporting and Exclusions

If a participant has received all doses of the vaccine, he/she will be considered compliant (as defined in 5.7) for statistical analysis. Participants who are considered off-agent (see section 8.3) will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. As mentioned earlier in the primary and secondary analyses, if a subject has missing data on some primary or secondary endpoints, multiple imputation techniques will be used to handle missing data.

13.7 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of vaccine. Descriptive statistics of the type and frequency of all adverse events will be generated, including 95% confidence intervals.

13.8 Evaluation of Response

All subjects with endpoint data will be assessed for response, based on the endpoints described above in Sections 13.4 and 13.5.

Sub-analyses may be performed on the subsets of participants, excluding those for whom major protocol deviations have been identified (e.g., early discontinuation of study, major protocol violations, etc.). However, sub-analyses may not serve as the basis for drawing conclusions concerning efficacy, and the reasons for excluding participants from the analysis should be clearly reported.

13.9 Interim Analysis

No formal interim statistical analyses are planned for this Phase IIA trial. Accrual, data collection, and any adverse events will be monitored on a regular basis.

13.10 Ancillary Studies

None.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents

14.2.1 Signed and dated current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in "Protection of Human Research Subjects" for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.6 Signed Investigator's Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the NCI DCP CPC CIRB (referred to as CIRB) . Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the CIRB prior to implementation.

14.4 Informed Consent

All potential study participants' legal representatives will be given a copy of the CIRB-approved Informed Consent to review. The participant will be given a copy of the CIRB-approved assent form. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant's legal representative agrees to allow him/her to participate in the study, the representative will be asked to sign and date the Informed Consent document. The participant will be asked to sign the assent form. The study agent(s) will not be released to a participant whose legal representative has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Prior to study initiation, the informed consent document and assent document will be reviewed and approved by the Consortium Lead Organization (CLO), NCI, DCP, and the CIRB. Each CLO and Participating organization at which the protocol will be implemented will also submit the study for Local IRB notification per site SOPs. Any subsequent changes to the informed consent/assent will be submitted by the Consortium Lead Organization to NCI DCP for approval and then to the CIRB, and then submitted to each organization's IRB for notification prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to the DCP Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates
2001 Gateway Place
Suite 350 West
San Jose, CA 95110
Phone: 650-691-4400
Fax: 650-691-4410

E-mail Submissions:
regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to the DCP Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

Study procedures performed during study visits will be covered by the study budget. Research tests will not be billed to the subject. Subjects may incur minimal out-of-pocket expenses for transportation but will not be charged for study agent or any study-related activities. Subjects will receive monetary compensation which they may use at their discretion for out of pocket costs such as transportation. For retention of participants whose families have moved further away from the study clinic since original consent, additional travel compensation will be provided for families who have to travel more than 100 miles round trip back to clinic. If injury occurs, medical care will be provided and charged to the subject's insurer.

REFERENCES

1. Munoz, N., F.X. Bosch, S. de Sanjose, R. Herrero, X. Castellsague, K.V. Shah, P.J. Snijders, C.J. Meijer, and G. International Agency for Research on Cancer Multicenter Cervical Cancer Study,

Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med, 2003. **348**(6): p. 518-27.
2. Walboomers, J.M., M.V. Jacobs, M.M. Manos, F.X. Bosch, J.A. Kummer, K.V. Shah, P.J. Snijders, J. Peto, C.J. Meijer, and N. Munoz, *Human papillomavirus is a necessary cause of invasive cervical cancer worldwide.* J Pathol, 1999. **189**(1): p. 12-9.
3. de Sanjose, S., W.G. Quint, L. Alemany, D.T. Geraets, J.E. Klaustermeier, B. Lloveras, S. Tous, A. Felix, L.E. Bravo, H.R. Shin, C.S. Vallejos, P.A. de Ruiz, M.A. Lima, N. Guimera, O. Clavero, M. Alejo, A. Llombart-Bosch, C. Cheng-Yang, S.A. Tatti, E. Kasamatsu, E. Iljazovic, M. Odida, R. Prado, M. Seoud, M. Grce, A. Usubutun, A. Jain, G.A. Suarez, L.E. Lombardi, A. Banjo, C. Menendez, E.J. Domingo, J. Velasco, A. Nessa, S.C. Chichareon, Y.L. Qiao, E. Lerma, S.M. Garland, T. Sasagawa, A. Ferrera, D. Hammouda, L. Mariani, A. Pelayo, I. Steiner, E. Oliva, C.J. Meijer, W.F. Al-Jassar, E. Cruz, T.C. Wright, A. Puras, C.L. Llave, M. Tzardi, T. Agorastos, V. Garcia-Barriola, C. Clavel, J. Ordi, M. Andujar, X. Castellsague, G.I. Sanchez, A.M. Nowakowski, J. Bornstein, N. Munoz, F.X. Bosch, S. Retrospective International, and H.P.V.T.T.S. Group, *Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study.* Lancet Oncol, 2010. **11**(11): p. 1048-56.
4. Maniar, K.P. and R. Nayar, *HPV-related squamous neoplasia of the lower anogenital tract: an update and review of recent guidelines.* Adv Anat Pathol, 2014. **21**(5): p. 341-58.
5. Woods, R., Sr., E.M. O'Regan, S. Kennedy, C. Martin, J.J. O'Leary, and C. Timon, *Role of human papillomavirus in oropharyngeal squamous cell carcinoma: A review.* World J Clin Cases, 2014. **2**(6): p. 172-93.
6. Lacey, C.J., C.M. Lowndes, and K.V. Shah, *Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease.* Vaccine, 2006. **24 Suppl 3**: p. S3/35-41.
7. Agosti, J.M. and S.J. Goldie, *Introducing HPV vaccine in developing countries--key challenges and issues.* N Engl J Med, 2007. **356**(19): p. 1908-10.
8. Stokley, S., J. Jeyarajah, D. Yankey, M. Cano, J. Gee, J. Roark, R.C. Curtis, L. Markowitz, N.C.f.I. Immunization Services Division, C.D.C. Respiratory Diseases, C. Centers for Disease, and Prevention, *Human papillomavirus vaccination coverage among adolescents, 2007-2013, and postlicensure vaccine safety monitoring, 2006-2014--United States.* MMWR Morb Mortal Wkly Rep, 2014. **63**(29): p. 620-4.
9. Romanowski, B., T.F. Schwarz, L.M. Ferguson, M. Ferguson, K. Peters, M. Dionne, K. Schulze, B. Ramjattan, P. Hillemanns, U. Behre, P. Suryakiran, F. Thomas, and F. Struyf, *Immune response to the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination: results from a randomized study.* Hum Vaccin Immunother, 2014. **10**(5): p. 1155-65.
10. Dobson, S.R., S. McNeil, M. Dionne, M. Dawar, G. Ogilvie, M. Krajden, C. Sauvageau, D.W. Scheifele, T.R. Kollmann, S.A. Halperin, J.M. Langley, J.A. Bettinger, J. Singer, D. Money, D. Miller, M. Naus, F. Marra, and E. Young, *Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial.* Jama, 2013. **309**(17): p. 1793-802.
11. Schiller, J.T. and D.R. Lowy, *Understanding and learning from the success of prophylactic human papillomavirus vaccines.* Nat Rev Microbiol, 2012. **10**(10): p. 681-92.
12. Kreimer, A.R., A.C. Rodriguez, A. Hildesheim, R. Herrero, C. Porras, M. Schiffman, P. Gonzalez, D. Solomon, S. Jimenez, J.T. Schiller, D.R. Lowy, W. Quint, M.E. Sherman, J. Schussler, and S. Wacholder, *Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine.* J Natl Cancer Inst, 2011. **103**(19): p. 1444-51.
13. Safaeian, M., C. Porras, Y. Pan, A. Kreimer, J.T. Schiller, P. Gonzalez, D.R. Lowy, S. Wacholder, M. Schiffman, A.C. Rodriguez, R. Herrero, T. Kemp, G. Shelton, W. Quint, L.J. van Doorn, A. Hildesheim, and L.A. Pinto, *Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial.* Cancer Prev Res (Phila), 2013. **6**(11): p. 1242-50.
14. Sankaranarayanan, R., P.R. Prabhu, M. Pawlita, T. Gheit, N. Bhatla, R. Muwonge, B.M. Nene,

P.O. Esmy, S. Joshi, U.R. Poli, P. Jivarajani, Y. Verma, E. Zomawia, M. Siddiqi, S.S. Shastri, K. Jayant, S.G. Malvi, E. Lucas, A. Michel, J. Butt, J.M. Vijayamma, S. Sankaran, T.P. Kannan, R. Varghese, U. Divate, S. Thomas, G. Joshi, M. Willhauck-Fleckenstein, T. Waterboer, M. Muller, P. Sehr, S. Hingmire, A. Kriplani, G. Mishra, S. Pimple, R. Jadhav, C. Sauvaget, M. Tommasino, M.R. Pillai, and H.P.V.V.S.G. Indian, *Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study.* Lancet Oncol, 2016. **17**(1): p. 67-77.

15. Smolen, K.K., L. Gelinas, L. Franzen, S. Dobson, M. Dawar, G. Ogilvie, M. Krajden, E.S. Fortuno, 3rd, and T.R. Kollmann, *Age of recipient and number of doses differentially impact human B and T cell immune memory responses to HPV vaccination.* Vaccine, 2012. **30**(24): p. 3572-9.
16. Dauner, J.G., Y. Pan, A. Hildesheim, C. Harro, and L.A. Pinto, *Characterization of the HPV-specific memory B cell and systemic antibody responses in women receiving an unadjuvanted HPV16 L1 VLP vaccine.* Vaccine, 2010. **28**(33): p. 5407-13.
17. Dauner, J.G., Y. Pan, A. Hildesheim, T.J. Kemp, C. Porras, and L.A. Pinto, *Development and application of a GuHCl-modified ELISA to measure the avidity of anti-HPV L1 VLP antibodies in vaccinated individuals.* Mol Cell Probes, 2012. **26**(2): p. 73-80.
18. Dessy, F.J., S.L. Giannini, C.A. Bougelet, T.J. Kemp, M.P. David, S.M. Poncelet, L.A. Pinto, and M.A. Wettendorff, *Correlation between direct ELISA, single epitope-based inhibition ELISA and pseudovirion-based neutralization assay for measuring anti-HPV-16 and anti-HPV-18 antibody response after vaccination with the AS04-adjuvanted HPV-16/18 cervical cancer vaccine.* Hum Vaccin, 2008. **4**(6): p. 425-34.
19. Safaeian, M., T.J. Kemp, D.Y. Pan, C. Porras, A.C. Rodriguez, M. Schiffman, B. Cortes, H. Katki, S. Wacholder, J.T. Schiller, P. Gonzalez, K. Penrose, D.R. Lowy, W. Quint, L.J. van Doorn, R. Herrero, A. Hildesheim, and L.A. Pinto, *Cross-protective vaccine efficacy of the bivalent HPV vaccine against HPV31 is associated with humoral immune responses: results from the Costa Rica Vaccine Trial.* Hum Vaccin Immunother, 2013. **9**(7): p. 1399-406.
20. Safaeian, M., A. Ghosh, C. Porras, S.W. Lin, A.C. Rodriguez, M. Schiffman, S. Wacholder, T. Kemp, P. Gonzalez, N. Wentzensen, M. Esser, A. Meuree, K. Matys, W. Quint, L.J. van Doorn, M.E. Sherman, R. Herrero, L.A. Pinto, and A. Hildesheim, *Direct comparison of HPV16 serological assays used to define HPV-naive women in HPV vaccine trials.* Cancer Epidemiol Biomarkers Prev, 2012. **21**(9): p. 1547-54.
21. LaMontagne, D.S., E. Mugisha, Y. Pan, E. Kumakech, A. Ssemaganda, T.J. Kemp, J. Cover, L.A. Pinto, and M. Safaeian, *Immunogenicity of bivalent HPV vaccine among partially vaccinated young adolescent girls in Uganda.* Vaccine, 2014. **32**(47): p. 6303-11.
22. Kemp, T.J., M. Safaeian, A. Hildesheim, Y. Pan, K.J. Penrose, C. Porras, J.T. Schiller, D.R. Lowy, R. Herrero, and L.A. Pinto, *Kinetic and HPV infection effects on cross-type neutralizing antibody and avidity responses induced by Cervarix((R)).* Vaccine, 2012. **31**(1): p. 165-70.
23. Chow, S.C., J. Shao, and H. Wang, *Sample Size Calculation in Clinical Research*. 2003, New York: Marcel Dekker.

PARENTAL CONSENT FORM

Study Title for Study Participants:
Study of alternative HPV vaccine schedule in young girls and boys

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
Protocol UAZ2015-05-01 A prospective, single-arm, open-label, non-randomized, phase IIA trial of a nonavalent prophylactic HPV vaccine to assess immunogenicity of a prime and deferred-booster dosing schedule among 9-11 year-old girls and boys.

Why is this study being done?

HPV is short for human papillomavirus, a common virus which usually causes infections that last only a few months, but sometimes can last a long time and cause cancers of the cervix, vagina, vulva, anus or oropharynx over many years among adults. There are three HPV vaccines approved for use in the U.S., Cervarix, Gardasil, and Gardasil 9, for females and males 9 through 26 years of age to protect against HPV infection and the health problems that HPV infection can cause. Gardasil 9 is the newest approved HPV vaccine that offers the broadest protection. It protects against 9 types of HPV. HPV vaccines have been given as a series of three injections over 6 months. In October 2016, a 2-injection schedule with the second injection given 6-12 months after the first injection was recommended for children ages 9 through 14 years.

The purpose of this study is to test if one injection of Gardasil 9 will produce long-term immune response. Previous research suggests that healthy preteen girls may not need all three injections of Cervarix or Gardasil to have protection against HPV infection. This means that even one or two doses in total may be protective and that delays in receiving second and third doses may not be risky. Previous research also suggests that one dose of Cervarix or Gardasil produces strong immune response for more than 24 months in healthy preteen girls. Since boys tend to generate a stronger immune response than girls, it is anticipated that these findings among girls will also be applicable to boys in the same age range. The study will recruit a total of 143 girls and 57 boys to receive the 2nd injection of Gardasil 9 at 24 months and an optional 3rd injection at 30 months after the first injection. The 3rd injection is optional because after this study began, the recommendation for the HPV vaccination was changed from three to two injections for children who received their first injection before the age of 15 years. You may decide whether you want your child to receive two injections or three. Receiving the 2nd and 3rd injections of Gardasil 9 at 24 and 30 months after the first injection is considered investigational and is not standard of care. This study may help researchers learn whether one injection of Gardasil 9 is sufficient to protect against HPV to help make HPV vaccination more practical and cost-effective in the future.

What is the usual approach to HPV vaccination?

HPV vaccines have been given as a series of three injections over 6 months. In 2016, a 2-injection schedule with the second injection given 6-12 months after the first injection was recommended for children ages 9 through 14 years. Receiving 3 injections over 6 months or 2 injections with the second injection give 6-12 month after the first injection are considered the standard schedules.

What are my child's other choices if he/she does not take part in this study?

If your child decides not to take part in this study he/she may:

- Choose to have the usual approach described above.
- Choose to take part in a different study, if one is available.
- Choose to do nothing

How long will my child be in this study?

Your child will be in the study for about 30 months (two and a half years).

What extra tests and procedures will my child have if he/she takes part in this study?

Your child will receive two or three HPV injections (first injection baseline, second at 24 months, and an optional injection 30 months after the first injection) and have a blood sample collected six times during study participation to measure his/her immune response.

Before your child begins the study:

He/she will need to have the following extra tests, and/or procedures in a **Screening Visit** to find out if he/she can be in the study:

- The study staff will discuss this consent form and answer any questions you and your child may have. Once the consent is signed, the following procedures will be done.
- Height, weight, and vital signs (blood pressure, pulse and temperature).
- A review of your child's medical history and current medications he/she may be taking. This will include menstrual history for girls.
- Urine pregnancy test for girls who have started their periods. If your daughter's urine pregnancy test shows that she might be pregnant, she will be told in private and her parents or guardians may also be told, depending on the legal requirements. If this happens, she will not be eligible for the study.
- You will be asked to complete a survey on your child's parental education and household income.

Baseline Visit -Start of study (may be combined with screening visit)
Tests and procedures include (some may not take place, if this visit occurs within 1 month from the screening visit):

- Height, weight, and vital signs (blood pressure, pulse and temperature).
- Urine pregnancy test if your daughter has started her periods. If she is pregnant, she will not receive the vaccine and will not continue her study participation.
- Your child will be asked about changes to medications and any adverse events that may have occurred since the prior visit.
- Collection of one teaspoon of blood for research samples.
- Your child will be given the first injection of Gardasil 9.
- Your child will be given a symptom diary to record any illness or injury that may occur for two weeks following the injection. This will be mailed back to the study office in a pre-stamped envelope. After the diary is returned, the study staff will contact you to clarify any of the diary entries, if necessary.

Months 6, 12, 18 Visits:

- Your child will be asked about changes to medications and any adverse events that may have occurred since the prior visit.

- Your daughter will be asked whether she has begun having menstrual periods yet.
- Weight and height at the Month 12 visit.
- Collection of one teaspoon of blood for research samples.

Months 24 and 30 Visit:

- Vital signs.
- Urine pregnancy test if your daughter has started her periods. If she is pregnant, she will not receive the vaccine and will not continue participation in the study.
- A review of your child's current medications and any adverse events that may have occurred since the prior visit.
- Your daughter will be asked whether she has begun having menstrual periods yet.
- Weight and height at the Month 24 visit.
- Collection of one teaspoon of blood for research samples.
- Your child will be given the booster injection of Gardasil 9 at 24 months following the first injection. A 3rd injection of Gardasil 9 will be offered at 30 months but is optional. If your child does not receive the 3rd injection at the Month 30 visit, the pregnancy test and collection of vital signs will not be required.

Someone from the research team will contact you once a month and within two weeks prior to each study visit. You will be reminded that your child should not receive HPV vaccination from any provider outside the study during study participation. Your child will keep a diary of any illness or injury for two weeks after each injection and mail the diary back to the study office in a pre-stamped envelope provided by the study office. After the diary is returned, the study staff will contact you to clarify any of the diary entries, if necessary, and to ask about your child's health status.

What possible risks can my child expect from taking part in this study?

Receiving the booster injections later than the standard schedules may pose some risk due to incomplete protection. It is not known if a single dose (prime injection) of Gardasil 9 will provide the same protection against HPV infection as the standard schedules. However, it is less likely that girls and boys in the age groups selected for this study (9-11 years of age at baseline) may be initiating or have initiated sexual activity that could put them at risk for HPV infection. However, whether given according to the standard schedules or alternative schedule, it is unknown whether Gardasil 9 provides complete long lasting protection from HPV infection. It is recommended that all vaccinated individuals follow guidelines for cervical cancer screening.

If your child chooses to take part in this study, there is a risk that she may:

- Spend more time in the hospital or doctor’s office than usual.
- Be asked sensitive or private questions which he/she normally does not discuss. There is a risk someone could get access to the personal information in your child's medical records or other information researchers have kept about your child. Someone might be able to trace this information back to your child. The researchers believe the chance that someone will identify your child is very small, but the risk may change in the future as people come up with new ways of tracing information.

There is also a risk that your child could have side effects.
Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away. Some side effects may be serious and may even result in death.

Here are important points about how you, your child and the study doctor can make side effects less of a problem:

- Tell the study doctor if your child notices or feels anything different so they can see if your child is having a side effect.
- The study doctor may be able to treat some side effects.

The tables below show the most common side effects that we know about Gardasil 9, some of which may be serious. These were reported in the clinical trials that included over 15,000 females and males. There might be other side effects that we do not yet know about. If important new side effects are found, the study doctor will discuss these with you and your child.

COMMON, SOME MAY BE SERIOUS In 100 people receiving, more than 20 may have:
• Pain, swelling and redness at the site of vaccine injection

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving, from 4 to 20 may have:
• Swelling with maximum size greater than 2 inches at the site of vaccine injection • Fever ≥100°F • Headache

RARE, SOME MAY BE SERIOUS In 100 people receiving, 3 or fewer may have:
• At the site of vaccine injection, pain that interferes with usual activity, bruising, skin changes, and redness with maximum size greater than 2 inches • Fever ≥102°F • Nausea • Dizziness • Diarrhea • Pain in the mouth and throat • Muscle pain • Pain in belly • Infection of the upper respiratory tract (nose, sinuses, throat, wind pipe, and voice box) • Swelling and redness of the tonsils, which may be caused by infection • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Sudden worsening of asthma which may cause difficulty breathing to the point of exhaustion, collapse, and not responding to the usual treatments

POSSIBLE, SOME MAY BE SERIOUS The frequency of some individual side effects has not yet been determined:
• Fainting • Damage to the body by own immune system

The risks of having blood drawn are low but include bruising, soreness, infection, and fainting.

In about 10% of the cases there is a small amount of bleeding under the skin which will produce a bruise. The risk of infection is less than 1 in 1,000. A local (skin) numbing gel may be used prior to the blood draw to lessen discomfort.

What possible benefits can my child expect from taking part in this study?

Your child will receive two or three injections of Gardasil 9 which may help protect him/her from HPV infection. However, we do not know whether your child will have a strong enough and long lasting immune response before they complete all injections. This study may help researchers learn whether one injection of Gardasil 9 is sufficient to protect against HPV to help make HPV vaccination more practical and cost-effective in the future.

Can my child stop taking part in this study?

Yes. Your child can decide to stop at any time. If your child decides to stop for any reason, it is important to let the study doctor know as soon as possible. If your child stops, you and your child can decide whether or not to let the study doctor continue to provide his/her medical information to the organization running the study.

The study doctor will tell you and your child about any new information or changes in the study that could affect your child's health or willingness to continue in the study.

The study doctor may take your child out of the study:

- If your child's health changes.
- If the study is no longer in his/her best interest.
- If your child receives an injection of the HPV vaccine from another source outside of the study.
- If new information becomes available.
- If your child does not follow the study rules.
- If the study is stopped early for any reason by the sponsor, IRB or FDA.

What are my child's rights in this study?

Taking part in this study is your child's choice. No matter what decision you and your child make, and even if your child's decision changes, there will be no penalty. Your child will not lose medical care or any legal rights.

For questions about your child's rights while in this study, call the _____ *<insert name of local IRB and phone number>***. You may also contact the IRB at** _____ *<insert name of local IRB's website or alternate contact information, if applicable>***.**

What are the costs of taking part in this study?

The Gardasil 9 vaccine will be supplied at no charge while your child takes part in this study. The cost of study-specific exams, tests, and any other procedures will be paid for by the study.

You will receive $30 per study visit, up to $210 during the course of the study, for your time and travel. If you have moved further away from the study clinic since original consent and are required to travel over 100 miles round trip to attend the study visit, you will receive extra

reimbursement. The extra reimbursement is based on the federal or state mileage reimbursement rate allowed by the study institution, up to $100 per study visit.

Your child will receive up to $450 for participation. Your child will receive $25 for the screening visit; $50 each for the baseline visit and month 6 visit; $75 each for the month 12, 18, 24 visits; $100 for the month 30 visit. The compensation for you and your child will be prorated if your child is not able to come to all the visits or complete the study.

What happens if my child is injured or hurt because he/she took part in this study?

If your child has been injured or hurt as a result of taking part in the study, it is important that you tell the study doctor immediately. Your child will get medical treatment if he/she is injured or hurt as a result of taking part in this study.

The study sponsors will not offer to pay for medical treatment for injury. Your child's insurance company may not be willing to pay for study-related injury. If your child has no insurance coverage, you would be responsible for any costs. Even though your child is in a study, he/she keeps all of his/her legal rights to receive payment for injury caused by medical errors.

Who will see my child's medical information?

Your child's privacy is very important to us and we will make every effort to protect it. This information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, we will do our best to make sure that any information that is released will not be able to identify your child. Some of your child's health information, and/or information about your child's specimens from this study will be kept in a central database for research. Your child's name or contact information will not be put in the database.

There are organizations that may inspect your child's records. These organizations are required to make sure your child's information is kept private. Some of these organizations are:

- The study sponsor, the National Cancer Institute (NCI) and NCI agents and partners, and the study Coordinating Center.
- _____ < *insert local institution name*> study team including the study doctor and study personnel.
- _____ <*insert name of other institution who may have access to PHI*>
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285.
- Representatives from the Food and Drug Administration.

Where can I get more information?

The National Cancer Institute will obtain information from this clinical trial under data collection authority Title 42 U.S.C. 285.

You may visit the NCI website at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service

to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, if required by US law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

Who can answer my questions about this study?
You and your child can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor < _____ <*name of local study PI> at <*_____ *insert PI's phone number>*

This section is about optional studies you and your child can choose to take part in.

After the study is complete, it may be important to test the long-term immune response of your child. The researchers ask your permission to contact you and your child in the future for the possibility of re-consenting for additional testing of the long-term immune response.
In addition, there may be some blood serum remaining once the study is complete. The researchers ask your permission to store and use your child's remaining samples and health information for future medical research. These samples may be stored indefinitely.

- **How will information about your child be kept private?**
  When your child's sample(s) and information are sent to the researchers, no information identifying your child (such as name or social security number) will be sent. Samples will be identified by a unique study code only. Researchers receiving the sample and information will not know who your child is. They must also sign an agreement that they will not try to find out who your child is. Information that identifies him/her will not be given to anyone, unless required by law. If research results are published, his/her name and other personal information will not be used.

- **What are the possible benefits?**
  Your child will not benefit from taking part in the option. The researchers, using the samples and information from your child and others, might make discoveries that could help people in the future.

- **Are there any costs or payments?**
  There are no costs to your child or your child's insurance. If any of the research leads to new tests, drugs, or other commercial products, your child will not share in any profits.

- **What if I change my mind?**
  If you decide you no longer want your child's samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

Please specify your consent to the options below. Consent to the options is entirely voluntary and may be withdrawn at any time. If you have any questions, please talk to the study staff or the

investigator.

The researchers may contact me and my child in the future for the possibility of re-consenting for additional testing. Yes No
(circle one)

My child's blood serum may be kept for use in future medical research. Yes No
(circle one)

This is the end of the section about optional studies.

Please indicate below if you consent for your child to receive the optional 3rd Gardasil vaccine injection 30 months following the 1st injection. The 3rd injection is optional because after this study began, the recommendation from the United States Centers for Disease Control and Prevention (CDC) for the HPV vaccination was changed from three to two injections for children starting their first injection before the 15th birthday. Since your child received his/her first injection before turning 15 years old, he/she is not required to receive the 3rd injection based on the new recommendations. Because this study had initially planned to provide three Gardasil injections to your child, the study team will continue to offer the 3rd injection free of charge. If you have questions, please discuss this with the study staff or your child's physician.

My child may receive the 3rd Gardasil vaccine injection 30 months following the 1st injection.
Yes No
(circle one)

My Signature Agreeing to Allow My Child to Take Part in the Study

I have read this consent form or had it read to me and am aware that I am being asked to allow my child to participate in a research study. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to allow my child to take part in this study.

_____
Name of Child (printed)

_____ _____
Name of Parent/Guardian (printed) **Signature of Parent/Guardian**

_____ _____
Relationship to participant **Date**

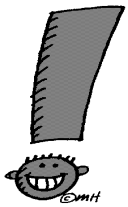
_____ _____
Signature of person obtaining consent **Date**

MINOR'S ASSENT FORM

What is a research study?

Research studies help us learn new things. We can test new ideas. First, we ask a question. Then we try to find the answer. This paper talks about our research and the choice that you have to take part in it. We want you to ask us any questions that you have. You can ask questions any time.

Important things to know…



- You get to decide if you want to take part.
- You can say 'No' or you can say 'Yes'.
- No one will be upset if you say 'No'.
- If you say 'Yes', you can always say 'No' later.
- You can say 'No' at anytime.
- We would still take good care of you no matter what you decide.
- Your grades and treatment in school will be the same no matter what you decide.

Why are we doing this research?

Either two or three shots of the HPV vaccine are given to girls and boys like you over a period of 6 to 12 months (standard schedules) to protect against HPV, a common virus. We are doing this research to test whether one shot of the HPV vaccine can enable the body to develop the same level of defense as two or three shots. You will be getting the 2nd shot and maybe a 3rd shot later than the standard schedules.

What would happen if I join this research?

If you decide to be in the research, we would ask you to do the following:

- Come to the clinic for up to 7 study visits over two and a half years. You will have measurements taken of your height, weight, blood pressure, pulse and temperature at some of the visits. You will be asked questions about any medicine you take or any illnesses you have had in the past.
- Tell us if you have started having periods yet. Girls who have started their periods will need to have a urine pregnancy test before receiving the vaccine. If a girl's urine test shows that she might be pregnant or another test shows something a doctor needs to see, she will be told in private and her parents may also be told. If she is pregnant, she will not receive the vaccine and will not continue to be in the study.
- You will receive a needle stick to collect a blood sample from your arm six times during the study.
- You will be given a shot with the HPV vaccine into your upper arm either two or three times during the study.

- You will be asked to keep a diary to record any illness or injury that may happen for 2 weeks after each injection.

Could bad things happen if I join this research?

The needle stick to test your blood and to give the vaccine can hurt. Sometimes the needle can leave a bruise on the skin. We can put a cream on your skin before we take blood. This cream would help so it won't hurt as much. The vaccine shot can hurt and you may develop some reactions to the injection. Also, the questions you will be asked might make you uncomfortable or may be hard to answer.

Could the research help me?

The vaccine you receive may help protect you from getting serious diseases including certain types of cancer in the future. However, the vaccine may not work perfectly, so in the future, you should ask your doctors about testing that can protect you from getting these diseases.

Will I be paid for the research?

You will get $25 for the first study visit, $50 for each of the 2nd and 3rd visits, $75 for each of the three visits in the second year, and $100 for the last visit. If you finish the study you will get a total of $450.

What happens after the research is over?

Your parent or guardian may choose to allow the researchers to contact you in the future for additional testing or to store your blood for future research.

Is there anything else?

Do you have any questions? If you do, <insert name of research staff> _____ will be happy to answer your questions. If you want to be part of this study, please print and sign you name below.

_____

Child's Name (print)

_____ _____

Child's Signature **Date**

_____ _____

Signature of person(s) requesting assent **Date**