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Human Papillomavirus (HPV) Vaccine in Cancer Survivors:
Cross Sectional Survey and Phase II Open-Label Vaccine Trial

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ABSTRACT

Advances in treatment for childhood cancer over the past five decades have resulted in a rapidly growing population of survivors.[1] A substantial number of these survivors are adolescents and young adults – an age group that is at the highest risk for sexually transmitted infection (STI).[2,3] Human papillomavirus (HPV) is the most common STI in the U.S. today,[2] with prevalence rates in sexually active young individuals ranging from 44.8% in females[4] to 51.2% in males[5]. Persistent infection with oncogenic strains of HPV (e.g., types 16 and 18) is strongly associated with the development of dysplasia and cancers affecting the genital tract and oropharyngeal mucosa.[6-11] Non-oncogenic HPV types (primarily 6 and 11) are associated with genital warts, low-grade dysplasia and recurrent respiratory papillomatosis.[4,8,12,13] Immunosuppression increases HPV persistence and risk of invasive HPV-related malignancies.[6,14-18] Systemic treatment for cancer (chemotherapy, radiation, hematopoietic cell transplantation [HCT]) may result in prolonged immunosuppression,[19-21] placing cancer survivors at higher risk for HPV-related morbidity.[22-26] In fact, cervical cancer risk is increased 13-fold and oral cancer risk 17-fold in HCT survivors compared with the age- and sex-matched general population.[23]

The quadrivalent HPV (qHPV) vaccine (HPV-6, -11, -16, -18; Gardasil®; Merck Research Laboratories)[27] was approved by the U.S. Food and Drug Administration (FDA) for females (in 2006) and for males (in 2009) 9 to 26 years of age, and has been used since that time for prevention of HPV-related cancers and precancerous lesions in both genders.[28] The safety, tolerability, immunogenicity, and efficacy of the qHPV vaccine have been demonstrated in healthy young individuals;[29-32] the vaccine confers protection against HPV types 6, 11, 16, and 18, which together account for more than 70% of all new cervical cancers[33] and 90% of genital warts.[34]

The nonavalent form of the HPV vaccine (9vHPV; Gardasil ®9) extends protection beyond that offered by the qHPV vaccine through inclusion of five additional oncogenic types (31, 33, 45, 52, and 58). A trial of 14,215 females between 16 and 26 years of age established efficacy of the 9vHPV vaccine against these 5 additional oncogenic HPV subtypes.[35] Clinical trials involving 20,334 immunocompetent males and females between 9 and 26 years of age demonstrated that the 9vHPV vaccine is safe and generally well tolerated and provides comparable (i.e., non-inferior) immunogenicity against HPV types 6, 11, 16, and 18 as compared to the qHPV vaccine.[35,36] The FDA approved the 9vHPV vaccine for licensure on 12-10-14. On 2-26-15, the Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) added the 9vHPV vaccine to the recommended vaccines for females and males age 9-26 in the United States.[37] During 2015-16, the 9vHPV vaccine has rapidly replaced the qHPV vaccine in clinical practice. However, studies of other vaccines, such as hepatitis B in immunocompromised populations including cancer survivors, have shown diminished immunogenicity and response persistence, requiring alteration of vaccine dose, schedule, or composition in order to improve immunological responses.[21,38,39] Importantly, no studies to date have reported immunogenicity, or safety/ tolerability of the qHPV or 9vHPV vaccines in cancer survivors.

Despite the excellent efficacy and safety profile of the qHPV vaccine in the general population, and 2006 recommendation by the Advisory Committee on Immunization Practices (ACIP) for routine vaccination of young females, only 44.3% of the 13- to 17-year old females have initiated the HPV vaccine series and only 26.7% have received all three doses.[40] There is paucity of data regarding HPV vaccine uptake in other age groups and none to date in males. Notably, there are no reports of the prevalence of HPV vaccine initiation or acceptability in cancer survivors. Despite their increased risk for HPV-related morbidity, it is possible that HPV vaccine uptake is even lower in cancer survivors than in the general population, due to reluctance on the part of patients/parents or clinicians when immunogenicity and safety/tolerability data for this population is lacking.

This trial uses an approach that combines a cross-sectional survey, to determine vaccine initiation rates in cancer survivors between 9 and 26 years of age who are between 12 and 60 months post completion of systemic therapy, to identify predictors of vaccine non-initiation in these survivors; and among cancer survivors identified to be unimmunized, a single arm phase II open-label trial, to determine the

immunogenicity and safety/tolerability of the qHPV vaccine (HPV-6, -11, -16, -18; Gardasil®; Merck Research Laboratories; for patients enrolled on or before 3-1-16) and the 9vHPV vaccine (HPV-6, -11, -16, -18, -31, -33, -45, -52 and -58; Gardasil ®9; Merck Research Laboratories; for patients enrolled after 3-1-16), and simultaneously explore response persistence.

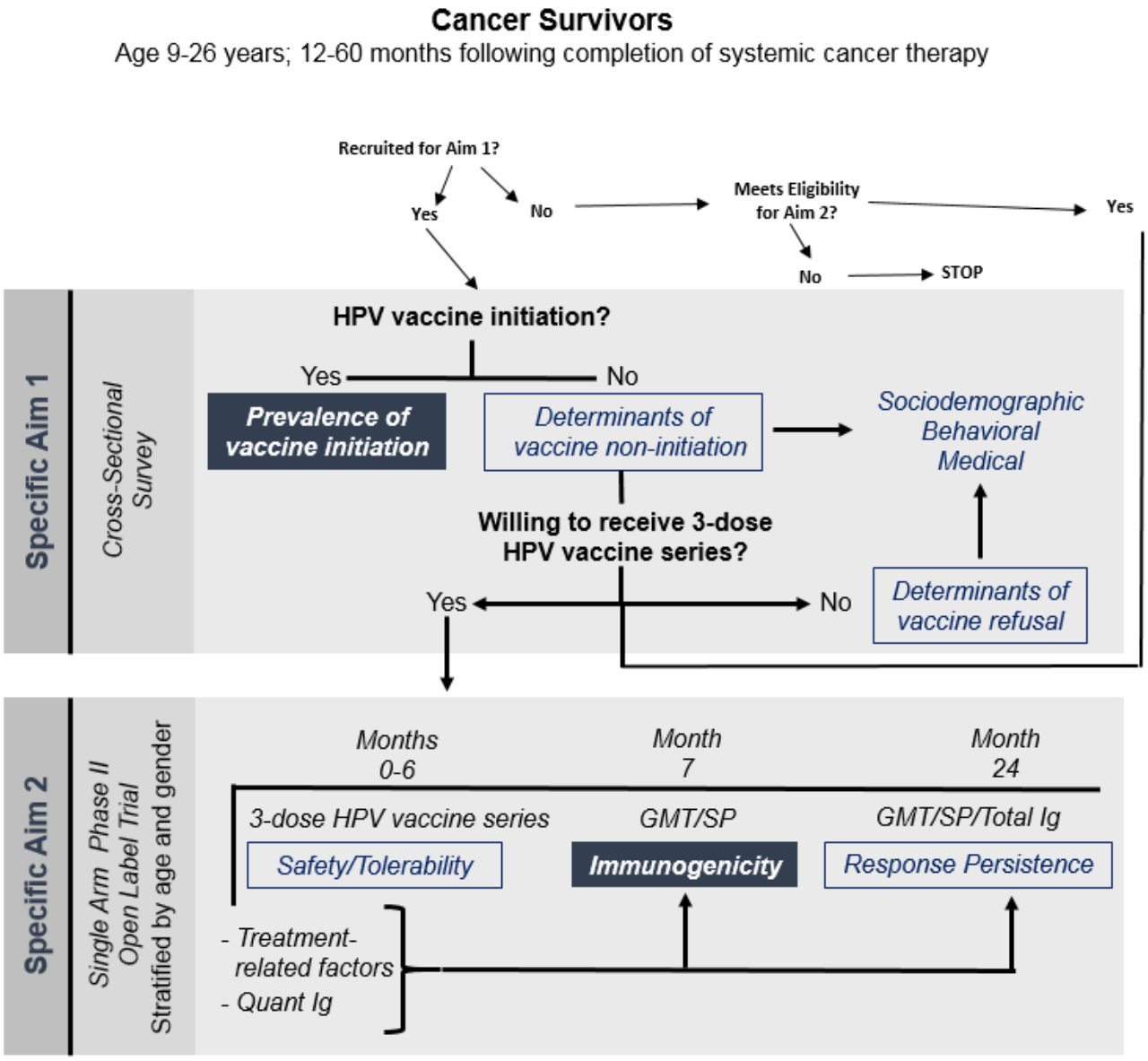
The primary aims of this study are to:

1. Using a cross-sectional survey approach, estimate the prevalence of HPV vaccine initiation in cancer survivors ages 9 to 26 years
    a. Examine the sociodemographic, behavioral, and medical determinants of HPV vaccine non-initiation
2. Among cancer survivors identified to be non-immunized in Aim 1 and by additional methods, use a single-arm, phase II, open-label, prospective longitudinal trial design, to evaluate the 3-dose qHPV vaccine series (for patients enrolled on or before 3-1-16) and the 3-dose 9vHPV vaccine series (for patients enrolled after 3-1-16), and measure the following endpoints:
    a. Determine immunogenicity following the third and final vaccine dose
    b. Identify clinical/host factors influencing immunogenicity
    c. Determine the safety/tolerability of the qHPV and 9vHPV vaccines in cancer survivors

3. As an exploratory aim, evaluate persistence of antibody response at 2 years post-vaccine initiation and identify clinical/host factors influencing response persistence

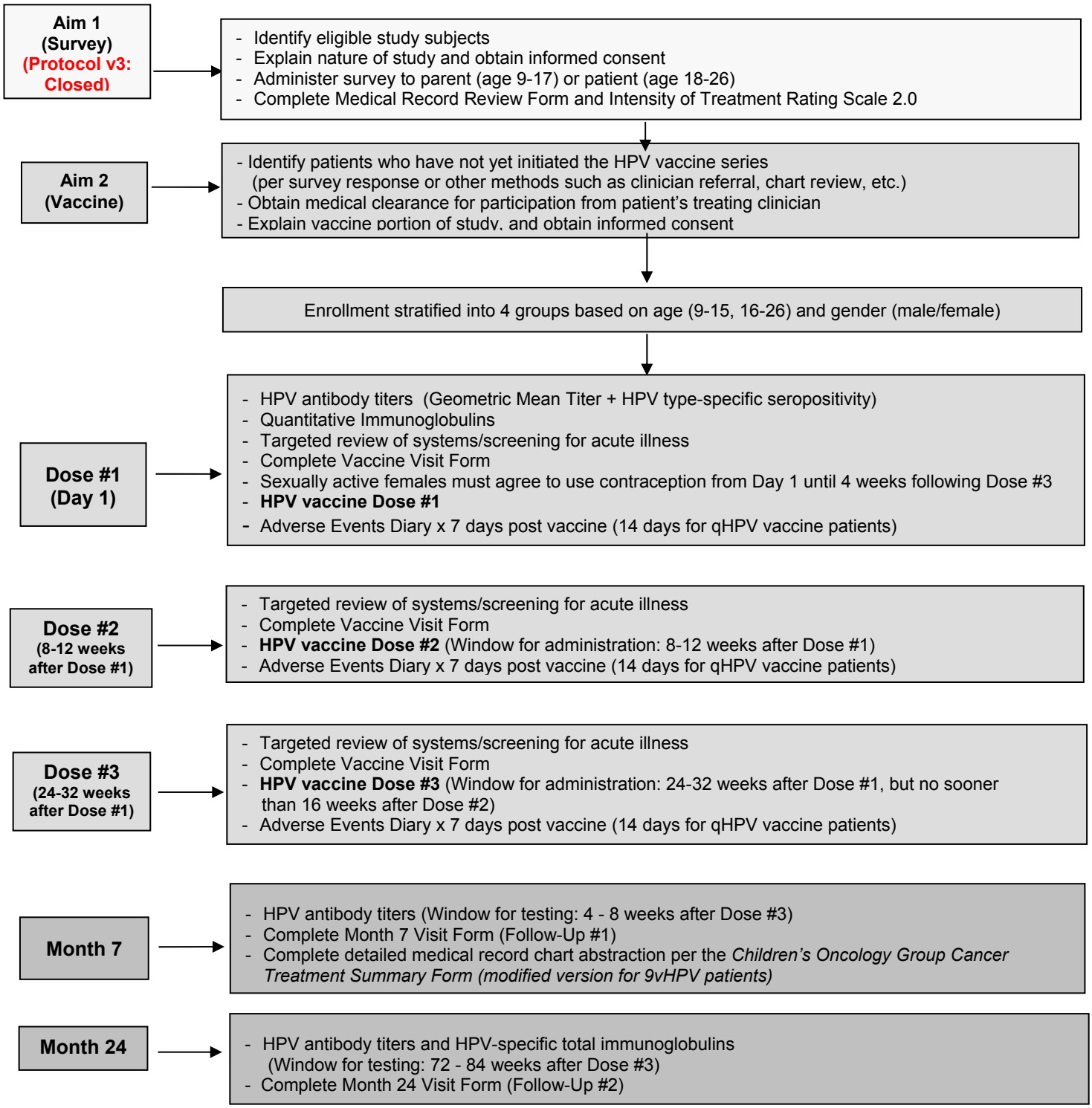
Cancer survivors between the ages of 9 and 26 years who are at least 12 months and no more than 60 months following completion of systemic therapy will complete a survey (closed with protocol version 03); unimmunized survivors will be offered the 3-dose qHPV vaccine series (for patients enrolled on or before 3-1-16) or the 3-dose 9vHPV series (for patients enrolling after 3-1-16); vaccine safety, tolerability, and immunogenicity will be determined according to the specified endpoint definitions. Findings will identify determinants of vaccine initiation, and provide evidence for immunogenicity, and safety/tolerability of the qHPV and 9vHPV vaccines, thus providing the needed evidence base for recommendations regarding HPV vaccination in cancer survivors.

STUDY SCHEMA (Overview)



Abbreviations: GMT = HPV-specific geometric mean titers; SP= Seropositivity; Quant Ig = Quantitative immunoglobulins; Total Ig=HPV-specific total immunoglobulins

STUDY SCHEMA (Detailed)



1.0 OBJECTIVES AND HYPOTHESES

Aim 1:

Using a cross-sectional survey approach, estimate the prevalence of HPV vaccine non-initiation

a. Examine sociodemographic, behavioral, and medical determinants of HPV vaccine non-initiation

Hypothesis 1: The HPV vaccine initiation rates for cancer survivors will be less than 40% (estimated rate in the general population); subgroups of cancer survivors with particularly low vaccine initiation rates will be identified.

Among cancer survivors identified to be non-immunized in Aim 1, and among additional non-immunized cancer survivors meeting study eligibility criteria:

Aim 2:

Using a single-arm, phase II, open-label, prospective longitudinal trial design, to evaluate the 3-dose qHPV (for patients enrolled on or before 3-1-16) or 9vHPV (for patients enrolled after 3-1-16) vaccine series and measure the following endpoints:

a. Determine immunogenicity following the third and final vaccine dose
b. Identify clinical/host factors influencing immunogenicity
c. Determine the safety/tolerability of the qHPV and 9vHPV vaccine in cancer survivors

Hypothesis 2: Immunogenicity to the qHPV and 9vHPV vaccines will be heterogeneous among cancer survivors, with subpopulations that received the most intense therapy demonstrating inferior immunogenicity. The qHPV and 9vHPV vaccines will be safe and well-tolerated by cancer survivors.

Exploratory sub-aim:

Evaluate the persistence of antibody response at 2 years post vaccine initiation and identify clinical/host factors influencing response persistence.

2.0 BACKGROUND

2.1. Size of the Targeted Cancer Survivor Population

Commensurate with the improvement in survival rates over the past five decades, the number of long-term survivors has increased substantially. Five year survival is estimated at 82.5% for children diagnosed between 0-14 years of age, 82.8% for those diagnosed between 15-19 years of age, and 85.1% for those diagnosed between 20-24 years of age.[3] There are over 325,000 long-term survivors of childhood/adolescent cancers (diagnosed at ages 0-19 years) in the U.S.;[1] 73,563 young cancer survivors are currently 10-19 years of age, while 156,152 are 20-29 years of age.[3] Thus, there are substantial numbers of survivors in the age group at highest risk for HPV infection, and who fall within the targeted age range for HPV vaccination (9 to 26 years).

2.2. Human Papillomavirus (HPV): Prevalence and Associated Malignancies

HPV is a double-stranded DNA virus enclosed in a non-enveloped capsid that infects cutaneous or mucosal epithelial surfaces.[41,42] Over 100 types of HPV have been identified, based on genetic sequence of the outer capsid L1 protein.[42] Over 40 HPV types are associated with infection of the anogenital and oropharyngeal epithelium.[10] HPV types are categorized as low or high risk based on their oncogenic potential. Persistent infection with high-risk HPV types is strongly associated with development of high-grade squamous intraepithelial neoplasia and cancers affecting the uterine cervix, vulva, vagina, penis, and anogenital and oropharyngeal mucosa.[7,14] Approximately 70% of cervical

cancer is caused by HPV types 16 and 18;[9-11] 90% of anal cancers, 40-50% of vulvar, vaginal, and penile cancers, 33-72% of oropharyngeal cancers, and 10% of laryngeal cancers are attributable to high-risk HPV infection.[8,43-45] Low-risk HPV types (primarily types 6 and 11) are associated with anogenital warts, low-grade dysplasia, and respiratory papillomatosis.[4, 12,13]

An estimated 6.2 million new cases of HPV infection occur annually in the U.S.[42] Prevalence of HPV infection is highest within the first few years following sexual debut.[46-49] Prior to widespread availability of the prophylactic HPV vaccine, the overall prevalence of HPV infection among females between 14 and 59 years of age was 26.8%, and the burden was highest among women age 20-24 (44.8%); prevalence among females age 14-19 was 24.5%.[4] In a recent study of 463 asymptomatic males age 18-40 years, 51% were positive for at least one HPV subtype.[5] In 2010, 12,200 women were diagnosed with cervical cancer and 4,210 died from the disease.[3] Total healthcare costs of HPV-related disease in the U.S. are estimated at $4 billion annually,[50] exceeding the economic burden of all other STIs with the exception of human immunodeficiency virus (HIV).

2.3. HPV in Immunocompromised Patients

Immunosuppression increases HPV persistence and is associated with an increased risk for developing HPV-related neoplasia in both males and females.[6,7,14,15,51] Immunosuppressed solid organ transplant recipients are at increased risk for HPV infection[17], HPV-associated cervical intraepithelial neoplasia (CIN),[18] squamous cell carcinoma of the skin,[52] and anogenital cancers[53-56] compared to the general population. Women infected with HIV have an increased prevalence of cervical HPV infection, a higher prevalence of CIN, and higher grades of CIN compared to the general population.[57] Additionally, the prevalence of cervical HPV infection, and higher grade of CIN increases with diminishing immune status.[58] Cervical cancer is known to occur at high rates in the HIV-positive population, and is an AIDS-defining illness.[59] Both men and women who are HIV positive are at increased risk for anal HPV infection, anal cancer,[60] and oropharyngeal cancer[61] than the general population. Hodgkin lymphoma is associated with deficits in cellular immunity that often persist long after treatment ends,[62] suggesting an increased vulnerability to HPV-related infection and cervical and anal cancer.[22] Pelvic irradiation is associated with impaired genital track epithelial cell function[63] and HPV-related dysplasia and carcinomas of the genital tract.[64-66] Patients who have undergone HCT for hematologic malignancies are at significantly increased risk for cervical and other HPV-associated cancers than the general population.[23-25] In addition to the 13-fold increased risk for cervical cancer and 17-fold increased risk for oral cancer reported in HCT survivors noted above,[23] the risk for cervical pathology is higher among allogeneic HCT recipients.[25] Prolonged immunodeficiency in combination with HPV exposure explains the elevated risks.[23,25]

2.4. HPV Vaccine Development and Testing in the General (Immunocompetent) Population

Vaccines against HPV are composed of noninfectious virus-like particles (VLPs) made of recombinant viral L1 protein identical to the naturally occurring viral capsid.[67] **qHPV vaccine:** The quadrivalent HPV (qHPV) vaccine (HPV-6, -11, -16, -18; Gardasil®; Merck Research Laboratories)[27] is currently approved by the FDA for administration to both males and females between 9 and 26 years of age[28] and is indicated for prevention of HPV-16 and -18 related cervical, vulvar, vaginal, and anal cancers in females and HPV-16 and -18 related anal cancer in males, with additional indications in both genders for protection against HPV-6, -11, -16, and -18 precancerous or dysplastic lesions and HPV-6 and -11 related genital warts. In clinical trials with healthy females, the qHPV vaccine demonstrated 98% efficacy in protecting HPV-naïve recipients from acquiring HPV vaccine types[68] and 100% efficacy for prevention of vaccine-type HPV-associated vaginal, vulvar, perineal and perianal intraepithelial lesions or warts and CIN grades 1 to 3 or adenocarcinoma in situ associated with vaccine-type HPV.[27] In healthy males, the qHPV vaccine demonstrated ~90% efficacy against external genital lesions including genital warts.[32] **9vHPV vaccine:** The nonavalent HPV (9vHPV) vaccine (HPV-6, -11, -16, -18, -31, -33, -45, -52, -58; Gardasil ®9; Merck Research Laboratories)[69] is currently approved by the FDA for

administration to both males and females between 9 and 26 years of age[70] and is indicated for prevention of HPV-16, -18, -31, -33, -45, -52, and -58 related cervical, vulvar, vaginal, and anal cancers in females and HPV-16, -18, -31, -33, -45, -52, and -58 related anal cancer in males, with additional indications in both genders for protection against HPV-16, -18, -31, -33, -45, -52, and -58 precancerous or dysplastic lesions and HPV-6 and -11 related genital warts.[69] The 9vHPV vaccine extends protection beyond that offered with the qHPV vaccine through inclusion of five additional oncogenic types (31, 33, 45, 52, and 58). A trial of 14,215 females between 16 and 26 years of age established efficacy of the HPV-9 vaccine against these 5 additional oncogenic subtypes.[35] The qHPV vaccine provides protection against approximately 70% of cervical cancers, 70-75% of vulvar cancers, 65% of vaginal cancers, and 85-90% of anal cancers. The 9vHPV vaccine targets 5 additional oncogenic subtypes, which account for approximately 15-20% of cervical cancers, 10-15% of vulvar cancers, 20% of vaginal cancers, and 5-10% of anal cancers; thus, the 9vHPV vaccine provides protection against 85-90% of the oncogenic HPV subtypes associated with cervical cancer, 85-90% of vulvar cancers, 80-85% of vaginal cancers, and 90-95% of anal cancers.[69]

2.4.1. *Immunogenicity:* The qHPV and 9vHPV vaccines are highly immunogenic in males and females in the general population,[29-31,35,36] and are primarily dependent on humoral immune response.[71] Immunogenicity varies by age and gender; the most robust responses are seen in younger individuals and in males.[30,69] There is paucity of data regarding the immunogenicity of the qHPV and 9vHPV vaccines in immunocompromised populations. In HIV-infected children 7-12 years of age who received the qHPV vaccine, >96% of vaccine recipients seroconverted to all 4 vaccine antigens (i.e. negative anti-HPV antibody titers at baseline and positive titers one month after completing vaccine series); however geometric mean titers (GMT) against vaccine subtypes 6 and 18 were 30-50% lower than those of age-matched historical controls.[27,72]

2.4.2. *Safety:* **qHPV vaccine:** The qHPV vaccine has been safe and well-tolerated in 5 clinical trials enrolling 21,480 subjects[73] and in post-licensure safety monitoring.[74] The most common adverse reactions were headache (vaccine, 28.2%; placebo 28.4%); fever (13.0% vs. 11.2%), and nausea (6.7% vs. 6.5%). The rates of serious adverse events (AEs) were comparable between vaccine and placebo groups[28] and occurred at 50% the rate reported for licensed vaccines. Severe injection site reactions were slightly higher in the vaccine group (2.2%) compared to placebo (0.9%).[73,74] In post-licensure monitoring, AEs were consistent with pre-licensure data with the exception of disproportional reporting (per 100,000 doses of qHPV vaccine distributed) of syncope (8.2/100,000) and venous thromboembolic events (VTE) (0.2/100,000); 94% of syncopal episodes were classified as non-serious and 90% of patients with VTE had a known risk factor.[74] **9vHPV vaccine:** In clinical trials involving 20,334 immunocompetent males and females between 9 and 26 years of age, the 9vHPV vaccine has been shown to be safe and generally well tolerated compared to the qHPV vaccine. Females age 16-26 who received 9vHPV were more likely to report mild to moderate injection site adverse events compared to those who received qHPV (90.7% vs. 84.9%), with the most common events being pain, swelling, erythema, and pruritis. Adverse event reports in males were lower than in females and were similar to qHPV. There was no increase in reported serious adverse events for 9vHPV compared to qHPV.[36,69]

2.5. Vaccination in Populations with Altered Immune Competence

The success of active vaccination relies on an intact immune system. Inactive or recombinant subunit vaccines (qHPV and 9vHPV) rely primarily on the humoral component.[42,71]

2.5.1. *Vaccination of young cancer survivors:* Current clinical practice arbitrarily calls for initiation of vaccination (of any type) at least 6-12 months after completion of cancer treatment in order to allow sufficient recovery of the immune system and avoid inferior responses generally observed when vaccines are given in the early months following cancer therapy.[75] However, there is lack of consensus

regarding vaccine re-initiation following successful completion of cancer treatment.[76,77] Impairment of immunity is seen to varying degrees after completion of cancer therapy, and is dependent on intensity of chemotherapy, radiation and other immunosuppressive agents;[78] immune competence can be particularly impaired following HCT, especially in patients with chronic graft-versus-host disease (GvHD).[79] Studies of hepatitis B, pneumococcal and Haemophilus influenzae type b (Hib) vaccines have shown diminished immunogenicity and response persistence in cancer survivors, requiring alteration of vaccine dose, schedule, timing, or composition in order to improve immunological responses.[21,38,39,80,81]

2.5.2. *Use of the qHPV and 9vHPV vaccine in cancer survivors:* Since the qHPV and 9vHPV vaccines are subunit vaccines, they do not contain viral DNA, and hence cannot impart a risk of vaccine-associated transmission of HPV infection. However, there is lack of information regarding immunogenicity of the qHPV and 9vHPV vaccines in cancer survivors. Cancer survivors who are at least one year following completion of systemic therapy generally have normal or near-normal measures of humoral immunity (i.e., quantitative immunoglobulins [Quant Ig]) for the most part.[19,82,83] Therefore, it is conceivable that survivors will mount an immunogenic response to qHPV and 9vHPV vaccines similar to that observed in the general population. However, subsets of survivors may not respond adequately,[79,84] since immune recovery following cancer treatment may be variable,[19,20] and in particular, immune reconstitution following HCT may vary based on donor source and presence of chronic GvHD.[85] Data regarding the immunogenicity and safety/tolerability of qHPV and 9vHPV vaccines in cancer survivors are needed in order to determine whether the 3-dose schedule recommended for the general population is appropriate for this population.

2.6. Prevalence of HPV Vaccine Initiation

Although adolescent females in the general population report high levels of acceptance regarding HPV vaccination, rates of actual vaccine initiation are low, ranging from 5-45%.[40,86,87] The U.S. Centers for Disease Control and Prevention reported that only 44.3% of 13-17 year old females in the general population had initiated the HPV vaccine series and only 26.7% had received all 3 doses.[40] Importantly, all reported HPV vaccination rates to date are significantly lower than the 90% target established by the Healthy People 2010 initiative.[88] There are no data regarding the prevalence of HPV vaccine initiation in the cancer survivor population. Furthermore, there are no studies regarding HPV vaccine uptake in males in any population.

2.7. Factors Relevant to HPV Vaccine Non-Initiation

2.7.1 *Sociodemographic factors:* Cervical cancer is associated with lower education, lower household income, and Hispanic ethnicity.[89] Socioeconomic differences in sexual behavior resulting in increased transmission of oncogenic HPV types, coupled with lack of access to cervical cancer screening, have been suggested as potential explanations for these findings.[45] Among childhood cancer survivors, women who are college educated, medically insured and older are more likely to have undergone Papanicolaou (Pap) testing for cervical cancer within the previous 3 years compared to survivors who are less educated, without insurance, and younger.[90] Childhood cancer survivors are more likely to report unemployment and lower educational attainment and income compared to their siblings,[91] and may therefore be at risk for suboptimal cervical cancer screening. Similar demographic findings have been reported specific to HPV vaccine initiation; for example, among healthy females there are several key factors that discriminate those who have or have not initiated HPV vaccination: socioeconomic status and education,[92-95] age,[40, 92,95,96] race, [97,98] and geographic region.[40]

2.7.2 *Behavioral factors:*

Vaccine acceptability – adolescent attitudes: Despite relatively low rates of HPV vaccine initiation, between 66 and 74% of adolescent/young adult females have reported intention to receive the

vaccine.[99,100] Studies of adolescent attitudes toward STI vaccination indicate high levels of acceptance, influenced by perceptions of vaccine characteristics (low cost, efficacy), health beliefs, provider recommendations, perceived increased susceptibility to STIs such as HIV, and perceived benefits of vaccination. [101-105] In contrast, greater perceived obstacles (e.g., difficulty keeping clinic appointments), fear of the vaccine causing infection, lower perceived risk, and fear of needles are related to lower acceptability.[101] Despite reports of generally high levels of HPV vaccination acceptance and intentions, actual vaccination rates remain low to date.[86]

Parental attitudes toward vaccination: Parents are also accepting of HPV vaccination, with 55-100% of parents indicating a willingness to vaccinate.[92,106,107] Factors associated with increased acceptance include parental history of HIV testing, higher number of lifetime sexual partners, older age of child at time of vaccination, having had a family member with cancer, and belief that the vaccine would be accepted by the parent's peers/partners.[106,108,109] A belief in the protective effects of childhood vaccines in general, and specifically in the protection offered by HPV vaccination, correlate with parental HPV vaccine acceptability.[110] Mothers willing to discuss cervical cancer, sex, STIs, or HPV with their daughters at earlier ages are more likely to accept HPV vaccination.[108] Perceived physician encouragement and HPV-related knowledge also appear to be associated with positive parental attitudes toward vaccination.[92] In contrast, parental anxiety regarding vaccine safety, conservative religious/cultural views, belief that vaccination encourages sexual activity, lack of disease-specific knowledge, risk of unknown harmful side effects, and low concern for child's HPV acquisition have characterized the opposition that some parents have to HPV vaccination.[92-94,111,112]

2.7.3 *Medical factors:*

Healthcare provider recommendation: Although 90% of pediatricians endorse HPV vaccination, many report parental barriers to HPV vaccine administration, including concerns regarding vaccine safety, reluctance to discuss sexuality and HPV transmission, belief that the child receives too many vaccines, denial that the child may be at risk for HPV, and concerns that vaccination would lead to riskier adolescent behaviors.[113,114] Nonetheless, medical providers have considerable influence regarding vaccination decisions for their patients.[103,115] Healthcare provider recommendation of HPV vaccine to cancer survivors may maximize the likelihood of vaccination; the current study will provide evidence to endorse such recommendations.

Cancer diagnosis and treatment history: Patients who have received more therapy that is immunosuppressive may experience a prolonged recovery period. Patients with hematological malignancies are more likely to require more intense therapies, including allogeneic HCT, which may result in chronic GvHD requiring ongoing immunosuppression.[116] Thus, cancer diagnosis and treatment-related factors may play a significant role in decisions related to vaccine initiation in the cancer survivor population; there is currently very little data to support this, resulting in a critical gap in the literature that this study will address.

2.8 Theoretical Model/Conceptual Framework

An integrative framework guided by the Health Belief Model (HBM),[117,118] and Theory of Planned Behavior (TPB),[119] will provide the theoretical basis for testing our predictive models of HPV vaccination initiation and intent. The HBM postulates that a health behavior (e.g., initiating HPV vaccination) is influenced by perceptions of both the threat posed by a health problem (e.g., HPV-related cancers) and the value of actions aimed at reducing the threat (e.g., HPV vaccination as a means of reducing risk of HPV-related cancers). The HBM includes 6 primary factors (perceived susceptibility, severity, barriers, benefits, cues to action, and self efficacy)[118] that explain a significant proportion of the variance regarding decision to engage in a health-promoting behavior. TPB posits that an individual's attitudes regarding a behavior, perceptions of the beliefs of significant others (norms), and perceived control over a behavior influence behavioral intent, which in turn drives engagement in the actual behavior.[119] This theory assumes that behavioral intention is the most significant determinant of engaging in a behavior,

with intent initially influenced by personal evaluation of a behavior and personal beliefs regarding whether important people would approve or disapprove of the behavior.[120] Thus, multiple factors influence HPV vaccine intent, which subsequently predicts initiation of HPV vaccine. In this aim, the primary dependent variable will be HPV vaccine non-initiation prior to study participation; by collecting survey data regarding vaccine intention and key factors influencing health behaviors informed through HBM and TPB (Table 1), we will identify potentially modifiable barriers to HPV vaccine initiation in cancer survivors, setting the stage for development of interventions to improve uptake of the HPV vaccine in this vulnerable population.

Table 1. Theoretical Basis for Testing Predictive Model

PROPOSED PREDICTORS OF HPV VACCINE INITIATION	SURVEY ITEMS ELICITING PREDICTORS
†Perceived susceptibility to HPV-related disease	D1a-e
†Perceived severity of HPV-related disease	D2a-h
†Perceived barriers to HPV vaccination	D3a-l
†Perceived benefits/efficacy of the HPV vaccine	D4a-g
†Cues to action	C1, C2a-m
†Self-efficacy	D5a-f, D6
Knowledge of HPV and related health risks	B1-10
Heath behaviors	G1-17
Demographic factors	A1-9
Sexual relationships/communication	H1a-t; I1-5; J1-13
§Attitude toward vaccine-related decision-making	C6-10; F1a-j
§Social and environmental influences on decision	E1a-q, E2-3
§Healthcare provider recommendation	C2c,d; E1a; G6,8,18
§Intention to vaccinate	C5a-d
OUTCOME OF INTEREST: HPV VACCINE INITIATION	
Vaccination status	C3-4

†Component of Health Belief Model §Component of Theory of Planned Behavior

2.9 Preliminary Studies

"*HPV among Survivors of Childhood Cancer*" (SJCRH-HPV-1; PI Klosky; Co-Investigator Hudson) is an IRB-approved and institutionally-funded exploratory study conducted at St. Jude Children's Research Hospital. This pilot study aimed to estimate the prevalence of HPV vaccination and examine predictors of vaccine initiation and intent in a cohort of cancer survivors from a single institution. As of 3-4-11, 220 parents (of female patients age 9-17) and 75 female cancer survivors (age 18-26) have been approached for participation in this study. Overall consent rate is 94.2% (95% for ages 9-17; 90% for ages 18-26) with an 86% survey completion rate. Reasons for non-participation (n=17) include "not interested" (88.2%) and "tired of filling out questionnaires" (11.8%). Self-/parent-reported HPV vaccine initiation rates in this cohort are 33.3% overall (33.1% for age 9-17; 38.9% for age 18-26), with lower vaccine initiation rates in patients with leukemia/lymphoma (29.0%) compared with solid tumors (38.2%). Vaccine initiation rates by race are 31.4% for Caucasians compared with 40.7% for all other races combined; initiation rates by religious preference are: Protestant 39.1%, Catholic 22.2%, Other 30%; and by annual income: <$20K: 50%, $20-99K:25.8%, ≥$100K: 40%. When unimmunized survivors were asked how likely they were to initiate the vaccine in the future, 46.0% indicated "likely/very likely/definitely will", 21.9% indicated "unlikely/very unlikely/definitely will not," and 32.1% were "unsure". When unimmunized survivors were asked about their willingness to receive the HPV vaccine in the setting of a clinical trial, 62.8% indicated willingness, 17.2% indicated unwillingness, 20.0% were unsure.

In the current study, we will expand upon this pilot initiative across geographically and racially/ethnically diverse populations in order to collect data that is generalizable to the broader cancer survivor population; and, for the first time, to include both males and females. Finally, we plan to explore predictors of vaccine refusal in unimmunized survivors (i.e., unimmunized participants will be offered the HPV vaccine after survey completion, and reasons for refusal will allow examination of translation of intent into action vs. refusal).

2.10 Overall Significance of the Study

2.10.1 *Importance of the Problem:* This study will address high priority areas identified by NIH

(NINR/NCI): (1) health promotion; (2) cancer prevention; and, (3) cancer survivorship. Several factors combine to make this research compelling: (1) availability of a licensed vaccine that is indicated for prevention of HPV-infection in females and now also in males and that is safe, highly immunogenic and efficacious in the general population; (2) the large and continually expanding population of young cancer survivors at risk for HPV-related infection and neoplasms; (3) the high burden of morbidity/mortality due to HPV infection in the cancer survivor population; and (4) the critical need to develop evidence to inform optimal utilization of the HPV vaccine in cancer survivors in order to optimize health promotion and disease prevention in this vulnerable population.

2.10.2 *Gaps in Scientific Knowledge to be Addressed:* The study will address the following important gaps in scientific knowledge relevant to health promotion and disease prevention among young cancer survivors: (1) prevalence and determinants of HPV vaccine initiation among cancer survivors; (2) adequacy of the 3-dose qHPV and the 3-dose 9vHPV vaccine series in inducing immunogenicity in individuals treated for cancer; (3) impact of humoral immune competence and therapeutic exposures on qHPV and 9vHPV vaccine immunogenicity; and (4) safety and tolerability of the qHPV and 9vHPV vaccines among cancer survivors. If the rates of HPV vaccine initiation are low among cancer survivors, and qHPV and 9vHPV vaccines are immunogenic, safe, and tolerable in cancer survivors, then, this study would provide strong rationale for developing intervention programs to improve HPV vaccine uptake in cancer survivors. Importantly, this research will inform development of these interventions, since we will determine facilitators and barriers in cancer survivors and identify subgroups of survivors at particularly high risk for poor vaccine uptake (and therefore likely to derive the most benefit from targeted interventions). Additionally, this research will inform recommendations for HPV vaccination of this vulnerable population. We will also identify clinical factors associated with inadequate immunogenic response to the vaccine, and the impact of humoral competence on this response, providing a foundation for future development of alternative vaccination strategies (e.g., alterations in timing, dose and/or schedule) in any subgroups that are unable to mount an adequate response to the standard 3-dose vaccine series. Given the large and ever-increasing number of young cancer survivors in the U.S., this research could potentially result in substantial benefits to this vulnerable population, including primary prevention of HPV-related malignancies and their associated morbidity and mortality. Additionally, this study will form the basis for future investigations aimed at determining the efficacy of the 9vHPV vaccine in reducing HPV-related morbidity in this population.

3.0 ELIGIBILITY

3.1 Inclusion Criteria: Aim 1 (Survey)

[Protocol v3, 8/17/15: Accrual goal for Aim 1 met, enrollment to survey closed]

3.1.1 Cancer survivor (9 to 26 years of age at study participation)

3.1.2 Between 12 and 60 months after completion of cancer therapy (chemotherapy, radiation, HCT)

3.1.3 Scheduled for a return clinic visit at one of the participating institutions
(An estimated 60%-80% of patients that are 12-60 months from therapy end are regularly followed in the clinic; sociodemographic and clinical characteristics will be compared between participants and non-participants to determine evidence of participation bias)

3.1.4 English or Spanish-speaking

3.1.5 Willing to provide informed consent/assent for study participation.

3.2 Inclusion Criteria: Aim 2 (Vaccine Evaluation)

3.2.1 Cancer survivor (9 to 26 years of age at study participation)

3.2.2. Between 12 and 60 months after completion of cancer therapy (chemotherapy, radiation, HCT)

3.2.3 Survey response indicated no prior history of HPV vaccination OR patient has no prior history of HPV vaccination by self- or parent/caregiver-report

3.2.4. English or Spanish-speaking

3.2.5 Medical clearance from treating clinician for study participation

3.2.6 Agrees to return to participating institution for 3 HPV vaccine injections

3.2.7 Willing to provide informed consent/assent for study participation

3.3 Exclusion Criteria: Aim 2 (Vaccine Evaluation)

3.3.1 Allergy to any component of the HPV vaccine including yeast and aluminum

3.3.2 Thrombocytopenia (platelet count <50K) or coagulation disorder that would contraindicate intramuscular injection

3.3.3 Transfusion of blood products or intravenous immune globulin within 3 months of study entry

3.3.4 Female, and a) currently pregnant or lactating, or b) of childbearing potential and unwilling to avoid pregnancy during the vaccine phase of study (beginning at Day 1 and continuing until at least 4 weeks after all 3 vaccine doses have been administered).

4.0 METHODS: AIM 1 (SURVEY)

[Protocol v3, 8/17/15: Accrual goal for Aim 1 met, enrollment to survey closed]

4.1 Study Design

The study design for Aim 1 is a cross-sectional survey to determine vaccine initiation rates and identify predictors of vaccine non-initiation in cancer survivors

4.2 Identification/Recruitment of Participants

This study will be conducted at the University of Alabama at Birmingham (UAB) and at 4 institutions affiliated with the Consortium for Pediatric Interventional Research (CPIR), including St. Jude Children's Research Hospital (SJCRH), City of Hope (COH), University of Michigan (UM), and Emory University/Children's Healthcare of Atlanta (EU/ CHOA). The coordinating center for this study is the University of Alabama at Birmingham (UAB), Birmingham, AL. The CPIR has established infrastructure to perform interventional research aimed at reducing morbidity among childhood cancer survivors.

The number of potentially eligible participants at each site is shown in Table 2.

Table 2. Potentially Eligible Participants by Institution

Institution	Male	Female	Total	#HCT	% HCT
City of Hope	137	116	**253**	116	45.8
Emory Univ - Children's Healthcare Atlanta	241	170	**411**	34	08.3
St. Jude Children's Research Hospital	524	411	**935**	159	17.0
C. S. Mott Children's Hospital – Univ Mich	99	63	**162**	42	25.9
University of Alabama at Birmingham (UAB)	220	180	**400**	60	15.0
Total	1221	940	**2161**	**411**	**19.0**

The study team at each site includes the consortium site principal investigator (PI), co-investigators, participating clinicians, and the protocol nurse and/or clinical research assistant (CRA). The study team will use patient rosters, cancer registry data, or similar methods to identify patients eligible for the Aim 1 (Survey) who have an upcoming clinic appointment at the participating site. Eligible patients ≥18 years of age (or parents of patients <18) will be approached by a study team member, who will fully explain

the study, including all risks, benefits and alternatives. Informed consent will be obtained in the patient/parent's preferred language. Assent, along with parental consent, will be obtained from minors according to the policies at the participating institutions. To reduce any potential recruitment bias, patients will be approached consecutively in order of scheduled medical visits. For eligible patients who refuse study participation, reasons for refusal will be documented.

4.3 Data Abstraction

The *Medical Record Review Form* and *Intensity of Treatment Rating Scale 2.0* will be completed for all patients enrolled in Aim 1 (Survey).

Medical Record Review Form: This form captures data elements abstracted from the medical record, including diagnosis, date of birth, date of diagnosis, time from diagnosis, treatment modalities (surgery, chemotherapy, radiation, HCT), and date of treatment completion (see Appendix 1).

Intensity of Treatment Rating Scale 2.0 (ITR-2): The ITR-2[121] (see Appendix 2) is a validated tool that uses cancer diagnosis, stage or risk level, and treatment modalities to produce an overall rating of cancer treatment intensity with 4 levels (least to most intensive); inter-rater reliability of this tool is .87.

The two instruments provide a concise record of the diagnosis and treatment intensity. Ten percent of randomly selected records will be rated independently by two reviewers to establish inter-rater reliability.

4.4 HPV Vaccination Survey

The patient (if 18 years or older) or parent (of patients 9-17 years of age) will be asked to complete a survey that elicits demographic information, current HPV vaccine status (including number of doses received, if any), knowledge regarding HPV,[112] patient/parent perspectives regarding HPV vaccine,[93,96,112,122] health-related practices,[95] HPV vaccine intent,[93] and standardized questions assessing health beliefs,[123] cues to action and self-efficacy,[96,106] sexual communication,[124-126] and sexual behavior.[127] The instrument is available in paper and HIPAA-compliant electronic formats in English/Spanish, Male/Female and Parent/Patient Versions (see Appendix 3). Participants may also complete the questionnaire via interview (in person or by phone) if preferred. Completion time is approximately 15 to 20 minutes. Derivation of questionnaire items is reviewed below and in Table 3, which summarizes the variables to be studied, the questionnaire item numbers and the participants queried, and the source(s) that guided development of the items.

4.4.1 Health Beliefs

The HPV Vaccine Health Beliefs Questionnaire[123] is a validated instrument designed to measure the parental health belief constructs of perceived severity, perceived vulnerability, perceived barriers, and perceived benefits/efficacy as it relates to the HPV vaccine. The questionnaire's instructions direct participants to respond to items on a Likert-type rating scale which ranges from "Strongly Disagree" to "Strongly Agree." The internal reliabilities (Cronbach's alpha coefficients) for the 4 scales are as follows: Perceived Severity (.84), Perceived Barriers (.89), Perceived Vulnerability (.70) and Perceived Vaccine Benefits/Efficacy (.90). The predictive validity of these health belief factors has been established in their relationships with HPV vaccination acceptability among mothers of girls aged 11-16.[123] Additional scales measuring vaccine-related Cues to Action and Self-Efficacy are also included as part of the study questionnaire, with these scales having been adapted from previously validated surveys.[86,96,106]

4.4.2 Sexual Communication

For parents, the Mother-Adolescent Sexual Communication (MASC) Instrument is used to measure parental-adolescent communication regarding sexual behavior and development.[124] Exploratory factor analyses of this 18 item measure resulted in 4 primary factors including Content, Context, Timing and Style of communications with internal reliabilities (Cronbach's alpha coefficients) of .87, .90, .82, and

.71 for these four factors respectively. Convergent validity for this instrument is found in its relationships with subscales from the Parent-Child Relationship Questionnaire,[128] while discriminant validity has been established in its low association with the Family Impact Questionnaire.[129] Questions have been adapted to allow for inclusion of male participants.

Young adult participants complete The Miller Sexual Communication Scale.[125] This scale consists of two subscales assessing the content and process of sexual communication between adolescents/ young adults and their parents. The Parent-Adolescent Sexual Topic Discussion subscale consists of ten questions addressing sexual topics such as contraception and coping with sexual aspects of their romantic relationships. Response choices are offered to a four-point Likert scale ranging from one (strongly disagree) to four (strongly agree) to correspond with the second subscale. This scale has been demonstrated to be internally valid with a reported alpha coefficients ranging from 0.72 - 0.78.[126] A second 10 item subscale is included which is labeled the Open Sexual Communication subscale. This subscale measures the process of sexual communication between adolescents/young adults and their parents. Higher scores on both subscales indicate greater communication on sex-related topics between adolescents/young adults and parents, with negatively worded items reverse-scored. The internal consistency of this subscale has been reported to be 0.86.[126] Questions have been adapted to allow for inclusion of male participants.

4.4.3. General Knowledge of HPV and Related Risk Factors

Knowledge of HPV, cervical cancer, and HPV vaccination is measured by a scale adapted from Brabin and colleagues.[112] Ten multiple choice items are used to assess knowledge of HPV-related health risks. Participants receive a score of 1 or 0 for each response and the number of correct answers is summed to create a knowledge score for each participant. Higher scores represent more accurate responses and greater levels of HPV-related knowledge. The content of the questionnaire was abstracted from the CDC's website for HPV vaccination information[122] as well as items previously formulated by Brabin and colleagues.[112]

4.4.4. Socio-Environmental Factors

Participants are asked to rate potential influences on their HPV vaccine decision-making. Twelve items are used to provide an overall measure of important influences on decision-making. Responses range from 1 (*not at all important*) to 4 (*very important*). One open-ended qualitative item also allows participants to comment on any other influences on the decision regarding HPV vaccination. Items regarding social influences on vaccine decision-making were adapted from questions used in previous studies.[93,96,112]

4.4.5. Medical Care and Demographic Factors

All participants are asked to provide demographic information including age, race/ethnicity, marital status, religious preference, education level, and annual household income. Parents are asked to provide their relationship to the patient, and their child's age and grade in school. Items were adapted from previous research instruments.[93,96,112] Medical background questions include relevant parental and patient health history (STI, HPV infection, genital warts, abnormal Pap smears, cervical cancer) and health behaviors (healthcare visits, vaccine history, and for females, history of obstetric/gynecologic care, mammography, and Pap smears). Items were adapted from previous self-report questionnaires.[95]

4.4.6. Current Vaccination Status (Primary Dependent Variable)

The patient's HPV vaccination status is determined by one item, the dependent variable for Primary Aim #1. The item reads "Have you (your son/daughter) received the HPV vaccination?" Brand name prompts (Gardasil – males and females, and Cervarix – females only) are included in the item.

Response choices include 4 options: "I (my son/daughter) have received… A) 0 of the 3 shot series (has not started the vaccine, B) 1 of the 3 shot series, C) 2 of the 3 shot series, and D) 3 of the 3 shot series (has completed the vaccine)." Responses will be dichotomized to reflect those who have and have not initiated HPV vaccination. An additional item for those who indicate prior initiation of the HPV vaccine series captures the age of the patient at the time of the first HPV vaccine dose.

4.4.7. HPV Vaccination Intent

For those participants who indicate that they (or their son/daughter) have not yet initiated the HPV vaccine series, 4 additional items assess HPV vaccine intent. Each item allows for responses that range from "Definitely Will Not" (0) to "Definitely Will" (6), generating scores ranging from 0 - 24, with higher scores indicating greater likelihood that the patient will receive the HPV vaccine in the future. Items regarding vaccinate intent were adapted from questions used in previous research.[93]

4.4.8. Sexual Behavior

Because HPV is a sexually transmitted infection, it is important that risky sexual behavior be considered among the factors influencing vaccination decisions. Parental perception of their child's dating/sexual activity are assessed with four items with response choices ranging from 1 (*not at all true for him/her*) to 4 (*very true for him/her*). Higher scores reflecting greater perceived sexual activity. One item will be reverse coded. Additionally, young adult participants are queried regarding their sexual behavior. The 11 questions included on the young adult version of the questionnaire are empirically validated items which query safe sexual practices (e.g. type and frequency of contraceptive use) and sexual history.[127,130,131]

Table 3. Derivation of Questionnaire Items

Variables	Questionnaire Items/Participants Queried	Source or Adapted Source
Demographic	A1-9 (parent) A1-6 (patient)	Brabin, et al., 2006[112] Constantine & Jerman, 2007[93] Dempsey, et al., 2006[96]
Knowledge of HPV & Related Health Risks	B1-10 (all)	Brabin, et al., 2006[112] CDC, 2007[122]
Vaccination Status	C3-4 (all)	Investigator-developed for this study
Intent to Vaccinate	IC5a-d (all)	Constantine & Jerman, 2007[93]
Vaccine Attitudes/Beliefs	C6a-d (all) C7-10 (all)	Cox, et al., 2010[123] Brabin, et al., 2006[112]
Health Belief Factors Perceived susceptibility Perceived severity Perceived barriers Perceived benefits	 D1a-d (males)/D1a-e (females) D2a-g (males)/D2a-h (females) D3a-l (all) D4a-g (all)	 Cox, et al., 2010[123] Dempsey, et al., 2006[96] Gerend, et al., 2007[106]
Cues to Action	C1, C2a-l (parents)/a-m (patients) G8 (parents of males), 18 (parents of females) G6 (male patients), 11 (female patients)	Dempsey, et al., 2006[96] Gerend, et al., 2007[106] Kahn, et al., 2008[86]
Self-Efficacy	D5a-g (all)	Kahn, et al., 2008[86]
Socio-Environmental Influences	D6 (all) E1a-l (male patients/parents of males) E1a-n (parents of females) E1a-p (female patients) E2-3 (all)	Brabin, et al., 2006[112] Constantine & Jerman, 2007[93] Dempsey, et al., 2006[96]
HPV Vaccine Decision-Making	F1a-j (all)	Brabin, et al., 2006[112]
Medical Factors	G1-3 (male patients/parents of males) G1-9 (parents of females) G6-7 (parents of males) G15-17 (parents of females) G 4-7 (female patients)	Rosenthal, et al., 2008[95]

Variables	Questionnaire Items/Participants Queried	Source or Adapted Source
Health behaviors	G4-5 (male patients/parents of males) G1-3, 8-10 (female patients) G 10-14 (parents of females)	Rosenthal, et al., 2008[95]
Sexual relationships/ communication	H1a-r (parents) H1a-t (patients) J1a-f (all) J2-13 (patients)	Cox, Fasolino, & Tavakoli, 2008[124] Miller, et al., 1998[125] Gomez & Marin, 1996[127] Kelly et al., 1992[130] Kelly et al., 1997[131]
HPV Communication	I1a-e (all) I2-5 (parents)	Brabin, et al., 2006[112]

4.5 Survey Completion Thank You Letter

A Thank You Letter (Appendix 4) will be sent to each subject who completes the survey portion of the study.

5.0 METHODS: AIM 2 (VACCINE EVALUATION)

5.1 Study Design

The study design for Aim 2 (Vaccine Evaluation) is a single arm phase II open-label trial, to determine the immunogenicity and safety/tolerability of the quadrivalent HPV vaccine (HPV-6, -11, -16, -18; Gardasil®; Merck Research Laboratories; for patients enrolled on or before 3-1-16), and the nonavalent HPV vaccine (HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58; Gardasil ®9; Merck Research Laboratories; for patients enrolled after 3-1-16) among those cancer survivors identified to be unimmunized, and to explore response persistence to the qHPV and 9vHPV vaccines.

5.2 Identification/Recruitment of Participants

Eligible patients for Aim 2 (Vaccine Evaluation) will be identified by Aim 1 survey responses that indicate non-initiation of the HPV vaccine series (i.e., patients who have not received any HPV vaccine doses). Additionally, potentially eligible patients may be identified at the participating sites through patient rosters, cancer registry data, clinician referrals, databases, and/or medical records, or by similar methods. Patients may also be self- or parent- referred to the study. The study may be publicized via flyers or brochures placed in clinic, and/or distributed at institutional events that eligible patients and/or their parents are likely to attend, such as health fairs, holiday, or survivorship events. Additionally, information about the study may be included in institution-affiliated newsletters and/or websites, and in announcements such as “call on hold” messages recorded for the institution’s telephone system (see Appendix 5 for sample recruitment materials). Potentially eligible patients (or parents of patients under the age of 18) will be contacted by a study team member, who will confirm eligibility, including self- or parent-reported non-initiation of the HPV vaccine series, and will fully explain the study, including all risks, benefits and alternatives. Informed consent will be obtained in the patient/parent’s preferred language. Assent, along with parental consent, will be obtained from minors according to the policies at the participating institutions. For eligible patients who are approached and refuse study participation, reasons for refusal will be documented. Prior to enrollment, the treating clinician of each eligible patient will be contacted by a member of the institutional study team to obtain medical clearance for the patient’s participation. Patients who become 18 years of age during the study period will be re-consented at the first visit following their 18th birthday, and will sign a new consent form at that time.

Participants will be stratified based on age and gender due to difference in vaccine immunogenicity between males and females, and in younger (age 9-15) vs. older (age 16-26) cohorts within the general population.[30] The coordinating center (UAB) will track enrollment to each of four age/gender-based strata. Strata will close to enrollment once each stratum has attained the targeted number of participants; additional participants will be enrolled as necessary to replace any non-evaluable participants. An Appointment Reminder Letter (Appendix 6) may be sent to study participants to

facilitate scheduling of vaccine and follow-up laboratory appointments.

5.3 Data Abstraction

In addition to the medical record data abstraction described in Section 4.3 (demographics, diagnosis, standardized intensity of treatment rating), the study team will abstract detailed data regarding the patient's medical history and therapeutic exposures (e.g., names of surgeries, chemotherapy, radiation, and related dates), according to the *Children's Oncology Group's Cancer Treatment Summary Form* (see Appendix 7; modified version applies to patients enrolled after 3-1-16),[132] including details such as cumulative doses of selected chemotherapy, radiation, and immunosuppressive agents; and if applicable, date and type of HCT; presence and extent of chronic GvHD; and dose and duration of selected immunosuppressive agents post-HCT.

5.4 Vaccination Protocol

5.4.1

Quadrivalent HPV Vaccine (for patients enrolled on or before 3-1-16): The qHPV vaccine (HPV-6, -11, -16, -18 vaccine, recombinant; Gardasil®; Merck Research Laboratories) is a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate). The quadrivalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of aluminum-containing adjuvant and the final purification buffer.

Each 0.5 ml dose of the vaccine contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein. The vaccine also contains approximately 225 mcg of aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, less than 7 mcg yeast protein/dose, and water for injection. The vaccine does not contain preservatives (including thimerosal) or antibiotics.

Nonavalent HPV Vaccine (for patients enrolled after 3-1-16): The 9vHPV vaccine (HPV-6, -11, -16, -18, -31, -33, -45, -52, -58) vaccine, recombinant; Gardasil ®9; Merck Research Laboratories) is a non-infectious recombinant nonavalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate). The nonavalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of aluminum-containing adjuvant and the final purification buffer.

Each 0.5 ml dose of the vaccine contains approximately 30 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 60 mcg of HPV 16 L1 protein, 40 mcg of HPV 18 L1 protein, 20 mcg of HPV Type 31 L1 protein, 20 mcg of HPV Type 33 L1 protein, 20 mcg of HPV Type 45 L1 protein, 20 mcg of HPV Type 52 L1 protein, and 20 mcg of HPV Type 58 L1 protein. The vaccine also contains approximately 500

mcg of aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, less than 7 mcg yeast protein/dose, and water for injection. The vaccine does not contain preservatives (including thimerosal) or antibiotics.

5.4.2 Vaccine Supply and Storage

HPV vaccine for this study will be dispensed from a single lot (or if not possible due to expiration dates, from subsequent similar lots) by Merck Research Laboratories to the Investigational Pharmacist at each participating site. The Pharmacist at each site is required to maintain complete records of all study vaccines received from Merck Research Laboratories and subsequently dispensed, discarded, or returned. All unused vaccines must be destroyed on-site at the Investigational Pharmacy after the study is completed or terminated. Damaged or expired study vaccines are to be handled in the same manner.

The vaccine should be kept refrigerated at 2°C to 8°C (36°F to 46°F), protected from light, and should not be frozen. Any vaccine that becomes inadvertently frozen must be discarded.

Additional storage considerations for 9vHPV vaccine: The 9vHPV vaccine should be administered as soon as possible after being removed from refrigeration. The 9vHPV vaccine can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours. These are not, however, recommendations for storage.

5.4.3 Vaccine Preparation and Administration

The qHPV and 9vHPV vaccines are supplied in 0.5 ml single-dose vials. The vaccine vial should be agitated thoroughly immediately prior to administration to obtain a uniform suspension. After thorough agitation, the vaccine appears as a white, cloudy suspension. The vaccine should be used as supplied. No dilution or reconstitution is necessary. The vaccine should not be mixed in the same syringe or injected at the same site as other vaccines, and should not be injected intravenously or intradermally.

0.5 ml of the vaccine should be withdrawn from the single-dose vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents. The vaccine should be administered intramuscularly in the deltoid region of the upper arm (preferred site) preferably in the nondominant arm, or in the higher anterolateral area of the thigh (if the deltoid site is contraindicated). A 22 to 23 gauge needle long enough to ensure intramuscular deposition of the vaccine should be used, based on the patient's gender, weight, and site of administration (see Table 4 for preferred needle lengths). As with all vaccines, a solution of 1:1000 epinephrine will be available for injection should an anaphylactic reaction occur.

Table 4. Preferred needle length based on patient gender, weight, and administration site

Gender	Weight	Deltoid: Needle length	Anterolateral Thigh: Needle Length
Male or female	<60 kg	5/8" to 1"	All patients: 1 to 1-1/2"
Male or female	60-70 kg	1"	
Female	>70-90 kg	1" to 1-1/2"	
Male	>70-118 kg	1" to 1-1/2"	
Female	>90 kg	1-1/2"	
Male	>118 kg	1-1/2"	

5.4.4 Vaccine Administration Schedule

Each participant will receive three doses of HPV quadrivalent vaccine (HPV-6, -11, -16, -18; Gardasil®; Merck & Co, Inc.; patients enrolled on or before 3-1-16) or the 9vHPV vaccine (HPV-6, -11, -16, -18, -31, -33, -45, -52 and -58; Gardasil ®9; Merck Research Laboratories; patients enrolled after 3-1-16), according to the FDA-recommended 3-dose schedule: Dose #1: Day 1; Dose #2: 8 weeks after first

dose; Dose #3: 24 weeks after first dose. All attempts should be made for participants to receive vaccine at the designated time points (Day 1, Week 8, Week 24). Vaccine should not be given sooner than the following required minimum time intervals between doses: Dose 1 to Dose 2: 8 weeks; Dose 2 to Dose 3: 16 weeks. Acceptable windows for vaccine administration are indicated in Table 5. If vaccine administration is delayed, participants should continue on study and an attempt should be made to delay subsequent vaccine visits, if possible, while maintaining the acceptable windows. For example, if vaccine Dose #2 is delayed from Week 8 to Week 12, all subsequent visits should be delayed by 4 weeks, if possible, so that vaccine Dose #3 will occur at Week 28 (Week 24 + 4 weeks), and the 4-week post-vaccine Dose #3 visit will occur at Week 32 (Week 28 + 4 weeks) and so on, while maintaining the acceptable windows for vaccine administration and laboratory studies specified in Tables 5 and 6.

Table 5: Acceptable windows for vaccine administration

Interval	Dose 1	Dose 2	Dose 3
Minimum interval between vaccine doses	--	8 weeks	16 weeks
Maximum interval between vaccine doses	--	12 weeks	24 weeks
Acceptable vaccine administration window	Day 1	8-12 weeks after Dose 1	24-32 weeks after Dose 1, but no sooner than 16 weeks after Dose 2

5.4.5 Concurrent Therapies

Medications that may interfere with evaluation of the safety and tolerability of the vaccine should not be administered during the indicated timeframes unless medically necessary. Medications in this category include:

- Any live attenuated vaccine administered within 28 days before or after any HPV vaccine injection
- Any subunit or killed vaccines (e.g., influenza, pneumococcal, antigen injections for allergy treatment) within 14 days before or after any HPV vaccine injection

All vaccines and immunosuppressive agents (e.g., corticosteroids, calcineurin inhibitors) taken within 28 days of Dose #1, between Doses #1 and #2, between Doses #2 and #3, and 28 days after Dose #3 will be elicited by the study team and recorded on the Vaccine Visit Form (Appendix 8; completed at Dose 1, Dose 2, and Dose 3) or the Month 7 Visit Form (Appendix 9, completed at Month 7) and if applicable, on the Premature Study Discontinuation (PSD) Form (Appendix 10, completed at PSD visit or at declaration of loss to follow-up, see Section 5.4.13).

5.4.6 Laboratory Studies

Quantitative immunoglobulins: A 6 ml blood specimen for Quantitative Ig (immunoglobulin subsets), collected in a tube supplied by the institution's laboratory, will be drawn on Day 1 (prior to the first vaccine dose). Specimens for Quantitative Ig will be processed and run in the CLIA-approved clinical laboratories at each participating institution and the results reported to the coordinating center.

Anti-HPV -6, -11, -16, -18 (4cLIA; for patients enrolled on or before 3-1-16): A 10 ml blood specimen will be obtained in a non-additive, non-serum separator (non-SST) red top tube on Day 1 and at Months 7 and 24 (designated time windows in Table 6) to measure serum neutralizing antibodies to the 4 vaccine types (HPV-6, -11, -16, -18) using competitive Luminex immunoassays (cLIA). Geometric Mean Titers (GMT) for anti-HPV-6, -11, -16, -18 responses will be reported in milli-Merck Units per milliliter (mMU)/ml.[133,134]

Anti-HPV -6, -11, -16, -18, -31, -33, -45, -52, -58 (9cLIA; for patients enrolled after 3-1-16): A 10 ml blood specimen will be obtained in a non-additive, non-serum separator (non-SST) red top tube on Day 1 and at Months 7 and 24 (designated time windows in Table 6) to measure serum neutralizing antibodies to the 9 vaccine types (HPV-6, -11, -16, -18, -31, -33, -45, -52, -58) using competitive Luminex immunoassays (cLIA). Geometric Mean Titers (GMT) for anti-HPV-6, -11, -16, -18, -31, -33, -

45, -52, -58 responses will be reported in milli-Merck Units per milliliter (mMU)/ml.[133,134]

HPV-specific total immunoglobulins: HPV-specific total immunoglobulins (9 IgG) testing will be done using the same 10 ml specimen collected for Anti-HPV-6, -11, -16, -18 (for patients enrolled on or before 3-1-16) or for Anti-HPV-6, -11, -16, -18, -31, -33, -45, -52, -58 (for patients enrolled after 3-1-16) at the Month 24 time point only.

Specimens for Anti-HPV (4cLIA or 9cLIA) and HPV-specific total immunoglobulins (9 IgG) will be processed immediately, frozen, and subsequently shipped on dry ice to UAB where they will be stored frozen and batch-shipped to the PPD Vaccines and Biologics Laboratory, Merck Laboratory, and/or Focus Diagnostics Laboratory. *Refer to Appendix 11 for detailed instructions regarding specimen collection, labeling, processing, shipping, and storage*. Samples will be tested at PPD Vaccines and Biologics Laboratory, Merck Laboratory, and/or Focus Diagnostics Laboratory in 4cLIA or 9cLIA and 9IgG assays for immunogenicity measurements, and data results will be transferred on quality assured CD. After testing, samples will be stored at PPD Vaccines and Biologics Laboratory, Merck Laboratory, and/or Focus Diagnostics Laboratory at -20°C or lower for 3 months.

Table 6: Acceptable windows for laboratory studies

Study Time Point	Day 1	Month 7	Month 24
Acceptable window when laboratory studies can be drawn	Day 1	4-8 weeks after Vaccine Dose #3	72-84 weeks after Vaccine Dose #3
Studies to be drawn	Quantitative Immunoglobulins (Quant Ig); Anti-HPV (4cLIA for patients enrolled on or before 3-1-16; 9cLIA for patients enrolled after 3-1-16)	Anti-HPV (4cLIA for patients enrolled on or before 3-1-16; 9cLIA for patients enrolled after 3-1-16)	Anti-HPV (4cLIA for patients enrolled on or before 3-1-16; 9cLIA for patients enrolled after 3-1-16); HPV-specific total immunoglobulin (9 IgG)
Specimen requirement	6 ml in tube supplied by institution's clinical lab 10 ml in non serum-separating (non-SST) red top tube	10 ml in non-SST red top tube	10 ml in non-SST red top tube

5.4.7 Vaccine Dose #1 (Day 1)

5.4.7.1 Participants will be provided with education regarding HPV and the HPV vaccine using the most recent versions of the Centers for Disease Control (CDC) fact sheet as posted at www.cdc.gov/std/hpv/STDFact-HPV.htm or other age- and sex-appropriate materials from the CDC, such as materials posted at www.cdc.gov/vaccines/teens or www.cdc.gov/vaccines/who/teens/vaccines/hpv.html (samples in Appendix 12) and the most recent version of the Gardasil® (for patients enrolled on or before 3-1-16) or Gardasil ®9 (for patients enrolled after 3-1-16) Vaccine Information Statement (VIS) as posted at www.cdc.gov/vaccines/pubs/vis/default.htm (sample in Appendix 13).

5.4.7.2 Sexually active female participants of childbearing potential will be instructed to use contraception beginning with first vaccine dose and continuing until at least 4 weeks after all 3 vaccine doses have been administered. Participants will be queried prior to each dose to determine if there is a possibility of pregnancy. If there is any possibility of pregnancy, a pregnancy test (urine or blood as per local institutional preference and procedures) will be obtained prior to vaccine administration and if positive, the vaccine will be withheld and the participant withdrawn from receiving further vaccine on the study. The vaccine will not be administered to sexually active females who refuse contraception.

5.4.7.3 The following blood specimens will be drawn:
- Quantitative immunoglobulins (6 ml whole blood in tube supplied by institution's

clinical laboratory) – this specimen will be processed and analyzed by the clinical laboratories at the participating institution and results will be submitted to the coordinating center.

- Anti-HPV: 4cLIA for patients enrolled on or before 3-1-16; 9cLIA for patients enrolled after 3-1-16 (10 ml whole blood in non SST red top tube)
- Specimens (other than for Quantitative immunoglobulins) will be processed and shipped to the coordinating center according to the instructions in Section 5.4.6. and Appendix 11.

5.4.7.4 Targeted review of systems/ screening for acute illness and medication review will be performed. Vaccine administration must be rescheduled if any of the following are present:

- Serious active infection (afebrile upper respiratory infection is not considered a serious infection)
- Fever ≥100°F or ≥37.8°C (oral) within 24 hours prior to the visit
- Receipt of any vaccines within 2-4 weeks prior to visit (as per Section 5.4.5)
- Receipt of any blood products or transfusions within 3 months prior to visit
- If acute or chronic medical or surgical conditions or contraindications not described above are present, the site investigator should consult with the coordinating center PI to obtain clearance to administer the vaccine

Vaccine Visit Form (Appendix 8) will be completed and submitted.

5.4.7.5 HPV Vaccine Dose #1 (Gardasil® for patients enrolled on or before 3-1-16; Gardasil ®9 for patients enrolled after 3-1-16) will be administered (0.5 ml IM per instructions in Section 5.4.3). Syncope has been reported following vaccine administration and may result in falling with injury; participant will be observed for 30 minutes following vaccine administration to assess for any adverse reactions. As with all vaccines, a solution of 1:1000 epinephrine will be available for injection in the event an anaphylactic reaction were to occur.

5.4.7.6 Participant will be provided with a Vaccine Report Card Kit (thermometer, metric tape measure, and Vaccine Report Card [adverse events diary]) and asked to record oral temperature 4 hours after the vaccine injection and then daily for 5 days following vaccine administration, and to record any adverse symptoms in the diary daily for 7 days (for patients enrolled after 3-1-16) or 14 days (for patients enrolled on or before 3-1-16) post vaccine administration (Appendix 14). The patient or parent/caregiver will be instructed to report any unusual reactions immediately; participants reporting any grade 3 or higher symptoms will be instructed to return to the clinic within 24 hours for evaluation and management. An Adverse Events/Research-Related Problems Reporting Form (AERF – Appendix 15) will be completed and submitted for all adverse events or unanticipated problems requiring expedited reporting (as defined in Section 9.3.2).

5.4.7.7 **For patients enrolled on or before 3-1-16**: Study team member will contact patient (or parent/caregiver) 2 to 3 days following vaccine administration (if unable to reach, regular attempts will continue to be made to contact the patient or parent/caregiver on business days up to 1 week post visit), and again 2 weeks (preferred timeframe: 15-20 days) following vaccine administration (if unable to reach, regular attempts will

continue be made to contact the patient or parent/caregiver on business days up to 3 weeks post visit and then weekly thereafter),to evaluate for any vaccine-related complications. If the patient or parent/caregiver does not respond, they will be asked to provide the information from their Vaccine Report Card at the next scheduled study visit. Data may continue to be collected outside of the suggested timeframes, if necessary. Each item on the Vaccine Report Card form (Appendix 14) will be reviewed with the patient or parent/caregiver and the information recorded by the study team member onto the electronic Vaccine Report Card form within the study database. The Vaccine Report Card completed by the study team member during the follow-up contacts, will be submitted to the study coordinating center via database export. An Adverse Events/Research-Related Problems Reporting Form (AERF – Appendix 15) will be completed and submitted to the coordinating center for all adverse events or unanticipated problems identified during these contacts that meet criteria for expedited reporting (as defined in Section 9.3.2) within 2 business days of becoming aware of the event/problem .

For patients enrolled after 3-1-16: The patient (or parent/caregiver) will be instructed to contact their healthcare provider (and, when feasible, notify the study team) should they experience any severe symptoms (as defined on the Vaccine Report Card) within 2 weeks of vaccine receipt. A study team member will contact the patient (or parent/caregiver) one week (i.e., Day 8, or the first business day after Day 8) following vaccine administration (if unable to reach, regular attempts will continue to be made to contact the patient or parent/caregiver on business days up to 2 weeks post visit) to evaluate for any vaccine-related complications. If the patient or parent/caregiver does not respond, they will be asked to provide the information from their Vaccine Report Card at the next scheduled study visit. Data may continue to be collected outside of the suggested timeframes, if necessary. Each item on the Vaccine Report Card form (Appendix 14) will be reviewed with the patient or parent/caregiver and the information recorded by the study team member onto the electronic Vaccine Report Card form within the study database. The Vaccine Report Card completed by the study team member during the follow-up contact, will be submitted to the study coordinating center via database export. An Adverse Events/Research-Related Problems Reporting Form (AERF – Appendix 15) will be completed and submitted to the coordinating center for all adverse events or unanticipated problems identified during this contact that meet criteria for expedited reporting (as defined in Section 9.3.2), within 2 business days of becoming aware of the event/problem.

5.4.8 Vaccine Dose #2

Note: this visit must be conducted no less than 8 weeks after Vaccine Dose #1, and no later than Week 12

5.4.8.1 Sexually active female participants of childbearing potential will be instructed to use contraception beginning with first vaccine dose and continuing until at least 4 weeks after all 3 vaccine doses have been administered. Participants will be queried prior to each dose to determine if there is a possibility of pregnancy. If there is any possibility of pregnancy, a pregnancy test (urine or blood as per local institutional preference and procedures) will be obtained prior to vaccine administration and if positive, the vaccine will be withheld and the participant withdrawn from receiving further vaccine on the study. The vaccine will not be administered to sexually active females who refuse contraception.

5.4.8.2 Targeted review of systems/ screening for acute illness and medication review will be performed. Vaccine administration must be rescheduled if any of the following are present:

- Serious active infection (afebrile upper respiratory infection is not considered a serious infection)
- Fever ≥100°F or ≥37.8°C (oral) within 24 hours prior to the visit
- Receipt of any vaccines within 2-4 weeks prior to visit (as per Section 5.4.5)
- If acute or chronic medical or surgical conditions or contraindications not described above are present, the site investigator should consult with the coordinating center PI to obtain clearance to administer the vaccine.

Vaccine Visit Form (Appendix 8) will be completed and submitted.

The most recent version of the Gardasil® (for patients enrolled on or before 3-1-16) or Gardasil ®9 (for patients enrolled after 3-1-16) Vaccine Information Statement (VIS), as posted at www.cdc.gov/vaccines/pubs/vis/default.htm (sample in Appendix 13), will be given to the patient/parent.

5.4.8.3 HPV Vaccine Dose #2 (Gardasil® for patients enrolled on or before 3-1-16; Gardasil ®9 for patients enrolled after 3-1-16) will be administered (0.5 ml IM per instructions in Section 5.4.3). Syncope has been reported following vaccine administration and may result in falling with injury; participant will be observed for 30 minutes following vaccine administration to assess for any adverse reactions. As with all vaccines, a solution of 1:1000 epinephrine will be available for injection in the event an anaphylactic reaction were to occur.

5.4.8.4 Participant was provided with a Vaccine Report Card Kit (thermometer, metric tape measure) on Day 1; this will be re-supplied if necessary. The participant will be given a Vaccine Report Card [adverse events diary] and asked to record oral temperature 4 hours after the vaccine injection and then daily for 5 days following vaccine administration, and to record any adverse symptoms in the diary daily for 7 days (for patients enrolled after 3-1-16) or 14 days (for patients enrolled on or before 3-1-16) post vaccine administration (Appendix 14). The patient or parent/caregiver will be instructed to report any unusual reactions immediately; participants reporting any grade 3 or higher symptoms will be instructed to return to the clinic within 24 hours for evaluation and management. An Adverse Events/Research-Related Problems Reporting Form (AERF – Appendix 15) will be completed and submitted for all adverse events or unanticipated problems requiring expedited reporting (as defined in Section 9.3.2).

5.4.8.5 **For patients enrolled on or before 3-1-16**: Study team member will contact patient (or parent/caregiver) 2 to 3 days following vaccine administration (if unable to reach, regular attempts will continue to be made to contact the patient or parent/caregiver on business days up to 1 week post visit), and again 2 weeks (preferred timeframe: 15-20 days) following vaccine administration (if unable to reach, regular attempts will continue be made to contact the patient or parent/caregiver on business days up to 3 weeks post visit and then weekly thereafter),to evaluate for any vaccine-related complications. If the patient or parent/caregiver does not respond, they will be asked

to provide the information from their Vaccine Report Card at the next scheduled study visit. Data may continue to be collected outside of the suggested timeframes, if necessary. Each item on the Vaccine Report Card form (Appendix 14) will be reviewed with the patient or parent/caregiver and the information recorded by the study team member onto the electronic Vaccine Report Card form within the study database. The Vaccine Report Card completed by the study team member during the follow-up contacts, will be submitted to the study coordinating center via database export. An Adverse Events/Research-Related Problems Reporting Form (AERF – Appendix 15) will be completed and submitted to the coordinating center for all adverse events or unanticipated problems identified during these contacts that meet criteria for expedited reporting (as defined in Section 9.3.2) within 2 business days of becoming aware of the event/problem .

For patients enrolled after 3-1-16: The patient (or parent/caregiver) will be instructed to contact their healthcare provider (and, when feasible, notify the study team) should they experience any severe symptoms (as defined on the Vaccine Report Card) within 2 weeks of vaccine receipt. A study team member will contact the patient (or parent/caregiver) one week (i.e., Day 8, or the first business day after Day 8) following vaccine administration (if unable to reach, regular attempts will continue to be made to contact the patient or parent/caregiver on business days up to 2 weeks post visit) to evaluate for any vaccine-related complications. If the patient or parent/caregiver does not respond, they will be asked to provide the information from their Vaccine Report Card at the next scheduled study visit. Data may continue to be collected outside of the suggested timeframes, if necessary. Each item on the Vaccine Report Card form (Appendix 14) will be reviewed with the patient or parent/caregiver and the information recorded by the study team member onto the electronic Vaccine Report Card form within the study database. The Vaccine Report Card completed by the study team member during the follow-up contact, will be submitted to the study coordinating center via database export. An Adverse Events/Research-Related Problems Reporting Form (AERF – Appendix 15) will be completed and submitted to the coordinating center for all adverse events or unanticipated problems identified during this contact that meet criteria for expedited reporting (as defined in Section 9.3.2), within 2 business days of becoming aware of the event/problem.

5.4.9 Vaccine Dose #3

Note: this visit must be conducted no earlier than 16 weeks after Vaccine Dose #2 and no later than Week 32

5.4.9.1 Sexually active female participants of childbearing potential will be instructed to use contraception beginning with first vaccine dose and continuing until at least 4 weeks after all 3 vaccine doses have been administered. Participants will be queried prior to each dose to determine if there is a possibility of pregnancy. If there is any possibility of pregnancy, a pregnancy test (urine or blood as per local institutional preference and procedures) will be obtained prior to vaccine administration and if positive, the vaccine will be withheld and the participant withdrawn from receiving further vaccine on the study. The vaccine will not be administered to sexually active females who refuse contraception.

5.4.9.2 Targeted review of systems/ screening for acute illness and medication review will be performed. Vaccine administration must be rescheduled if any of the following are

present:

- Serious active infection (afebrile upper respiratory infection is not considered a serious infection)

- Fever ≥100°F or ≥37.8°C (oral) within 24 hours prior to the visit

- Receipt of any vaccines within 2-4 weeks prior to visit (as per Section 5.4.5)

- If acute or chronic medical or surgical conditions or contraindications not described above are present, the site investigator should consult with the coordinating center PI to obtain clearance to administer the vaccine

Vaccine Visit Form (Appendix 8) will be completed and submitted.

The most recent version of the Gardasil® (for patients enrolled on or before 3-1-16) or Gardasil ®9 (for patients enrolled after 3-1-16) Vaccine Information Statement (VIS), as posted at www.cdc.gov/vaccines/pubs/vis/default.htm (sample in Appendix 13), will be given to the patient/parent.

5.4.9.3 HPV Vaccine Dose #3 (Gardasil® for patients enrolled on or before 3-1-16; Gardasil ®9 for patients enrolled after 3-1-16) will be administered (0.5 ml IM per instructions in Section 5.4.3). Syncope has been reported following vaccine administration and may result in falling with injury; participant will be observed for 30 minutes following vaccine administration to assess for any adverse reactions. As with all vaccines, a solution of 1:1000 epinephrine will be available for injection in the event an anaphylactic reaction were to occur.

5.4.9.4 Participant was provided with a Vaccine Report Card Kit (thermometer, metric tape measure) on Day 1; this will be re-supplied if necessary. The participant will be given a Vaccine Report Card [adverse events diary] and asked to record oral temperature 4 hours after the vaccine injection and then daily for 5 days following vaccine administration, and to record any adverse symptoms in the diary daily for 7 days (for patients enrolled after 3-1-16) or 14 days (for patients enrolled on or before 3-1-16) post vaccine administration (Appendix 14). The patient or parent/caregiver will be instructed to report any unusual reactions immediately; participants reporting any grade 3 or higher symptoms will be instructed to return to the clinic within 24 hours for evaluation and management. An Adverse Events/Research-Related Problems Reporting Form (AERF – Appendix 15) will be completed and submitted for all adverse events or unanticipated problems requiring expedited reporting (as defined in Section 9.3.2).

5.4.9.5 **For patients enrolled on or before 3-1-16**: Study team member will contact patient (or parent/caregiver) 2 to 3 days following vaccine administration (if unable to reach, regular attempts will continue to be made to contact the patient or parent/caregiver on business days up to 1 week post visit), and again 2 weeks (preferred timeframe: 15-20 days) following vaccine administration (if unable to reach, regular attempts will continue be made to contact the patient or parent/caregiver on business days up to 3 weeks post visit and then weekly thereafter),to evaluate for any vaccine-related complications. If the patient or parent/caregiver does not respond, they will be asked to provide the information from their Vaccine Report Card at the next scheduled study visit. Data may continue to be collected outside of the suggested timeframes, if necessary. Each item on the Vaccine Report Card form (Appendix 14) will be reviewed with the patient or parent/caregiver and the information recorded by the

study team member onto the electronic Vaccine Report Card form within the study database. The Vaccine Report Card completed by the study team member during the follow-up contacts, will be submitted to the study coordinating center via database export. An Adverse Events/Research-Related Problems Reporting Form (AERF – Appendix 15) will be completed and submitted to the coordinating center for all adverse events or unanticipated problems identified during these contacts that meet criteria for expedited reporting (as defined in Section 9.3.2) within 2 business days of becoming aware of the event/problem .

For patients enrolled after 3-1-16: The patient (or parent/caregiver) will be instructed to contact their healthcare provider (and, when feasible, notify the study team) should they experience any severe symptoms (as defined on the Vaccine Report Card) within 2 weeks of vaccine receipt. A study team member will contact the patient (or parent/caregiver) one week (i.e., Day 8, or the first business day after Day 8) following vaccine administration (if unable to reach, regular attempts will continue to be made to contact the patient or parent/caregiver on business days up to 2 weeks post visit) to evaluate for any vaccine-related complications. If the patient or parent/caregiver does not respond, they will be asked to provide the information from their Vaccine Report Card at the next scheduled study visit. Data may continue to be collected outside of the suggested timeframes, if necessary. Each item on the Vaccine Report Card form (Appendix 14) will be reviewed with the patient or parent/caregiver and the information recorded by the study team member onto the electronic Vaccine Report Card form within the study database. The Vaccine Report Card completed by the study team member during the follow-up contact, will be submitted to the study coordinating center via database export. An Adverse Events/Research-Related Problems Reporting Form (AERF – Appendix 15) will be completed and submitted to the coordinating center for all adverse events or unanticipated problems identified during this contact that meet criteria for expedited reporting (as defined in Section 9.3.2), within 2 business days of becoming aware of the event/problem.

5.4.10 Month 7: 4-8 Weeks Following Final Vaccine Dose

Note: this visit must be conducted no earlier than 4 weeks and no later than 8 weeks after Vaccine Dose #3

5.4.10.1 The following blood specimens will be drawn:

- Anti-HPV 4cLIA for patients enrolled on or before 3-1-16 or 9cLIA for patients enrolled after 3-1-16: 10 ml whole blood in non-SST red top tube

Specimens will be processed and shipped to the coordinating center according to the instructions in Section 5.4.6. and Appendix 11.

5.4.10.2 Month 7 Visit Form (Follow-Up #1; Appendix 9) will be completed and submitted.

5.4.11 Month 24: 72-84 Weeks (~ 2 Years) Following Vaccine Dose #1

Note: this visit must be conducted no less than 72 weeks and no later than 84 weeks after Vaccine Dose #3.

5.4.11.1 The following blood specimens will be drawn:

- Anti-HPV 4cLIA for patients enrolled on or before 3-1-16 or 9cLIA for patients enrolled after 3-1-16, and HPV-specific total immunoglobulin (9 IgG): 10 ml whole

blood in non-SST red top tube

Specimens will be processed and shipped to the coordinating center according to the instructions in Section 5.4.6. and Appendix 11.

5.4.11.2 Month 24 Visit Form (Follow-Up #2; Appendix 16) will be completed and submitted.

5.4.12 Premature Study Discontinuation Visit

Administration of the study vaccine must stop permanently and a Premature Study Discontinuation Visit scheduled if any of the following occur:

- A confirmed Grade $\geq$ 3 toxicity that is deemed possibly, probably, or definitely vaccine-related and not resolved to $\leq$ Grade 1 by the next due date for vaccine administration
- A Grade $\geq$3 toxicity recurs after the next administration of the study vaccine
- A Grade 4 life-threatening toxicity whose relationship to the vaccine is possibly, probably, or definitely related
- The investigator determines that receipt of additional study vaccines would be detrimental to the participant's health or well-being
- The participant becomes pregnant
- The participant withdraws consent
- The participant fails to comply with study requirements so as to cause harm to herself/himself or seriously interfere with the validity of the study results
- The subject is unable to continue participation due to circumstances preventing completion of study procedures
- The study is stopped by a government agency, such as the National Institutes of Health (NIH)
- The study is stopped for other administrative reasons

Participants who are to be permanently discontinued from the study will complete a final premature study discontinuation visit before going off study, at which time the following data will be collected:

5.4.12.1 The following blood specimens will be drawn:

- Anti-HPV 4cLIA for patients enrolled on or before 3-1-16 or 9cLIA for patients enrolled after 3-1-16: 10 ml whole blood in non-SST red top tube

Specimens will be processed and shipped to the coordinating center according to the instructions in Section 5.4.6. and Appendix 11.

5.4.12.2 Premature Study Discontinuation Form (Appendix 10) will be completed and submitted.

5.4.13 End of Study

For patients completing the study prematurely (e.g., due to withdrawal), a Premature Study Discontinuation Form (Appendix 10) will be completed and submitted. For subjects who are lost to follow-up prior to Month 24, the Premature Study Discontinuation Form will be completed at the time the subject is deemed by the site PI to have ended their participation in the study. For subjects who complete all study time points, no study completion form is required. A Thank You Letter (Appendix 17) will be sent to each subject that completes the Month 24 time point.

6.0 HUMAN SUBJECTS ISSUES

6.1 Potential Benefits

Aim 1 (Survey): There are no potential benefits to survey participation; however, benefits to future patients may occur, including increased knowledge regarding prevalence and determinants of HPV vaccine initiation among cancer survivors, which could potentially inform future interventions to improve HPV vaccine uptake among cancer survivors.

Aim 2 (Vaccine Evaluation): Potential benefits to the participant include the administration of the HPV vaccine, which has been shown in the general population to be highly protective for HPV infection. The 3-dose vaccine series will be provided at no charge to the participant. Additionally, benefits to future patients may potentially occur as a result of the increased knowledge gained from this study regarding safety, tolerability, and immunogenicity of the quadrivalent and nonavalent HPV vaccine in cancer survivors.

6.2 Potential Risks

Aim 1 (Survey): It is possible that some participants may be uncomfortable answering questions regarding their sexual history and activity; however, these questions are considered part of standard adolescent/young adult health care. Nevertheless, participants will be informed that if they do not want to answer any questions for any reason, they may skip those questions.

Aim 2 (Vaccine Evaluation): The primary risk associated with Aim 2 are the risks associated with administration of the HPV vaccine, which is believed to be safe when administered in the general population, but which has not been studied in cancer survivors. Common side effects reported in the general population have included skin redness, pain, swelling, and/or muscle soreness at the injection site. Syncope has been reported following vaccine administration and may result in falling with injury; participants will therefore be observed for 30 minutes in the clinic following vaccine administration. Some patients may experience mild to moderate fever, chills, nausea, fatigue, or headache following the vaccine. These symptoms are usually transient and resolve without intervention. Although rare, serious side effects can occur and may include rash, urticaria, dyspnea, stridor, wheezing, edema of the face, lips, or throat, pruritis, seizures, tachycardia, hypotension, and shock, or other side effects that are currently unknown in this population. As with all vaccines, a solution of 1:1000 epinephrine will be available for injection should an anaphylactic reaction occur. Since the HPV vaccine has not been tested in cancer survivors, severity of side effects could potentially be increased in this patient population and side effects that are currently unknown could potentially occur. Additionally, the drawing of blood specimens may cause local discomfort, bleeding, or bruising; rarely a small clot or infection can occur at the site of the venipuncture.

6.3 Risk to Benefit Ratio

Aim 1 (Survey): The primary risks associated with survey completion include participant discomfort regarding answering questions regarding their sexual history and activity; however, these questions are considered part of standard adolescent/young adult health care. There is no direct benefit to participation; however, there is potential benefit in regard to knowledge gained that may be of benefit to future patients.

Aim 2 (Vaccine Evaluation):
The primary risk associated with Aim 2 are the risks associated with administration of the HPV vaccine, which is believed to be safe when administered in the general population, but which has not been

studied in cancer survivors. Reactions to the vaccine may include pain, swelling, muscle soreness and/or skin redness at the site of the injection, fever, chills, nausea, fatigue, and headache. Although rare, serious side effects can occur and may include rash, urticaria, dyspnea, stridor, wheezing, edema of the face, lips, or throat, pruritis, seizures, tachycardia, hypotension, and shock, or other side effects that are currently unknown in this population. Additionally, the drawing of blood specimens may cause local discomfort, bleeding, or bruising; rarely a small clot or infection can occur at the site of the venipuncture. Benefits include potential protection against the HPV vaccine subtypes, including the highly oncogenic subtypes 16 and 18, which currently are known to cause 70% of all cervical cancers and protection against subtypes 6 and 11, which are currently known to cause 90% of genital warts;[29] Additionally, patients enrolled after 3-1-16 will receive the nonavalent vaccine, which has been shown in the general population to provide protection against 85-90% of the oncogenic HPV subtypes associated with cervical cancer, 85-90% of vulvar cancers, 80-85% of vaginal cancers, and 90-95% of anal cancers. Therefore, if the vaccine is adequately immunogenic in this population, participants may potentially receive the significant benefit of protection against cervical, penile, anal, and orophyrangeal cancers and genital warts. Additionally, future patients may benefit from the determination of the safety, immunogenicity, and optimal timing of HPV vaccine administration among cancer survivors.

6.4 Precautions

Protection against Risk. In order to protect participants from any potential risks associated with the current study, the following assurances will be adhered to: (1) participation is voluntary and consent to participate can be withdrawn at any point within the study without penalty, (2) prospective participants who do not wish to volunteer for the current study will not lose their access to medical services at their treating institution (3) all participants will be informed of foreseeable benefits and risks, (4) all data collected from participants or via medical chart review will be stored on a secure computer and/or locked file cabinet(s). In addition, participants will be informed that they have the right to refuse to continue their participation without penalty for any personal reason. If participants indicate that they are experiencing emotional or psychological issues related to topics raised by the study questionnaire, they will be evaluated by a nurse or social worker. Referrals to a psychologist will be available if applicable. If significant reactions to the study vaccine occur, the treating clinician, site PI, and/or the study PI may remove a participant from the study.

Safety Monitoring: Participant safety will be monitored as outlined in Section 9.0 (Data Safety and Monitoring Plan).

6.5 Alternatives

The patient may choose (or for minors the parent/guardian may choose for the patient) not to participate in the study.

6.6 Confidentiality

All data collected by the researchers will remain confidential. Study information will be made as anonymous as possible through the use of codes, files will be stored in locked cabinets, and all database records will require a password in order to access study data. Only personnel directly involved with the study will have access to the study data, including the primary investigator, co-investigators, research assistants, and study personnel. Patient data in published study results will not include personal identifying information such as name.

6.7 Financial Obligations and Compensation

There is no charge for participation in this study. Vaccines and related preparation and administration charges and all study-related labs will be provided without cost to the participant. To compensate Aim 2: Vaccine Evaluation participants for their time and transportation expenses related to study participation, participants will receive $100 (or equivalent voucher/gift card) at Month 7 and $75 (or

equivalent voucher/gift card) at Month 24.

6.8 Informed Consent Process

Informed consent will be obtained from each patient (of age of majority) according to the approved procedures of the institutional review board (IRB) or Ethics Committee at each participating institution. Consent of the parent/guardian and assent of the patient will be obtained for each minor participant according to the policies and procedures in place at each participating institution and according to the laws in the state where the informed consent is being signed. The original consent form will be placed in the medical record. A copy will be given to the participant and a copy will be filed with the research record.

7.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

7.1 Evaluable Patients

Aim 1 (Survey): A subject will be considered evaluable if they complete the survey item indicating HPV vaccine initiation/non-initiation and for whom medical record abstraction data is submitted as described in Section 4.3.

Aim 2 (Vaccine Evaluation): A subject will be considered evaluable for the primary (immunogenicity) aim if they are seronegative for HPV-16 and/or HPV-18 at baseline, complete all 3 HPV vaccine doses within the specified administration windows (Section 5.4.4), have evaluable Month 7 Anti-HPV 4cLIA (for patients enrolled on or before 3-1-16) or 9cLIA (for patients enrolled after 3-1-16) results that were drawn within the acceptable window (Section 5.4.6), and for whom medical record abstraction data is submitted as described in Section 5.3. Safety data will be reported on all eligible subjects who receive at least one dose of vaccine, regardless of whether they are evaluable for the additional study aims.

7.2 Primary Endpoints

Aim 1 (Survey):

1. HPV vaccine non-initiation

Aim 2 (Vaccine Evaluation):

1. HPV antibody titers (Anti-HPV 4cLIA [for patients enrolled on or before 3-1-16] or 9cLIA [for patients enrolled after 3-1-16] [Geometric Mean Titers; Seropositivity] (Day 1, Month 7, and Month 24) [Immunogenicity]
2. Vaccine Report Card (participant/parent diary of adverse events, collected for 7 days (for patients enrolled after 3-1-16) or 14 days (for patients enrolled on or before 3-1-16) following each vaccine dose, and Adverse Events/Research-Related Problems Reporting Forms [Safety/tolerability]

7.3 Schema – Aim 1: Survey

Aim 1: Survey

[Protocol v3, 8/17/15: Accrual goal for Aim 1 met, enrollment to survey closed]

Requirement	Pre-Entry	Study Entry
Verification of eligibility (Protocol Section 3.1)	**X**	
Informed consent/assent		**X**
Registration		**X**
Medical record abstraction: - Medical Record Review Form (Appendix 1) - Intensity of Treatment Rating Scale (Appendix 2)		**X**
Survey completion (Appendix 3)		**X**

7.4 Schema – Aim 2:Vaccine Evaluation

Aim 2: Vaccine Evaluation

Requirement	Pre-entry	Day 1	Dose #2	Dose #3	Month 7	Month 24	PSD*
Verification of eligibility (Protocol Sections 3.2 and 3.3)	X						
Permission for participation from treating clinician	X						
Informed consent/assent		X					
Medical record abstraction: Cancer Treatment Summary Form (Appendix 7)					X		
Patient/parent education (Appendix 12, 13)		X	X	X			
Targeted review of systems Screening for acute illness Screening for pregnancy (if indicated) Vaccine Visit Form (Appendix 8)		X	X	X			
HPV Vaccine		**Dose #1**	**Dose #2**	**Dose #3**			
Vaccine Report Card (Appendix 14) x 7 days (if enrolled after 3-1-16) or 14 days (if enrolled on or before 3-1-16) post each vaccine dose, including home temperature monitoring 4 hours after each vaccine dose, then daily x 5 days		X	X	X			
Quantitative Ig [humoral immunity]		X					
Anti-HPV 4cLIA (if enrolled on or before 3-1-16) or 9cLIA (if enrolled after 3-1-16) [geometric mean titers and HPV type-specific seropositivity]		X			X	X	X
HPV-specific total immunoglobulin [qualitative aspects of HPV-specific humoral response]						X	
Adverse Events/Research-Related Problems Form (AERF; Appendix 15)		→	→	→	→	→	→
Month 7 Visit Form (Follow-Up #1) (Appendix 9)					X		
Month 24 Visit Form (Follow-Up #2) (Appendix 16)						X	
Premature Study Discontinuation (PSD) Form (Appendix 10)†							X

*PSD = Premature Study Discontinuation (collected at PSD clinic visit or when deemed lost to follow-up; see Section 5.4.12)

→ = AERF to be completed as needed at any study time point

†PSD Form will also be completed as needed at any time point that participation is terminated prematurely

8.0 STATISTICAL METHODS

8.1 Sample Size

Aim 1 (Survey): A sample size of 1090 eligible subjects is required to address Specific Aim 1. We have chosen this sample size based on our preliminary study (Section 2.9), from which we can assume that 90% (n=981) of those approached will participate in the survey. A sample of 981 survey participants for Specific Aim 1 will provide 80% power to reject the null hypothesis that the prevalence (p) of HPV vaccine initiation is ≤0.4 if the true p is at least 0.44 (one-sided test, Type I error=0.05). It will also provide a 2-sided 95% confidence interval (CI) of sample p±.061 if true p=0.4.
[Protocol v3, 8/17/15: Accrual goal for Aim 1 met, enrollment to survey closed]

Aim 2 (Vaccine Evaluation):

qHPV Vaccine Cohort (patients enrolled on or before 3-1-16): Based on national vaccine initiation rates and our preliminary data (Section 2.9),[40] we conservatively assume that 60% (n=589) of the 981 survey participants will have not initiated the HPV vaccine. Based on our data (Section 2.9) and prior trials,[30,31,135] we conservatively assume that of the non-vaccinated survey participants, 60% (n=353) will agree to receive the vaccine, 96% (n=339) will be seronegative at baseline (Intent to Treat [IT] sample), and 92% (n=312) will complete all 3 doses, yielding 312 (Per-Protocol [PP]) subjects who will have received all 3 doses of qHPV vaccine for examining Aim 2.1. This sample size was calculated using the mean GMT and SD reported by Merck & Co.[28] for healthy males and females aged 9-15 years and 16-26 years as the historical healthy population. The following assumptions were made: i) cancer survivors were similarly distributed in regard to immunogenicity with the same SD as in this healthy population; ii) margin of equivalence (E) was ½ of the mean GMT of the healthy population (Table 7). Using the method of Korn and Freidlin[136] for sample size calculations using historical controls, a total of 312 subjects (72 younger females, 77 older females, 82 younger males, and 81 younger males) will provide 80% power to demonstrate non-inferiority with respect to anti-HPV-16, and/or -18 GMT in cancer survivors compared to the healthy population assuming a one-sided t-test, Type I error =0.00312 (for an overall Type I error =0.025), and margin of equivalence (E) shown in Table 7 by sex and age for each vaccine type.

Table 7. Sample Size for Aim 2 (Vaccine Evaluation)

Females

Anti-HPV	9-15y (younger)					16-26y (older)				
	Healthy	Cancer	E	SD	N	Healthy	Cancer	E	SD	N
16	4918.5	2459.3	2459.25	5585.26	**72**	2411.3	1205.65	1205.65	2915.77	**77**
18	1042.6	521.3	521.30	1161.91	69	475.6	237.80	237.80	500.01	58

Males

16	6056.5	3028.3	3028.25	6895.81	72	2401.5	1200.75	1200.75	2747.45	72
18	1357.4	678.7	678.70	1641.08	**82**	402.6	201.30	201.30	489.9	**81**

Sample size required = 312

The coordinating center will track enrollment to each stratum (Younger Females, Older Females, Younger Males, Older Males), and will close enrollment to each stratum once the targeted number of evaluable participants has been reached.

9vHPV Vaccine Cohort (patients enrolled after 3-1-16): Results of interim data analysis on the qHPV vaccine cohort (performed in January 2016 with data from patients who had a Month 7 sample available for analysis on or before 8-28-15; N=133) indicate that the cohort enrolled on or before 3-1-16 (N=254) who have received/are receiving the qHPV vaccine will be more than sufficient to address non-inferiority (i.e., lower limit of the multiplicity-adjusted 95% confidence intervals for the ratio of the mean geometric mean titer for anti-HPV-16 and -18 in the cancer vs. healthy population >0.5 for each

age/gender group) of the qHPV vaccine in cancer survivors. We are therefore extending the study to evaluate non-inferiority of the 9vHPV vaccine; interim data analysis results from the qHPV vaccine cohort indicate that an additional 200 patients will be sufficient to perform this evaluation in cancer survivors.

8.2 Data Analysis

8.2.1. Aim 1 (Survey)

8.2.1.1. Estimate the prevalence of HPV vaccine initiation in cancer survivors ages 9 to 26 years. Examine the sociodemographic, behavioral, and medical determinants of HPV vaccine non-initiation

The outcome is HPV vaccine initiation status (Yes: received at least one dose/ No: never received any doses) at the time of survey completion. The prevalence (p) of qHPV vaccine initiation among 981 survey participants and its 2-sided 95% CI will be calculated. A one-sided t-test of H_o: $p \leq 0.4$ will be conducted using Type I error=0.05. Significant predictors of vaccine initiation will be identified using logistic regression. We will consider predictors relevant to vaccine acceptance or refusal, including sociodemographic (e.g., age, sex, education, race/ethnicity, income), medical (e.g., cancer diagnosis, intensity of treatment, conventional treatment vs. HCT), and behavioral (e.g., perceived susceptibility to HPV, perceived severity of consequences of HPV infection, attitudes toward vaccination, attitudes toward healthcare provider recommendation of vaccine, engagement in health promotion behaviors, knowledge regarding association of HPV with cancer, familial decision-making style). A sample size of 981 will provide 80% power at 5% significance level to detect an odds ratio of 1.45 to 2.0 for a dichotomous variable with 50% of the sample in one group.

8.2.2. Aim 2 (Vaccine Evaluation)

8.2.2.1. Determine immunogenicity of qHPV and 9vHPV vaccine 1 month following the third and final vaccine dose

The primary analytic approach will be per-protocol (PP)[30] analysis; intention to treat analysis will also be conducted. The evaluation will be completed separately for the qHPV and 9vHPV cohorts. The sample size is powered to determine whether vaccine-induced anti-HPV-16 and -18 neutralizing antibody response in cancer survivors is comparable to the age- and sex-matched general population (Table 7); PP immunogenicity population includes participants who are seronegative for the oncogenic vaccine components of primary interest (HPV-16, -18) on Day 1, complete all three vaccine doses within the protocol-specified time frames, and have immunogenicity data available at the time of analysis. Each vaccine component will be analyzed separately, and we will adjust for intensity of treatment. Anti-HPV-6 and -11 (and in the 9vHPV cohort, Anti-HPV-31, -33, -45, -52, and -58) response will also be explored. The primary outcome of interest is GMT. We will also assess seropositivity rates among cancer survivors. Seropositivity (binary variable) is defined as: <u>qHPV cohort</u>: Anti-HPV-6, -11, -16, and -18 titer <u>≥</u> 20, 16, 20, and 24 mMU/ml respectively;[30] <u>9vHPV cohort</u>: Anti-HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58 titer <u>≥</u> 30, 16, 20, 24, 10, 8, 8, 8, and 8 mMU/ml, respectively.[69]

<u>*Outcome measure (GMT):*</u> Using the historical healthy population for qHPV[28] and 9vHPV[69] respectively, a multiplicity-adjusted 95% 2-sided confidence intervals for the ratio of mean GMT for HPV-16 and -18 in the cancer and healthy population will be computed. If the lower 95% limit is greater than 0.5, immunogenicity in cancer survivors will be considered non-inferior.[30]

Outcome measure: (seropositivity) [Exploratory only; study is not powered for this]: The percent of seropositive participants at Month 7 will be compared to the percent of age- and sex-matched seroconverted individuals in the historical healthy population for each of 2 vaccine components. Two one-sided tests of noninferiority (for each of 2 HPV types) will be conducted for each age-sex group at the 0.025 level (multiplicity adjusted) according to the methods of Miettinen and Nurminen.[137] Seroconversion in cancer survivors will be considered non-inferior if the lower 95% CI for the difference in percent seropositive between the healthy and cancer population is <5 percentage points.[30] The above analyses will be conducted for PP and IT samples. Although not powered to detect non-inferiority for HPV-6 and -11 (and in the 9vHPV cohort, HPV-31, -33, -45, -52, and -58), we will also conduct similar analyses for GMT and seropositivity for these types.

8.2.2.2. Identify clinical/host factors influencing immunogenicity in cancer survivors

Subjects whose GMT at Month 7 is less than ½ of the mean GMT of the corresponding age-sex matched health population will be classified as having lowered immunogenicity. Logistic regression will be used to identify significant predictors of lowered immunogenicity. Potential predictors include sex, primary diagnosis, current age, age at diagnosis/HCT, prior therapy (all therapeutic exposures, including cumulative doses of all immunosuppressive agents), intensity of therapy (conventional therapy vs. HCT), time from completion of therapy, presence/extent of chronic GvHD, dose/duration of immunosuppressive agents post-HCT, and Day 1 Quant Ig. This analysis will be conducted for HPV-16 and -18. At Type I error=0.5, 312 subjects will achieve 80% power to detect odds ratios of 2.0 to 3.2 depending on the hypothesized and true proportions of subjects with lowered immunogenicity (Table 8) or a dichotomized covariate with 50% of the sample in each group.

Table 8. Proportion of Subjects with Lowered Immunogenicity and Associated Odds Ratios

P0	P1	OR
0.05	0.143	3.18
0.1	0.215	2.47
0.2	0.34	2.06
0.3	0.453	1.93
0.4	0.558	1.89
0.5	0.656	1.91
0.6	0.748	1.98

P0 = Hypothesized proportion of subjects with lowered immunogenicity
P1 = True proportion of subjects with lowered immunogenicity
OR = Odds Ratio

8.2.2.3. Determine the safety/ tolerability of the qHPV and 9vHPV vaccine in cancer survivors

In the IT sample, the number of vaccine-associated AE within 7 (for 9vHPV) or 14 (for qHPV) days of each dose will be compared to those reported for the age- and sex-matched general population: % of subjects with injection site AEs (e.g., pain, erythema), % of subjects with systemic AEs (e.g., fever, syncope, headache, hives, rashes, diarrhea), % of subjects with serious AEs (e.g., life-threatening, result in persistent disability or death). Overall cohort: % of subjects who discontinue vaccine related to AE. AEs will be summarized descriptively as frequencies and percentages by type (injection site, systemic, serious), by vaccine dose (i.e., #1, #2, #3), and across all vaccine doses. Chi-square and exact tests will be used for comparison depending on the rarity of events. Our smallest PP subsample of 72 young females will provide 80% power to detect a difference of 0.0485 in AE rates if true rate=0.01, and a difference of 0.1068 if the true rate=0.85. For the largest PP subsample of 82 young males, the corresponding detectable differences are 0.0415 and 0.1021. For the entire PP sample of 312, the corresponding differences are 0.0189 and 0.0534. Type I error=.05 is assumed for each comparison.

8.2.2.4. (Exploratory sub-aim): Evaluate the persistence of antibody response at 2 years post vaccine initiation and identify clinical/host factors influencing response persistence.

Outcome measure (GMT): We will calculate mean GMT and 2-sided 95% CI for HPV-16 and -18 at Month 24 following vaccine initiation for PP subjects and compare them to age-, sex, and time-matched means in the historical healthy population.[28] Cancer survivors will be considered to have non-inferior persistence of antibody response to a subtype at a time point if the lower 95% confidence limit for the ratio of GMT in cancer survivors to historical healthy population is ≥50%.[30]

Outcome measure (seropositivity): Seropositivity is defined as: qHPV cohort: Anti-HPV-6, -11, -16, and -18 titer ≥ 20, 16, 20, and 24 mMU/ml respectively;[30] 9vHPV cohort: Anti-HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58 titer ≥ 30, 16, 20, 24, 10, 8, 8, 8, and 8 mMU/ml, respectively.[69] Among PP participants, the percent seropositive to each vaccine subtype will be computed and compared to age-and sex-matched seropositive rates at Month 24 in the healthy population.[28] One-sided tests of noninferiority for each HPV type will be conducted at the 0.025 (multiplicity adjusted) level according to the methods of Miettinen and Nurminen.[137] For each subtype and time point, persistence of seropositivity will be considered non-inferior in cancer survivors if the lower 95% CI for the difference in percent seropositivity between the healthy and cancer population is less than 5 percentage points. To identify factors associated with response persistence at each time point, we will classify cancer survivors as having impaired response persistence if their GMT is lower than ½ of the mean GMT in the age-sex-time matched healthy population. Logistic regression will be conducted at each time point to identify significant predictors of impaired response persistence. Potential predictors include sex, primary diagnosis, current age, age at diagnosis/HCT, prior therapy (all therapeutic exposures, including cumulative doses of all immunosuppressive agents), intensity of therapy (conventional therapy vs. HCT), time from completion of therapy, presence and extent of chronic GvHD, and Day 1 Quant Ig. In this exploratory sub-aim, we will also measure HPV-specific total immunoglobulin (total Ig) at Month 24 to better characterize the qualitative aspects of the HPV-specific humoral immune response.[138,139] We recognize that we may not have sufficient power to test persistence of response to qHPV or 9vHPV vaccine; as such, this aim is exploratory.

9.0 DATA AND SAFETY MONITORING

9.1 Definition of Risk Level

This is a Risk Level 3 study, because it includes a phase II clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result. This study involves open-label administration of 3 doses of the quadrivalent (for patients enrolled on or before 3-1-16) or nonavalent (for patients enrolled after 3-1-16) HPV vaccine. While the vaccine has not been studied in the targeted population of cancer survivors, and its immunogenicity and safety profile are unknown in this group, the vaccine is FDA-approved for administration to males and females between 9 and 26 years of age, including immunocompromised individuals.

9.2 Monitoring and Personnel Responsible for Monitoring

The UAB DSMC (UAB CTMC-Clinical Trials Monitoring Committee) will serve as the safety board of record for this study.

The Protocol Management Team (PMT), consisting of the co-PIs, co-investigators, CRA, protocol nurse, and statistician, is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Data and safety will be reported to the UAB DSMC. Protocol-specific data collection will include the following items: Target and actual accrual by site, aggregate demographics and demographics by site, data completeness for Aim 1 (survey) and Aim 2 (vaccine evaluation), and the following safety reporting: Aim 1 (survey): % of subjects with unexpected adverse events; Aim 2 (vaccine evaluation): % of subjects with injection site adverse events (e.g., pain, erythema), % of subjects with systemic adverse events (e.g., fever, syncope, headache, hives, rashes, diarrhea), % of subjects with serious adverse events (e.g., life-threatening, result in persistent disability or death), % of subjects who discontinue vaccine related to adverse events, and number of subjects who become pregnant during the vaccine administration phase of the study. Adverse events will be summarized descriptively as frequencies and percentages by type (injection site, systemic, serious), by vaccine dose (i.e., #1, #2, #3), and across all vaccine doses. The *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials,* U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, September 2007 (Tables 9.3.2, 9.3.3, and 9.3.4) will be used to assess toxicity and stopping rules (see Sections 9.3 and 9.4 respectively). The study will utilize the Vaccine Adverse Event Reporting System (VAERS – www.vaers.hhs.gov) for AE reporting (see Appendix 18 for VAERS Reporting Form). For reporting purposes, attribution is defined as the assessment of the likelihood that an AE is caused by the research agent or protocol intervention. The attribution is assigned by the Principal Investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. The attribution is subject to change as follow-up information becomes available and it can be changed by the DSMC or by the IRB during the process of review.

Reporting of data and safety to the DSMC will occur at the time of enrollment of 981 subjects to Aim 1, at the time of enrollment of 353 subjects to Aim 2, and if 2 or more cases of the same grade 3-4 toxicity with probable attribution that do not resolve in 72 hours are reported in separate patients enrolled on Aim 2 (see Section 9.4), or at least every 6 months, using the PMT report (Appendix 19).

9.3 Adverse Events

9.3.1. Definitions

Adverse Event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a) – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) [21 CFR 312.32] **-** A serious adverse event (SAE) is defined as *any expected or unexpected adverse event* that results in any of the following outcomes:

- Death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity

- A congenital anomaly/birth defect
- Secondary malignancy, or
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated Problem (UP) – Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

9.3.2. Reporting of Unanticipated Problems and Adverse Events:

Unanticipated Problems (UP): Unanticipated problems must be reported by the study coordinating center site personnel to the UAB DSMC and IRB within 5 calendar days of receiving notification from the participating sites according to definitions and guidelines at http://www.uab.edu/policies/content/Pages/UAB-RA-PRO-0000293.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and the central (UAB) IRB.

Serious Adverse Events (SAE) - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at **http://www.uab.edu/**policies/content/Pages/UAB-RA-PRO-0000293.aspx and Table 9.3.1 below. Those SAEs that require expedited reporting will be submitted via fax or electronic transmission.

Adverse Events (AE) - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the protocol continuation reports and PMT report (see Table 9.3.1 below).

Table 9.3.1. Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required*
Unlikely, Unrelated	No reporting required*	No reporting required*
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	5 calendar days
Unlikely, Unrelated	5 calendar days	5 calendar days
	Grade 1 and 2 AND resulting in hospitalization#	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

*Such events are not required to be reported to the DSMC. These events should be included with the SAE/AE summary provided to the DSMC in the PMT reports and to the IRB in the Annual Continuation reports.

Hospitalization = Unplanned admission equal to or greater than 24 hours

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

9.3.2.1. Additional reporting requirements

9.3.2.1.1. Expedited reporting by participating sites. All participating sites will submit Adverse Events/Research-Related Problems Reporting Forms (AERF - Appendix 15) to the coordinating center when reporting Adverse Events or Unanticipated Problems requiring expedited reporting (i.e., requiring reporting to the DSMC and/or central [UAB] IRB more frequently than every 6 months) and the events will be reported by the study coordinating center. Adverse events that do not require expedited reporting will be reported by the participating sites to the coordinating center on a quarterly basis and will be reported in aggregate at the time of protocol continuation reports and PMT report (per the requirements outlined in Table 9.3.1).

9.3.2.1.2. Additional reporting to be done by the study coordinating center.

Merck Sharp & Dohme Corp. (Attn: Worldwide Product Safety; FAX 215 993-1220) will be provided with copies of **all serious adverse experiences, regardless of causality, within two working days**. Additionally, any pregnancy occurring in association with use of a Merck Product will be reported to Merck Sharp & Dohme Corp. (Attn: Worldwide Product Safety; FAX 215-993-1220).

To the extent required by applicable law, a copy of all 15 Day Reports and Annual Progress Reports will be submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators by the investigator. This submission will be cross referenced according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, a copy of these reports will be submitted to Merck Sharp & Dohme Corp. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

The coordinating center will also notify VAERS (www.vaers.hhs.gov) within 2 business days of receiving notification from the participating sites of any vaccine-related Adverse Event requiring expedited reporting (as defined above and in Table 9.3.1).

A summary table of potential adverse events and adverse event reporting requirements for this study is included in Appendix 20.

9.3.3. Toxicity Management

Any symptoms that occur will be managed according to good medical practices and clinical judgment of the site investigator. Toxicities related to the vaccine will be monitored using the *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials,* U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, September 2007 (Tables 9.3.2, 9.3.3, and 9.3.4). Toxicities will generally be considered potentially vaccine-associated if their onset occurs within 7 days after receipt of a study vaccine dose. If evaluated, the toxicity should be documented on the Adverse Events/Research-Related Problems Reporting Form (AERF) within 2 working days of the evaluation. All subjects will be followed for the reporting of toxicities for 14 days following each vaccine dose. In addition, any severe or unexplained toxicity occurring after the 14 days of follow-up brought to the attention of the investigator will be evaluated for possible vaccine-association, and documented on the AERF within 2 working days of the evaluation if found to be possibly, probably, or definitely related to the vaccine. Toxicities will not be considered vaccine-associated AEs if clearly recognized alternative etiologies are identified. Alternative explanations for clinical abnormalities must be sought prior to study vaccine discontinuation.

Therapeutic interventions that may interfere with evaluation of the safety/tolerability of the vaccine should be avoided during the indicated timeframes unless medically necessary. These include a) any live attenuated vaccine administered within 28 days of any HPV vaccine dose; b) any subunit or killed vaccines (e.g., influenza, pneumococcal, antigen injections for allergy treatment) within 14 days of any HPV vaccine dose.

General toxicity management:
- If a subject develops a persistent $\geq$ Grade 3 clinical toxicity, the subject will not be permitted to participate in this study until the toxicity has resolved to $\leq$ Grade 1.
- All $\geq$ Grade 3 clinical toxicities occurring within 14 days following any vaccine dose, and their

proposed management, must be reported to the coordinating center using the AERF within 2 business days of the site's awareness of the event, regardless of relatedness. Clinical toxicities not identified in Tables 9.3.2, 9.3.3, and 9.3.4 should be graded according to the Common Terminology Criteria for Adverse Events v4.0 (http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx).

9.3.4. Pregnancy: Sexually active females of childbearing potential will be instructed to use contraception throughout the 6-month period when the vaccine is administered. Participants will be queried prior to each dose to determine if there is a possibility of pregnancy; if so, a pregnancy test (urine or blood as per local institutional preference) will be obtained prior to vaccine administration. If positive, the participant will be withdrawn from receiving further vaccine on the study. Any pregnancy occurring during the vaccine phase of the study (i.e., Vaccine Day 1 through 4 weeks after all 3 vaccine doses have been administered) will be reported to the study coordinating center. There are no data indicating an association of adverse pregnancy outcomes or adverse effects of the developing fetus with the vaccine. Thus, if a vaccine dose is administered during pregnancy, no intervention is indicated other than withholding further doses and reporting as specified. The patient should be followed by the participating site for pregnancy outcome data (e.g., termination, miscarriage, pre-term or full-term delivery, fetal death/stillbirth, complications, single vs multiple birth, condition of infant(s), presence of congenital anomalies, etc.), which should be reported to the study coordinating center when available. The study coordinating center will report the pregnancy, and later the pregnancy outcome (with de-identified subject information only), as follows: **qHPV vaccine recipients (patients enrolled on or before 3-1-16)**: Merck Worldwide Product Safety; Fax 215-993-1220. **9vHPV vaccine recipients (patients enrolled after 3-1-16)**: Gardasil ®9 Pregnancy Registry maintained by Merck (URL: www.merckpregnancyregistries.com/gardasil9; Phone: 1-800-986-8999; Fax 215-993-1220) and Merck Worldwide Product Safety; Fax 215-993-1220.

9.3.5. Grading of Clinical Abnormalities

The *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials,* U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, September 2007 (Tables 9.3.2, 9.3.3, and 9.3.4) will be used to assess toxicity and stopping rules outlined in Sections 9.3 and 9.4 respectively.

Table 9.3.2. Local Injection Site Reaction

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Table 9.3.3. Systemic Reaction - Vital Signs

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)** (°F)**	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 - 104	>40 >104
Tachycardia – beats per minute	101-115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute***	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mmHg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mmHg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate (breaths per minute)	17 – 20	21 – 25	>25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 and 100 beats per minutes. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Table 9.3.4. Systemic Reaction – General

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or <400 gms/24 hours	4 – 5 stools or 400 – 800 grams/24 hours	6 or more watery stools or >800 gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

From: Food and Drug Administration. *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.* U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, September 2007.

9.4 Study Stopping Rules

If two or more cases of the same grade 3-4 toxicity with *probable* attribution that do not resolve in 72 hours are reported in separate patients, accrual will be held until further review by the UAB Clinical Trials Monitoring Committee to determine whether or not the study should be stopped based on the data available at that time.

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APPENDICES

Appendix	Content
1	Medical Record Review Form
2	Intensity of Treatment Rating Scale 2.0
3	HPV Vaccination Survey
	- Parent/caregiver version – male patient (age 9-17)
	- Parent/caregiver version – female patient (age 9-17)
	- Patient version - male (age 18-26)
	- Patient version – female (age 18-26)
4	Thank You Letter – Survey
5	Sample Patient Recruitment Materials
6	Appointment Reminder Letter - Vaccine
7	Children's Oncology Group Cancer Treatment Summary Form
8	Vaccine Visit Form
9	Month 7 Visit Form (Follow-Up #1)
10	Premature Study Discontinuation (PSD) Form
11	Blood Specimen Collection, Processing, Storage, and Shipping Guidelines
12	Sample CDC Teaching Tools: Human Papillomavirus
13	Sample VIS: HPV vaccine
14	Vaccine Report Card (7- and 14-day versions)
15	Adverse Events/Research-Related Problems Reporting Form (AERF)
16	Month 24 Visit Form (Follow-Up #2)
17	Thank You Letter - Vaccine
18	VAERS Reporting Form
19	PMT Report
20	Summary of Potential Adverse Events/Research-Related Problems Reporting Requirements