COVER PAGE

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Immunogenicity of Nonavalent HPV Vaccine Administered Prior To Renal Transplantation in Adults: A Prospective, Single-Arm, Multi-Center Clinical Trial

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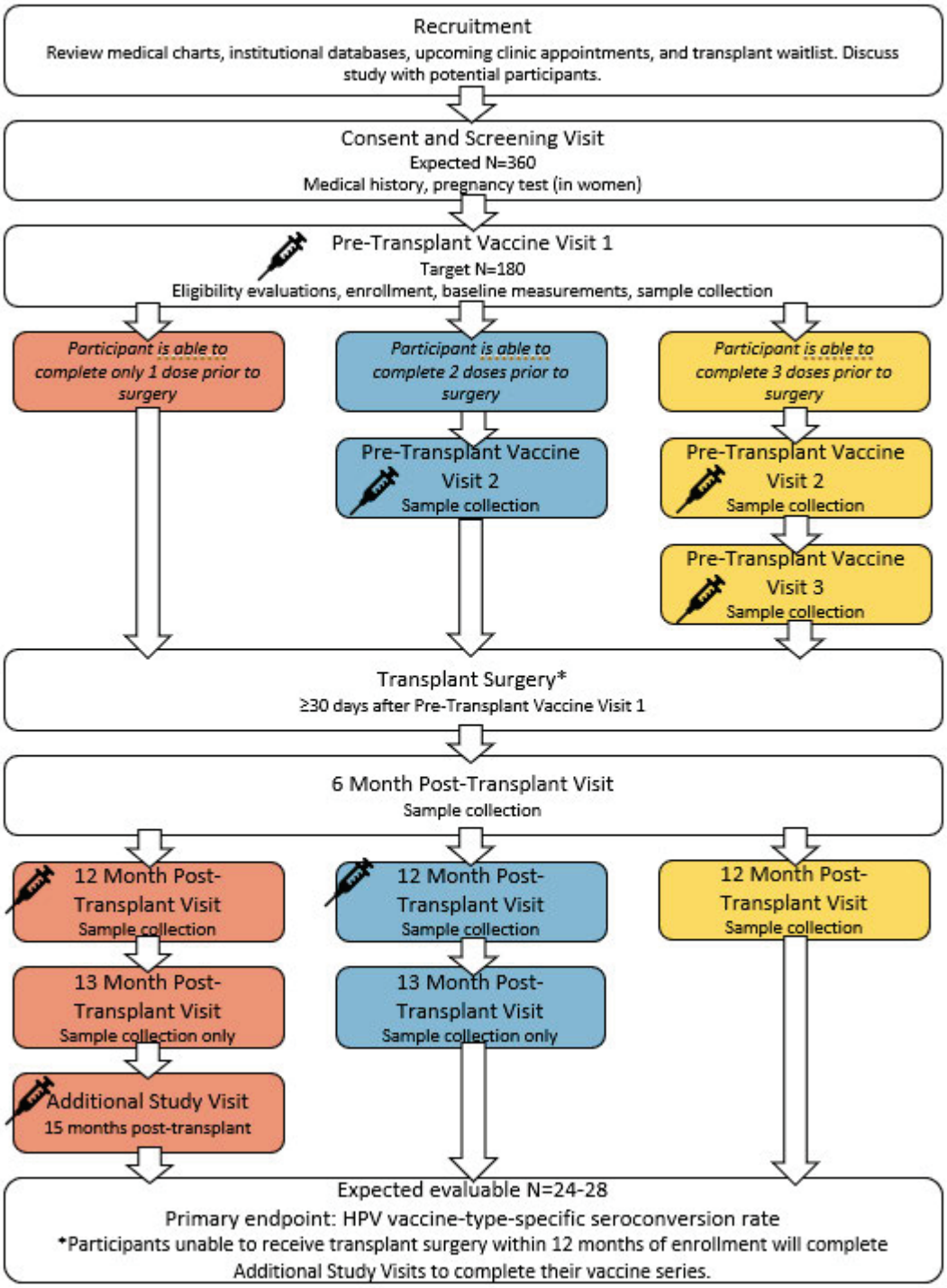
SCHEMA

Immunogenicity of Nonavalent HPV Vaccine Administered Prior To Renal Transplantation in Adults: A Prospective, Single-Arm, Multi-Center Clinical Trial



** **[NOTE: For COVID-19 Contingency Plan, please see Appendix G and Appendix H]**

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1. OBJECTIVES

The objective of this prospective single-arm trial is to evaluate if the Gardasil® 9 HPV vaccine induces and sustains an adequate immune response at 12-months post-transplantation among 18-49 year old kidney transplant recipients when ≥ 1 doses of the vaccine are administered prior to transplantation.

1.1 Primary Objectives

To assess HPV vaccine-type-specific seroconversion rates at 12-months post-transplantation among kidney transplant recipients who receive ≥ 1 doses of the Gardasil® 9 HPV vaccine ≥ 30 days prior to transplantation.

1.2 Secondary Objectives

To assess HPV vaccine-type-specific seroconversion rates at 6- and 12-months post-transplantation stratified by number of doses (1, 2, or 3) of the vaccine given pre-transplant among kidney transplant recipients who receive ≥ 1 doses of the Gardasil® 9 HPV vaccine prior to transplantation:

1.3 Exploratory Objectives

To assess the following among kidney transplant recipients who receive ≥ 1 doses of the Gardasil® 9 HPV vaccine ≥ 30 days prior to transplantation:

1) HPV vaccine-type-specific seroconversion rates at 12-months post-transplantation stratified by:
   a) time elapsed between last vaccine dose and the transplant procedure;
   b) variations in dosing and types of post-transplant immunosuppressant medications; and interactions with type of transplant surgery (living donor/deceased donor);
   c) differences in Human Leukocyte Antigen (HLA) histocompatibility between donor and recipient;
   d) differences in biological sex (i.e. male vs. female) of the transplant recipient.

2) Stability of HPV vaccine-type-specific geometric mean titers (GMT) at 6 and 12-months post-transplantation and rise in HPV vaccine-type-specific GMT at the 13-month post-transplant visit.

3) Vaccine safety profile and allograft rejection/opportunistic infections stratified by number of vaccine doses and time between the last vaccine dose and the transplant procedure.

4) HPV detection in samples from the cervix/vagina and oral cavity at baseline (pre-vaccination) and at 6- and 12-months post-vaccination, overall and by number of vaccine doses (1, 2, or 3), sexual behavior, type-specific seroconversion rates, and time elapsed between the last vaccine dose and the transplant procedure.

2. BACKGROUND

2.1 Study Disease

Adult solid organ transplant recipients are at increased risk of developing several types of malignant tumors related to the use of immunosuppression to prevent transplant rejection [1]. Cancers causally linked to infections with carcinogenic human papillomavirus (HPV) genotypes, including squamous cell carcinomas of the anogenital region and oropharynx, are among the higher incidence cancers in this group

and potentially the most preventable [2-4]. The number of solid organ transplant recipients has increased along with their post-transplant lifespan. As such, the need for prevention of HPV-associated cancers is projected to increase [5].

2.2 Study Agent

Gardasil® 9 Human Papillomavirus vaccine is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer [6].

Gardasil® 9 is indicated for prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58; and for the prevention of genital warts caused by HPV types 6 or 11; in females 9-26 years of age. Gardasil® 9 also adds protection against precancerous or dysplastic cervical, vulvar, vaginal, and anal lesions caused by the covered HPV types.

The safety of Gardasil® 9 was evaluated in six clinical studies that included 13,234 individuals who received at least one dose and had safety follow-up. The most common (≥ 10%) local and systemic adverse reactions of the Gardasil® 9 HPV vaccine in females and males 16 through 26 years of age were injection site pain (90%, 63%), injection site swelling (40%, 20%), injection site erythema (34%, 21%), and headache (15%, 7%). Pyrexia may be experienced by 5% of female vaccine recipients and 2% for male vaccine recipients. Contraindications include hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous Gardasil® dose [6]. Individuals who develop symptoms indicative of hypersensitivity after the first dose should not receive additional doses. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. Participants must be monitored for 30 minutes following vaccination for syncope/convulsive syncope and allergic reactions. There have been no adequate and well-controlled studies of Gardasil® 9 in pregnant women. The Gardasil® 9 HPV vaccine is not recommended for pregnant women.

2.3 Rationale

The nonavalent Gardasil® 9 prophylactic HPV vaccine is nearly 100% efficacious in preventing infection with the seven carcinogenic (HPV 16, 18, 31, 33, 45, 52, 58) and two condyloma-inducing viruses (HPV 6, 11) when given to individuals who have not been exposed to these specific HPV types. The body of evidence [41-45] that has influenced the current approval of Gardasil® 9 by the US Food and Drug Administration (FDA) for ages 9-45 years in both females and males include:

(i) clinical trial data about clinical efficacy of Gardasil® 9 (endpoints such as persistent infection, genital warts, and precancerous lesions related to HPV types covered by the vaccine) in 16-26 years old women and men;

(ii) inferential data from clinical trial data about clinical efficacy of quadrivalent Gardasil® prophylactic HPV vaccine (the forerunner to Gardasil® 9 with a similar manufacturing process) in 27-45 years old women for the four key HPV types (HPV 16, 18, 6 & 11) covered by both the quadrivalent and nonvalent vaccines

(iii) immunogenicity and immunobridging data (i.e., inferring efficacy based on similar or higher vaccine-induced serologic immune titers in age-groups where efficacy has not been directly studied, e.g., individuals <16 years at vaccination, or men 27-45 years)

The protective effect of Gardasil® 9 among older immunosuppressed adults is unknown. Given the continued HPV-related risk in the post-transplant years (evidenced by a high proportion of women and men testing positive for cervical/anogenital HPV DNA [7], even with no additional sexual acquisition risk of new HPV infections, it is speculated that this represents a consequence of activation of latent HPV infections. Empirical studies to demonstrate the phenomenon of reactivation of HPV infection and the effect of HPV vaccination on this purported phenomenon are lacking.

Guidelines from both the Centers for Disease Control and prevention (CDC) and American Society of Transplantation recommend that immunosuppressed individuals, including transplant candidates, receive the same HPV vaccines according to the same schedule as individuals in the general population [8,9]. Only two small observational immunogenicity studies have evaluated post-transplantation serologic responses to the quadrivalent Gardasil® vaccine [10,11]. Although the safety of the virus-like particle (VLP)-based subunit HPV vaccines has not been a major concern, the strength of the immunologic responses (and consequent efficacy) among immunosuppressed transplant recipients remains uncertain [5,12]. Research questions related to the efficacy of the prophylactic HPV vaccination among adult solid organ transplant candidates and recipients include the levels and inter-person variability of peak and plateau antibody titers and avidity of antibody responses, as well as the optimal timing of vaccine administration either pre- or post-transplant. The possibility that reactivation or latent HPV infection may occur with immunosuppression is supported by descriptive clinical studies, but the potential of vaccination to suppress this reactivation is untested. The relationship between HPV vaccine response and post-transplantation immune status measurements – both non-specific immune monitoring assays, as well as opportunistic pathogen-specific response assays – is unclear and merits further exploration [13]. Renal transplant candidates represent an ideal population in which to evaluate prophylactic vaccine efficacy in organ transplant recipients because many such transplants are planned months in advance, and patients have frequent medical contacts, facilitating recruitment and required visits.

Given the strong biological rationale, a recently convened International Agency for Research on Cancer/National Cancer Institute workshop has recommended seroconversion, and specifically immunological non-inferiority, as sufficient for a presumption of efficacy for the HPV vaccine in immunobridging studies focused on the expansion of vaccine indications [14]. Thus, the endpoint for this trial is seroconversion, and we will define efficacy as greater than or equal to 90% of the study population achieving seroconversion. The definition for positivity, or seroconversion, will be based on results of the HPV-9 cLIA (Merck) or, alternatively, a validated 9-valent HPV multiplex assay developed at the NCI Frederick National Laboratory for Cancer Research (FNLCR), which measures HPV type-specific antibodies to neutralizing epitopes on VLPs from a patient's serum sample. Seropositivity is not part of the eligibility criteria for enrollment.

Vaccine Doses and Timing in relation to Transplant Surgery and Immunosuppression.
Current (2018) CDC recommendations suggest that Gardasil® 9 be given in a 3-dose schedule at 0, 2, and 6 months for immunocompromised individuals (such as transplant recipients) between the ages of 16 and 45 years. (There are no recommendations for vaccination for individuals over 45 years of age, and such use is considered off-label.) Furthermore, there are no recommendations on the optimal number and timing of doses in relation to the transplant surgery. This trial will seek to enroll both living-donor and deceased-donor transplant recipients, and the number and timing of vaccine doses will be dependent on two factors:

i. The time remaining between enrollment date and transplant surgery.
ii. Need for avoiding administering any vaccine doses for at least 12 months in the post-transplant period when the strongest regimens of immunosuppressive medications to prevent transplant rejection are being administered.

Due to these caveats, participants may receive one, two, or three doses of vaccines prior to transplant. If all three doses are not administered before transplant then the rest of the doses in the three dose vaccine

series will be administered at or after 12-months after transplant. An abbreviated schedule of vaccination (permitted by current vaccine label/CDC recommendations) may also be utilized to allow administration of as many vaccine doses prior to transplantation as possible. If participants do not undergo transplant surgery within 12 months of study enrollment and have not received the recommended three dose series in the intervening 12 months, the remaining doses will be offered via Additional Study Visit(s) at 12 months and, if necessary, at 15 months after the first vaccine dose.

Desensitization. Both vaccines and infections are known to cause both humoral and cellular immune activation, which is of particular interest in transplant populations because alloreactive T-cells and the development of anti-HLA antibodies mediate transplant allograft injury. Transplant recipients who are already highly sensitized to alloantigens are at higher risk for rebound immune activation through a process called heterologous immunity, potentially leading to allograft injury. Furthermore, the potential for a 'shared epitope' between viral products and Human Leukocyte Antigen (HLA) proteins suggests that vaccination can produce *de novo* HLA antibody formation [15]. Desensitization procedures vary somewhat among the five participating transplant centers, which does not permit proposing uniform criteria across all study sites for determining exclusion due to desensitization . In general, adults who have received a prior transplant, have unsuitable scores on Calculated Panel Reactive Antibody (PRA) percentage (institution-specific thresholds), or an ABO incompatible donor are likely to undergo desensitization at one or more of the study centers. These factors, among others, will be used by the study clinician to determine exclusion due to anticipated desensitization in the study.

HPV Vaccination and Risk of Allograft Rejection. Current recommendations allow for HPV vaccine administration before or after transplantation, and that it is safe to do so because it is not a live vaccine [16]. Studies that have examined safety of the vaccine in the post-transplant setting have reported no elevation in rejection episodes attributed to the vaccine [10,11].

Sexual Behavior, Detectable HPV Infection, and Vaccine-Induced Seroconversion. The possibility that reactivation of latent HPV infection may occur with immunosuppression is supported by descriptive clinical studies, but the potential of vaccination to suppress this reactivation is untested. Only a few studies have examined the prevalence of oral/anal/genital HPV in renal transplant recipients, generally following transplant [17]. The first longitudinal study of cervical-vaginal HPV prevalence before and after renal transplant found an increase from 19% pre-transplant to 31% post-transplant [18]. This increase occurred in the absence of reported changes in sexual behavior, suggesting re-activation of latent viral infection. Although the clinical impact of these findings are presently uncertain, an increased prevalence of cervical-vaginal HPV in the absence of person-to-person transmission has implications for patient management [19]. This will be the first study among renal transplant recipients to show whether there is a difference in Gardasil® 9-associated seroconversion between individuals with detectable versus undetectable HPV infections (cervical-vaginal and oral) that cannot be explained by sexual behavior.

Hypothesis: The Gardasil® 9 nonavalent vaccine given before the solid organ transplant procedure will induce and maintain adequate immunogenicity in the post-transplant period despite immunosuppression.

3. SUMMARY OF STUDY PLAN

Design Overview. This will be a prospective single-arm trial to evaluate if the Gardasil® 9 HPV vaccine induces and sustains an adequate immune response at 12-months post-transplantation among 18-49 years old kidney transplant recipients when ≥ 1 doses of the vaccine are administered prior to transplantation (see Schema). The study population will include candidates who are scheduled to undergo kidney transplant within 12 months of enrollment at five transplant centers in the United States: Cedars-Sinai Medical Center (CSMC); the University of California, San Francisco Medical Center (UCSF); Northwestern University Feinberg School of Medicine (NW); University of Alabama at Birmingham (UAB); and the University of North Carolina at Chapel Hill (UNC). The local study teams at the clinical sites, which include transplant infectious disease specialists, transplant nephrologists, and transplant surgeons, will determine each

potential participant's eligibility for the study based on chart review and patient history. Prior to enrollment, women who are able to become pregnant will be required to have a negative pregnancy test and agree to the use of contraception or abstinence for the study period.

Screening of Potential Participants: Potential participants will be identified through clinical encounters in the transplant clinic, review of medical charts, review of transplant waiting lists, and review of upcoming transplants and donor evaluations. Renal transplant candidates on institutional waitlist for a deceased donor renal transplant expected to receive a kidney within 12 months, or currently having a potential living donor undergoing workup in anticipation of a living donor transplant, will be reviewed for eligibility.

Pre-transplant work-up and vaccinations: The timing of vaccination in relation to the transplant surgery are considered in relation to several factors. The time available between enrollment and the transplant surgery and the feasibility of study visits in the pre-transplant period will vary by type of surgery (living donor versus deceased donor transplant). Further, the possibility of integrating with the schedule for pre-transplant clinical work-up or visiting for a study-specific purpose alone will vary by the clinical condition of the potential participants and the institutional transplant center visit requirements for every clinic site. All enrolled participants are expected to receive at least 1 dose of the vaccine prior to transplant surgery with at least 30-days between the first dose and transplant surgery. There are specific CDC recommendations about the minimum time between doses which will affect when the second and third doses are administered (see section 5.1). Other than requiring adherence to these minimum intervals (within +/- 2 weeks), the protocol will not mandate specific time windows for receiving the vaccine, considering challenges of accrual/retention in the study. Transplant candidates are typically burdened with ongoing pre-transplant clinical issues and have non-uniform follow-up visit schedules. Study staff will attempt to maximize opportunities for coordinating study-related visits on the same day as scheduled transplant-related/clinical care-related visits. However, the timing of transplant surgery is dependent on a range of factors, several of which are unpredictable at the time of study enrollment. Therefore, not all participants in the study may be able to receive all three doses of the vaccine prior to transplant. In fact, the second and third doses can be administered in the pre-transplant period or be administered at or after 12-months post-transplant.

With a few exceptions (see below), most participants will undergo the following study visits based on the number of doses that might be able to be administered prior to surgery:

	Participant is able to complete only 1 dose prior to surgery	**Participant is able to complete 2 doses prior to surgery**	**Participant is able to complete 3 doses prior to surgery**
Consent and Screening Visit	Consent	Consent	Consent
Pre-Transplant Vaccine Visit 1	Vaccine #1 & specimen collection	Vaccine #1 & specimen collection	Vaccine #1 & specimen collection
Pre-Transplant Vaccine Visit 2	~~	Vaccine #2 & specimen collection	Vaccine #2 & specimen collection
Pre-Transplant Vaccine Visit 3	~~	~~	Vaccine #3 & specimen collection
Transplant Surgery	Occurs; specimen collection	Occurs; no research procedures	Occurs; no research procedures
6 Month Post-Transplant Visit	Specimen collection	Specimen collection	Specimen collection
12 Month Post-Transplant Visit	Vaccine #2 & specimen collection	Vaccine #3 & specimen collection	Specimen collection
13 Month Post-Transplant Visit	Specimen collection	Specimen collection	~~
Additional Study Visit 1	Vaccine #3	~~	~~

*Specific details regarding the timing of study visits can be found in Appendix B.

There might be situations when a transplant surgery is scheduled within a few weeks after the first, second, or third doses, but it gets postponed/rescheduled/cancelled. Although study staff will attempt to complete the remaining doses in the 12-months post-enrollment period, there might be situations, albeit uncommon, where the transplant surgery does not occur within 12-months of enrollment and the participants are not able to complete all vaccine study visits. In such situations, participants who have received only one or two doses will be offered two or one Additional Study visit(s) to complete the three-dose series and will be considered and notified that they will be off-study (See Section 8.4). The Additional Study Visit 1 will occur 12 months (±2 weeks) after Pre-Transplant Vaccine Visit 1, and Additional Study Visit 2 will occur 3 months (+ 4 weeks) after Additional Study Visit 1. Also, participants who have completed all three doses but their transplant surgery gets postponed/rescheduled and eventually does not occur within 12-months of enrollment will be considered off-study. The three possible scenarios discussed above will have the study visit schedule as illustrated below:

	Participant completes 1 dose, but transplant does not occur within 12 months of enrollment	**Participant completes 2 doses, but transplant does not occur within 12 months of enrollment**	**Participant completes 3 doses, but transplant does not occur within 12 months of enrollment**
Consent and Screening Visit	Consent	Consent	Consent
Pre-Transplant Vaccine Visit 1	Vaccine #1 & specimen collection	Vaccine #1 & specimen collection	Vaccine #1 & specimen collection
Pre-Transplant Vaccine Visit 2	~~	Vaccine #2 & specimen collection	Vaccine #2 & specimen collection
Pre-Transplant Vaccine Visit 3	~~	~~	Vaccine #3 & specimen collection
Transplant Surgery	Does not occur	Does not occur	Does not occur
6 Month Post-Transplant Visit	~~	~~	~~
12 Month Post-Transplant Visit	~~	~~	~~
13 Month Post-Transplant Visit	~~	~~	~~
Additional Study Visit 1	Vaccine #2 & specimen collection	Vaccine #3 & specimen collection	~~
Additional Study Visit 2	Vaccine #3	~~	~~

*Specific details regarding the timing of study visits can be found in Appendix B.

Schedule of Study Visits.
Participants will complete the study visits below according to the schedules indicated above. No participant will complete every visit.

Consent and Screening Visit: This visit may be combined with the Pre-Transplant Study Visit 1 (below), depending on possibilities of confirmation of eligibility in the same visit.

Pre-Transplant Vaccine Visit 1: Administration of the first vaccine dose, and specimen collection for baseline measurements. This visit is will be required to be scheduled at least 30 days before the patient's kidney transplant procedure.

Pre-Transplant Vaccine Visit 2: Administration of the second vaccine dose, and specimen collection.

Pre-Transplant Vaccine Visit 3: Administration of the third vaccine dose, and specimen collection.

6 Months Post-Transplant Visit will be completed for the purpose of collecting study-related specimens.

12 Month Post-Transplant Visit: This visit will entail specimen collection at 12-months (+/- 2 weeks) after the transplant surgery. If all three doses of the vaccine have been administered prior to transplant, this visit will involve specimen collection and no vaccination. If only one vaccine dose was administered prior to transplant, this visit will also entail administering the second vaccine dose. If two vaccine doses were administered prior to transplant, this visit will also entail administering the third vaccine dose.

13 Month Post-Transplant Visit will be completed when the second/third vaccine dose is administered at the 12-months Post-Transplant Visit. This visit is for the purpose of collecting study-related specimens.

Additional Study Visit(s) for completing vaccine series:
Additional Study Visits will be offered to participants whose medical schedules did not permit them to complete their vaccine series earlier in the study.

Study Measurements. All visits discussed above, except the 13 Month Post-Transplant Visit and Additional Study Visits will, include the following study measurements. The 13 Month Post-Transplant Visit will include a blood draw only, and Additional Study Visits will only include administering the remaining vaccine doses to complete the series.

- History and physical exam
- Blood specimen for measurement of the primary and secondary endpoints
- Collection of cervical/vaginal and oral samples for HPV DNA testing
- Optional collection of urine for HPV DNA testing.
- Optional collection of eyebrow hair samples for future viral DNA testing.
- Optional collection of male genital samples for future HPV DNA testing.
- Baseline and follow-up questionnaires.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Candidate for renal transplant, expected to undergo transplant surgery ≥30 days and ≤12 months after enrollment.

a. For potential participants on the institutional waiting list for deceased donor transplant, a study clinician confirms the candidate is likely to receive a transplant within the next 12 months, taking into account the candidate's priority on the waiting list, age, medical status, institutional policies, and scores like the Estimated Post-Transplant Survival (EPTS) Score and Calculated Panel Reactive Antibody (CPRA) percentage, etc.

b. For potential participants expected to undergo a living donor transplant, one or more donor(s) have been identified and is/are in work-up (even though all work-up status may or may not be complete). A study clinician confirms the living donor transplant is likely to be scheduled within the next twelve months after taking into account donor work-up progress, age and medical status, and institutional policies.

*Notes:

i) Living and Deceased Donor Transplant Recipients: The study was originally restricted to participants who were expecting to receive only living donor renal transplants. However, less than a third of kidney transplants in the United States occur with kidneys from living donors. A majority of transplants are in the setting of donation of kidneys from deceased donors. To permit efficiencies in accrual, the study is amended (from version 3.5) to also open enrollment to recipients of deceased donor kidneys.

ii) Transplant recipients of both genders: The study was originally designed to be conducted only

among women. However, in October 2018, the FDA approved an age expansion indication for the Gardasil 9 HPV vaccine for both women and men up to 45 years (from the originally approved upper age limit of 26 years), thus opening a new clinical cancer preventative option for middle-age adults of both genders [38]. The primary endpoint for the study is HPV-vaccine-type-specific seroconversion rates, which are not expected to be differential by gender, based on extrapolating from the uniformly high (>99%) seroconversion rates observed regardless of gender in studies among immunocompetent individuals. However, HPV vaccine-type-specific titer levels (GMT) differences by gender will be analyzed as a secondary endpoint, given variability in immune response titer levels observed between males and females in immunocompetent individuals (related to the differences in body mass index or hitherto unproven factors related to hormone-immune interactions [20,21]). Another advantage of expanding this study to males will be to facilitate efficiencies in accrual, since men constitute the majority (55%-65%) of all kidney transplant recipients in the United States. Although a majority of current HPV-associated cancers among solid organ transplant recipients occur among women, [2] there is increasing evidence of the link between HPV infection and oropharyngeal cancers that disproportionately affect men [39]. HPV-related oropharyngeal cancers are now the most common HPV-related cancers in the United States, surpassing even the incidence of cervical cancer. [39] The expansion of enrollment to men will also allow this study to look at the effect of HPV vaccination on persistence of oral HPV infection as a secondary/exploratory endpoint in the context of transplant-related immunosuppression.

4.1.2 Age 18-49 years. We have chosen to focus on adults aged 18-49 for this initial study in transplant recipients for a few reasons. Prior data for HPV vaccine response exists for adults up to 49 years of age, providing an important external comparison group for our study. Immune response and exposure wane as age increases and we want to minimize the potential for age-related confounding of our study outcome. For this initial trial, we thought it best to maintain homogeneity in the study population to the extent possible. Finally, given that about half of renal transplant recipients in the U.S. are between the ages of 18-49 years, selecting this age range permits efficiency in study accrual.

4.1.3 ECOG performance status ≤ 1 (Karnofsky ≥ 70%; see Appendix A)

4.1.4 The effects of the Gardasil® 9 HPV vaccine on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because there have been no adequate and well-controlled studies of Gardasil® 9 in pregnant women, women who are able to become pregnant must have a confirmed negative pregnancy test result within the past 28 days prior to enrollment and must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Women who have had a both ovaries removed or a tubal ligation will not be required to have a pregnancy test. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

4.1.5 Ability to understand and the willingness to sign a written informed consent document and medical release form

4.1.6 Willing and able to comply with trial protocol and follow-up

4.2 Exclusion Criteria

4.2.1 Previous prophylactic HPV vaccination

4.2.2 Prior organ transplant

4.2.3 Anticipated desensitization treatment. This decision to exclude a participant who may need desensitization will be based on the site clinician's judgement. Desensitization procedures vary somewhat among the five participating transplant centers, which does not permit proposing uniform criteria across all study sites for determining exclusion due to desensitization. In general, women who have received a prior transplant, have unsuitable scores on Calculated Panel Reactive Antibody (PRA) percentage (institution-specific thresholds), or an ABO incompatible donor are likely to undergo desensitization at one or more of the study centers. These factors, among others, will be used by the study clinician to determine if exclusion due to anticipated desensitization is warranted for a particular participant in the study.

4.2.4 Current use of any other investigational agents

4.2.5 History of allergic reactions to yeast or attributed to compounds of similar chemical or biologic composition to Gardasil® 9 HPV vaccine

4.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

4.2.7 For female participants: Pregnant or intention to get pregnant, or breastfeeding. Pregnant women are excluded from this study because the safety and effectiveness of Gardasil® 9 HPV vaccine have not been established in pregnant women. It is not known whether Gardasil® 9 is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Gardasil® 9 is administered to a nursing woman. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Gardasil® 9, women who are breastfeeding will be excluded.

4.2.8 History of cervical cancer or anal cancer.

4.2.9 History of active malignancy, including basal/squamous cell skin cancer

4.2.10 Concurrent illness, such as known psychiatric disorders or substance abuse (i.e., average alcohol consumption of more than 3 drinks per day), which in the opinion of the investigators would compromise either the patient or the integrity of the data

4.2.11 Patients on anticoagulation or with bleeding disorders should be evaluated by a physician for risk/benefit of bleeding disorders with intramuscular injections prior to study enrollment. Patients determined to be at high risk for bleeding with intramuscular injections will be excluded.

4.3 Inclusion of Women and Minorities

Adult females and males of all races and ethnic groups are eligible for this trial. HPV-related malignancies are unequally distributed among men and women, Gardasil® 9 protects women against cervical, vaginal, vulvar, and anal cancers; and men against anal cancer caused by the seven oncogenic HPV types covered by the vaccine.

The study was originally designed to be conducted only among women 18-49 years of age. However, as noted in Section 4.1.1 above, with version 3.6, the study is also expanded to men 18-49 years of age.

4.4 Recruitment and Retention Plan

Recruitment
A waiver of consent to access patient records to allow for the identification of potential study participants for recruitment has been obtained from the CIRB. Potential participants will be identified for study recruitment by physicians or study staff:

1. Before or during clinical encounters
2. By review of medical charts
3. By review of institutional databases
4. By review of the deceased donor transplant waitlist
5. Through consultation with the institution's transplant coordinator(s)
6. By referral from other physicians
7. By reviewing upcoming donor workup evaluations
8. By reviewing upcoming living donor surgery lists
9. By other site-specific methods

Medical charts of potential transplant recipients will be reviewed for eligibility, including sex, age, prior organ transplant, laboratory results, previous malignancies, and medical contraindications. The physician will review the eligibility information and assess the likelihood of undergoing surgery within 12 months of enrollment, and notify research staff whether the patient may be considered for participation. The research staff may approach potential participants through any of the following methods:

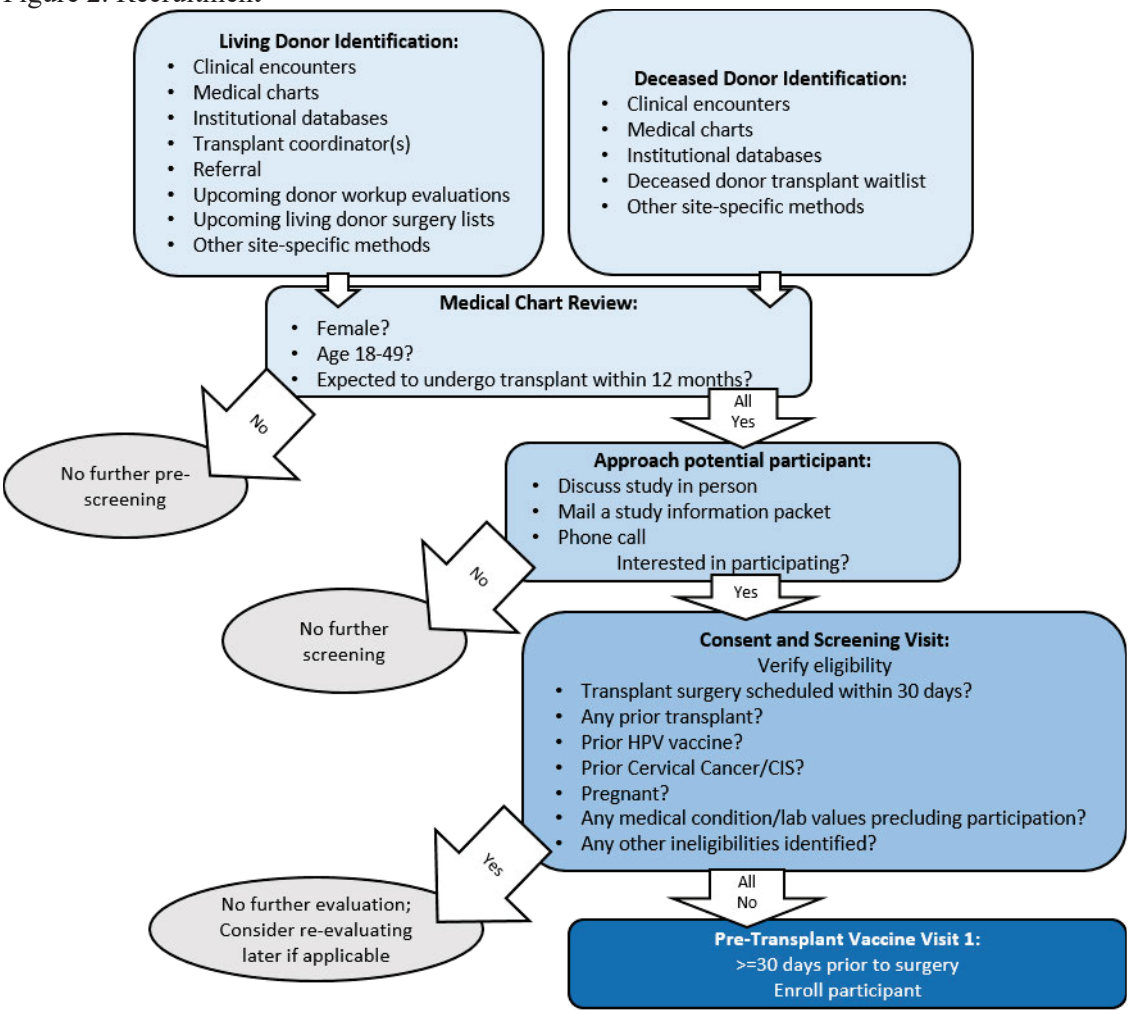
1. Preparing and mailing a study information packet that introduces the study to potentially eligible patients. The packet may include materials such as the study consent form (ICF), HIPAA authorization, and IRB-approved recruitment materials (e.g., introductory letter, leaflet; each participating site will choose what materials to include).
2. Contacting potential participants by phone.
3. Approaching potential participants at their clinic visits.

Patients will be encouraged to review the consent documents with family, friends, and/or other physicians. The patient will be told that the decision to join or not join the study will not affect the medical treatment that patients receive, and that patients can withdraw from the study at any time. If the participant is approached at the clinic, and wishes to review the consent form at home, research staff may follow-up with a phone call to the patient a few days later to evaluate interest in study participation and answer additional questions. If the potential participant is still interested, research staff may schedule a return visit to discuss the study further with the research staff and sign the consent form.

Because this protocol has many possible schedules depending on the occurrence and the timing of each participants' transplant surgery, and in order to limit the length of the Consent Form, Appendix C (Study Procedures for Potential Participants) and Appendix D (Study Schedule for Potential Participants) are provided. Study teams may optionally use these materials with potential participants.

In an effort to minimize participant burden and increase the likelihood of enrollment and follow-up, we will schedule study visits to coincide with usual care appointments, whenever possible. A packet of material, including a map and parking instructions may be provided to the study participant prior to the scheduled study visit. At the completion of all study visits except the Additional Study Visits, participants will receive compensation for their time, transportation, parking, and other expenses related to the study.

Figure 2. Recruitment



Feasibility

According to the 2017 Organ Procurement Transplantation Network data reports [22], a total of 467 first-time kidney transplants in adults aged 18-49 were performed at these five sites (Table 1). First-time renal transplant recipients in adults aged 18-49 at these institutions included 34.7% white, 26.5% African American, 25.9% Hispanic, 11.8% Asian, 0.6% Pacific Islander, and 0.6% Multiracial – a larger percentage of non-white living donor transplant recipients (65%) than the national average (34%). Recruitment of pre-renal transplant recipients will occur over a period of 18 months. Investigators will review all listed individuals undergoing evaluation for transplantation on a weekly basis.

We project that 815 adults, ages 18-49 years, will receive a first-time kidney transplant during an 18-month period based on the 543 adult first-time kidney transplant recipients aged 18-49 in 2017 by the participating transplant centers (Table 1), suggesting that our recruitment goal is highly feasible. The final analytic sample for follow-up will include an estimated 64 adults (which are projected to include 23 white, 17 African-American, 17 Hispanic, 7 Asian based on current racial/ethnic composition of kidney transplant recipients) who have received two doses of the Gardasil® 9 HPV vaccine and have undergone a kidney transplant ≥ 30 days after the first vaccine dose. To meet this goal, we estimate that we need to recruit and consent 180 participants.

Table 1. Numbers of Kidney Transplants in 2017 by Center						
	CSMC	UCSF	NW	UAB	UNC	Total
First-time living donor kidney transplants in women age 18-49, 2017*	10	18	16	19	4	67
First-time living donor kidney transplants in men age 18-49, 2017*	10	28	40	31	4	113
First-time deceased donor kidney transplants in women age 18-49 years, 2017*	19	30	30	31	16	126
First-time deceased donor kidney transplants in men age 18-49 years, 2017*	32	40	21	54	14	161
Total first-time kidney transplants in women and men age 18-49, 2017	71	116	107	135	38	467
*https://optn.transplant.hrsa.gov/data/view-data-reports/center-data accessed on 11/06/2018.						

Time for kidney transplants will vary significantly between those receiving a living donor transplant and those receiving a deceased donor transplant. Typically, living donor kidney transplants are performed within 90 days after approval of an acceptable living donor at each of the participating transplant centers. We will make every effort to complete the screening evaluations and schedule the baseline visit ≥30 days before the patient's living donor kidney transplant procedure to maximize the number of eligible, consented participants who receive at least one dose of the Gardasil® 9 HPV vaccine prior to the transplant. Study participants who are expected to receive a kidney transplant from a deceased donor will be selected based on their likelihood of receiving the transplant within 12 months of enrollment, and depending on when the transplant actually gets scheduled (unpredictable time frame, given the knowledge of availability of a donor kidney and transplant surgery is usually a matter of <24 hours), the participants may be able to receive one, two or all three doses of the HPV vaccine prior to transplant.

Over an 18-month period we expect that 180 kidney transplant candidates will be consented and pass the medical chart review and pre-transplant clinic evaluations; 120 will receive one or two doses of the Gardasil® 9 HPV vaccine prior to transplant; 96 women will complete the 12-month post-transplant follow-up visit and receive the booster vaccine dose; and 64 women who have received the first vaccine dose ≥ 30 days before their transplant will complete all follow-up.

Although all eligible, consented kidney transplant candidates will receive their first vaccine dose, we expect that a substantial fraction (perhaps one-third) of these candidates may not receive a transplant within the study period, largely because the identified donor will not pass through all the transplant eligibility screening testing in case of living donor transplant recipients, or no matching kidney from deceased donors becomes available in case of participants on the deceased donor transplant waiting list. Therefore, to meet the sample size requirement (N=64) for analysis of our primary endpoint, we enroll a higher number of participants than our expected target, expecting losses to follow-up at several stages in the study enrollment and follow-up cascade.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

- Agent: Gardasil® 9 nonavalent HPV vaccine
- Dose and regimen for agent: 0.5 mL single-dose for intramuscular administration
- Duration for agent: Gardasil® 9 must be administered according to the following requirements:
  - Dose 1: ≥ 30 days prior to transplant
  - Dose 2: ≥ 30 days after Dose 1
  - Dose 3: ≥5 months after Dose 1 AND ≥ 3 months after Dose 2
- All participants will be offered the entire 3-dose series. Due to differences in the timing of transplant surgery, the feasibility of additional study-related visits prior to transplant surgery, and the possibility that transplant surgery will not occur within 12 months of enrollment, there are six different dosing schedules, outlined in Table 2 below.

Table 2. Dose Regimens

	Participant is able to complete only 1 dose prior to surgery	Participant is able to complete 2 doses prior to surgery	Participant is able to complete 3 doses prior to surgery	Participant completes 1 dose, but transplant does not occur within 12 months of enrollment	Participant completes 2 doses, but transplant does not occur within 12 months of enrollment	Participant completes 3 doses, but transplant does not occur within 12 months of enrollment
Dose 1	≥ 30 days prior to Transplant Surgery					
Dose 2	12 months (±2 weeks) after Transplant Surgery	≥30 days after Dose 1	≥30 days after Dose 1	12 months (±2 weeks) after Dose 1	≥30 days after Dose 1	≥30 days after Dose 1
Dose 3	3 months (+4 weeks) after Dose 2	12 months (±2 weeks) after Transplant Surgery	≥5 months after Dose 1 AND ≥3 months after Dose 2	3 months (+4 weeks) after Dose 2	12 months (±2 weeks) after Dose 2	≥5 months after Dose 1 AND ≥3 months after Dose 2

5.2 Study Agent Administration

- The CDC HPV Vaccine Information Statement (VIS) that explains the benefits and risks of the vaccine will be provided to participants prior to administration of each vaccine dose (http://www.immunize.org/vis/hpv.pdf).
- A licensed provider at each site will administer the Gardasil® 9 vaccine as a 0.5 mL injection in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.
- Shake the Gardasil® 9 vaccine vial well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.
- Single-Dose Vial Use: Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use promptly.
- Prefilled Syringe Use: This package does not contain a needle. Shake well before use. Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.
- Gardasil 9 should not be diluted or mixed with other vaccines. After thorough agitation, Gardasil 9 is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container

permit for such inspection. Do not use the product if particulates are present or if it appears discolored.

- Administer the entire dose as per standard protocol and instructions in the package insert.
- Participants will be required to be afebrile (oral temperature < 37.8° C) for 24 hours before vaccination.
- Participants must be monitored for 30 minutes following vaccination for syncope/convulsive syncope and allergic reactions. There will be an accessible crash cart during vaccine administration which will include medications for anaphylaxis.
- The CDC discourages deviating from the recommended route and encourages that all vaccines be administered by the manufacturer's recommended route [47,48]. The HPV vaccine should be administered intramuscularly if a physician familiar with the patient's bleeding risk determines that the vaccine can be administered by this route with reasonable safety. A fine-gauge needle (23-gauge or smaller caliber) should be used for the vaccination, followed by firm pressure on the site, without rubbing, for at least 2 minutes. The patient or family should be given information on the risk for hematoma from the injection. In patients with clotting factor disorders receiving antihemophilia or similar therapy, the intramuscularly administered vaccination can be scheduled shortly after such therapy is administered. Patients receiving anticoagulation therapy (or aspirin) presumably have similar bleeding risk as patients with clotting factor disorders and should follow the same guidelines for intramuscular administration. If possible, vaccination could be scheduled prior to the use of these medications, so that the patients' risk of bleeding is not increased by their therapeutic action.

5.3 Run-in Procedures

None.

5.4 Contraindications

Gardasil® 9 is contraindicated in individuals who are hypersensitive to the active substances or to any of the excipients of the vaccine, including severe allergic reactions to yeast (a vaccine component), or after a previous Gardasil® 9 dose.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to Gardasil® 9. Immunosuppressive therapies are not prohibited concomitant medications for this study.

5.5 Concomitant Medications

The regimen type, duration, and dosing of all concomitant medications which, in the judgment of the study clinician, are expected to modulate the immune system (including, but not limited to, immunosuppressive agents, anti-virals, and anabolic steroids) will be documented on the concomitant medication CRF.

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant *during a Serious Adverse Event* will be documented. Medications taken for the transplant procedure do not need to be included; however, if the patient's transplant hospitalization is extended because of an adverse event, medications taken during the extended portion of the hospitalization will be included.

Other medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant during the regular course of the study will be documented at the discretion of the study clinician.

5.6 Dose Modification

No dose modifications are planned. The study agent will be stopped in the event of an AE ≥ grade 3 considered possibly, probably, or definitely related to the study agent. The second or third dose of Gardasil® 9 will not be administered to participants who experienced symptoms indicative of hypersensitivity after the first and/or second dose(s).

5.7 Adherence/Compliance

Study visits will coincide with usual care appointments whenever possible to increase compliance with the study protocol/vaccine dosing schedule. Research staff will contact study participants by phone 24-72 hours after receiving each vaccine dose to ask about potential side effects of the immunization. If the participant reports adverse symptoms there will be a follow-up call on day 7 ± 2 days to assess resolution. Participants will also be contacted 5-7 days before each study visit to confirm the appointment. Contact can be made using site standard procedures and/or mechanisms (i.e. automated or manual phone call, text message, or email).

6. PHARMACEUTICAL INFORMATION

6.1 Study Agent (IND # [redacted] (Exempt), IND Sponsor: NCI/DCP)

This clinical study investigating the preventive efficacy of recombinant human papillomavirus (HPV) nonavalent vaccine, Gardasil® 9, is being conducted under an IND exemption sponsored by NCI/DCP. Gardasil® 9 is indicated for prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, and for the prevention of genital warts caused by HPV types 6 or 11 in females 9-45 years of age. Gardasil® 9 is indicated for prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52 and 58, and for the prevention of genital warts caused by HPV types 6 or 11 in males 9-45 years of age.

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

6.2 Reported Adverse Events and Potential Risks

The manufacturer evaluated the safety of Gardasil® 9 in six clinical studies that included 15,703 individuals who received at least one dose and had safety follow-up. The vaccine was administered on the day of enrollment, with subsequent doses administered approximately two and six months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of Gardasil® 9. The individuals who were monitored using VRC-aided surveillance included 9,097 girls and women 16-26 years of age, 1,394 boys and men 16-26 years of age, and 5,212 girls and boys 9-15 years of age (3,436 girls and 1,776 boys) at enrollment.

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

The most common (≥10%) local and systemic adverse reactions in females 16-26 years of age who received Gardasil® 9 were injection site pain (89.9%), injection site swelling (40.0%), injection site erythema (34.0%), and headache (14.6%). The most common (≥10%) local and systemic adverse reactions in males 16-26 years of age who received Gardasil® 9 were injection site pain (63.4%), injection site swelling (20.2%), injection site erythema (20.7%), and headache (7.3%). The most common (≥10%) local and systemic reactions in girls 9-15 years of age who received Gardasil® 9 were injection site pain (89.3%), injection site swelling (47.8%), injection site erythema (34.1%), and headache (11.4%). The most common (≥10%) local and systemic reactions in boys aged 9-15 years who received Gardasil® 9 were injection site pain (71.5%), injection site swelling (26.9%), and injection site erythema (24.9%).

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

In all of the clinical trials with Gardasil® 9, participants were evaluated for new medical conditions potentially indicative of a systemic autoimmune disorder. In total, 2.4% (321/13,234) of Gardasil® 9 recipients reported new medical conditions potentially indicative of systemic autoimmune disorders, which were similar to rates reported following Gardasil®, AAHS control, or saline placebo in historical clinical trials.

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

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

The safety and effectiveness of Gardasil® 9 have not been established in pediatric patients below nine years of age. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to Gardasil® 9. However, immunosuppressive therapies are not prohibited concomitant medications for this study.

6.3 Availability

Gardasil® 9 will either be provided by Merck and distributed via NCI, DCP's repository contractor MRIGlobal (Kansas City, MO), procured and distributed by MRIGlobal, or procured locally at the study sites.

6.4 Agent Distribution

Agents will only be released by NCI, DCP after documentation of NCI Central IRB (CIRB) approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

NCI, DCP-supplied agents may be requested by the Investigator (or their authorized designees) at each participating organization. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be prepared and administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). DCP does not automatically ship agents; the site must make a request. Agents are requested by completing the DCP Clinical Drug Request form (NIH-986) (to include complete shipping contact information) and faxing or mailing the form to the DCP agent repository contractor:

John Cookinham
MRIGlobal
DCP Repository
1222 Ozark Street
North Kansas City, MO 64116
Phone: (816) 360-3805
FAX: (816) 753-5359
Emergency Telephone: (816) 360-3800
Email: NCI.DCP@mriglobal.org

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI Drug Accountability Record Form (DARF). The Investigator is required to maintain adequate records of receipt, dispensing, and final disposition of study agent. This responsibility has been delegated to the study pharmacists or their designees at each site . Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

6.6 Packaging and Labeling

Gardasil® 9 will be supplied by NCI DCP in the original manufacturer's packaging and not re-labeled for study purposes.

6.7 Storage

Gardasil® 9 is supplied in single-dose vials or pre-filled syringes and should be stored in a secure location protected from light at temperatures between 2°C and 8°C (36°F and 46°F). Gardasil® 9 will be stored in a safe, secure, temperature monitored limited access drug storage area specifically for research medication at the Research Pharmacy at each site.

6.8 Registration/Randomization

The Lurie Cancer Center Clinical Trials Management System (CTMS) will be the database of record. The study coordinator must upload (via CTMS), a signed and complete informed consent along with HIPAA authorization and a completed registration form for each participant identified as eligible to be entered into the study.

All participants must be registered in CTMS M-F between the hours of 9:30 a.m. and 5:00 p.m., Central Time (CT). Participants must not start protocol treatment prior to registration in CTMS.

This is a non-randomized trial.

6.9 Blinding and Unblinding Methods

Not applicable.

6.10 Agent Destruction/Disposal

At the completion of the study, all unused study agent will be returned to NCI, DCP Repository according to the DCP "Guidelines for AGENT RETURNS" and using the DCP form "Return Drug List".

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Study Procedures	Consent and Screening Visit	Pre-Transplant Vaccine Visit 1[1]	Pre-Transplant Vaccine Visits 2 and 3[2]	Transplant Surgery	6 Month Post-Transplant Visit[3]	12 Month Post-Transplant Visit[4]	13 Month Post-Transplant Visit[5]	Additional Study Visit(s)[6]
Assess eligibility	X	X						
Informed consent form and HIPAA authorization	X							
Pregnancy test[7]	X					X[8]		
Enrollment		X						
Demographics (race, ethnicity, education)		X						
Review medical history, medications, and laboratory test results		X	X		X	X		
Symptoms assessment and ECOG performance status		X	X		X	X		

Physical exam including vital signs and weight		X	X		X	X		
Gardasil® 9 HPV vaccination		X	X			X[8]		X
Collect blood specimen for research		X[9]	X[9]	X[10]	X[9]	X[9]	X[11]	
Self-collection of cervical/vaginal, and oral samples for HPV DNA		X	X		X	X		
Self-collection of urine samples for HPV DNA (optional)[12]		X	X		X	X		
Collection of eyebrow hairs for future viral DNA testing (optional)[12]		X	X		X	X		
Self-collection of male genital samples for future HPV DNA testing (optional)[12]		X	X		X	X		
Interviewer-administered risk factor questionnaire[13]		X	X		X	X		
Review eligibility criteria	X	X						
Assess adverse events[14]		X	X			X		
Telephone contact[15]	X	X	X		X	X		X

[1] Pre-Transplant Vaccine Visit 1 may occur the same day as the Consent and Screening Visit, and will be scheduled ≥30 days prior to the planned transplant surgery.

[2] Pre-Transplant Vaccine Visits 1 and 2 are optional, guided by the timing of surgery and feasibility of additional study-related visits. Participants who do not have Pre-Transplant Vaccine Visits 1 and/or 2 will still receive the complete 3-dose series of the vaccine (the remaining vaccination(s) will occur post-transplant; see Appendix B for a detailed schedule). If the Pre-Transplant Vaccine Visits 1 and 2 occur, the following intervals must be used:

- Pre-Transplant Vaccine Visit 2 should occur ≥30 days after Pre-Transplant Vaccine Visit 1.
- Pre-Transplant Vaccine Visit 3 should occur ≥3 months after Pre-Transplant Vaccine Visit 2, and ≥5 months after Pre-Transplant Vaccine Visit 1.

[3] The 6 Month Post-Transplant Visit will occur 6 months (±2 weeks) after the participant's renal transplant procedure.

[4] The 12 Month Post-Transplant Visit will occur 12 months (±2 weeks) after the participant's renal transplant procedure.

- Participants who received only one dose of the vaccine prior to transplant will receive the second dose of the vaccine at this visit.
- Participants who received two vaccine doses prior to transplant will receive the third dose of the vaccine at this visit.
- Participants who received three vaccine doses prior to transplant will not receive a third dose of the vaccine at this visit.

[5] The 13 Month Post-Transplant Visit will occur 1 month (+2 weeks) after the 12 Month Post-Transplant Visit. This visit will occur only for participants who received a vaccine at the 12 Month Post-Vaccine Visit.

[6] Additional Study Visit(s) will be offered for participants only for the purpose of completing their vaccine series (second and/or third doses) in the following scenarios:

- Participants who receive only one dose prior to transplant and second dose at the 12 Month Post-Transplant Visit will be offered an Additional Study Visit at 3 months (+4 weeks) after 12 Month Post-Transplant Visit.
- Participants who receive one vaccine dose, but their transplant surgery is postponed/rescheduled/cancelled and eventually not scheduled within 12 months of the study enrollment date, will be offered two Additional Study Visits to complete the three dose vaccine series. Additional Study Visit 1 will occur 12 months (±2 weeks) after Pre-Transplant Vaccine Visit 1, and Additional Study Visit 2 will occur 3 months (+ 4 weeks) after Additional Study Visit 1.

- Participants who receive two vaccine doses, but their transplant surgery does not occur within 12 months of the study enrollment date, will complete an Additional Study Visit to complete the three dose vaccine series at 12 months (±2 weeks) after Pre-Transplant Vaccine Visit 1.

[7] Pregnancy test (urine/blood) for women able to become pregnant. Women who are able to become pregnant must have a confirmed negative pregnancy test result within the past 28 days prior to enrollment. Women with both ovaries removed/tubal ligation will not be required to have a pregnancy test. Women who are pregnant will be excluded and will not receive vaccine.
[8] Gardasil 9 vaccine and the pregnancy test (for women able to become pregnant) at the 12 Month Post-Transplant Visit will occur only for participants who complete 1-2 vaccines prior to transplant.
[9] A 28 mL blood specimen will be collected.
[10] For participants who completed only one vaccine prior to surgery, a 28 mL blood specimen will be collected. For participants who received 2-3 vaccines prior to surgery, no blood will be collected.
[11] A 10 mL blood specimen will be collected.
[12] For participants who noted in the consent form that they agree to the optional collection of these specimens.
[13] A detailed interviewer-administered questionnaire (Appendix E) will be used at baseline (Pre-Transplant Vaccine Visit 1) and a shortened questionnaire (Appendix F) will be used at subsequent visits to ask about changes in exposures/behaviors between visits.
[14] Adverse event assessments after Gardasil® 9 vaccination will include monitoring for syncope/convulsive syncope, pain, swelling, redness or itching at the vaccine injection site, headache, fever, nausea, and signs of a severe allergic reaction: hives, a fast heartbeat, dizziness, weakness, difficulty breathing, or swelling of the face and throat.
[15] Participants will also be contacted by telephone 24-72 hours after receiving each vaccine dose to ask about potential side effects. If participant reports adverse symptoms there will be a follow-up call on day 7 ± 2 days to assess resolution. Participants will also be contacted 5-7 days before each study visit to confirm the appointment. Contact can be made using site standard procedures and/or mechanisms (i.e. automated or manual phone call, text message, or email)

7.2 Pre-Study Evaluation

Consent and Screening Visit

Renal transplant candidates who are 18-49 years of age, expected to undergo transplant surgery within 12 months of enrollment, and interested in participating in the study will be consented into the trial during a clinic visit. Research staff will be present at the clinic during this visit and will be available to review study materials with the patient and answer questions about the study. Patients will be encouraged to review the consent documents with family, friends, and/or other physicians. The patient will be told that the decision to join or not join the study will not affect the medical treatment that patients receive, and that patients can withdraw from the study at any time. Patients who have had all their questions about the study answered on the day they first learn about the study, and who wish to participate, may be consented the same day they are first informed of the research. Otherwise, another appointment may be scheduled.

Research staff will obtain signatures on the consent documents for kidney transplant candidates who wish to volunteer for the study after all clinical options have been presented and the patient's questions have been answered. The patient will carefully review and sign the study consent form and HIPAA authorization. Copies of each form will be given to the patient and placed in the medical record. Written consent will be obtained before any research related procedures are initiated.

At the Screening and Consent visit, the following procedures will be performed:

1) Consent will be obtained. Appendix C and Appendix D are optional to use when consenting the participant.
2) A thorough review of the patient’s medical history will be done, including past cervical cytology results
3) Inclusion and exclusion criteria will be evaluated for the patient
4) Women able to become pregnant will be required to have a confirmed negative pregnancy test (urine or blood) within 28 days prior to enrollment. Women who have had a both ovaries

removed or a tubal ligation will not be required to have a pregnancy test.

7.3 Baseline Testing and Evaluation During Study Intervention

Pre-Transplant Vaccine Visit 1

The first vaccine visit may occur the same day as the Consent and Screening Visit, and will occur ≥ 30 days before the patient's kidney transplant procedure. The following procedures will be performed during this visit:

1) Review of medical and surgical history, medications, and laboratory test results
2) Symptom assessment and ECOG performance status
3) Physical exam including vital signs, height, and weight
4) Review of inclusion/exclusion criteria and study requirements, final determination of eligibility, and enrollment
5) The first dose of Gardasil® 9 will be administered to the participant.
6) Blood draw – A 28 mL blood specimen will be collected from each participant.
7) Self-collection of cervical/vaginal and oral samples for HPV DNA detection.
8) Self-collection of urine for HPV DNA detection from participants who consent to collection of optional urine samples.
9) Collection of eyebrow hairs (collected by research staff) for future viral DNA testing from participants who consent to collection of optional samples for biobanking for future studies
10) Self-collection of male genital samples for future HPV DNA testing from participants who consent to collection of these optional samples for biobanking for future studies
11) Interviewer-administered baseline questionnaire to obtain demographic information (detailed race and ethnicity, education); skin sensitivity and type; tobacco and alcohol use; recent sexual activity; medical history, including frequency of Pap smears; and medication use (Appendix E)

Pre-Transplant Vaccine Visits 2 and 3

These visits are optional, and should be guided by the timing of surgery and feasibility of additional study-related visits. Participants who do not have Pre-Transplant Vaccine Visits 1 and/or 2 will still receive the complete 3-dose series of the vaccine (the remaining vaccination(s) will occur post-transplant. See Appendix B for a detailed schedule). If the Pre-Transplant Vaccine Visits 1 and 2 occur, the following intervals must be used:

- Pre-Transplant Vaccine Visit 2 should occur ≥30 days after Pre-Transplant Vaccine Visit 1. If possible (but not required), Pre-Transplant Vaccine Visit 2 should occur at least 30 days prior to Transplant Surgery.
- Pre-Transplant Vaccine Visit 3 should occur ≥3 months after Pre-Transplant Vaccine Visit 2, and ≥5 months after Pre-Transplant Vaccine Visit 1. If possible (but not required), Pre-Transplant Vaccine Visit 3 should occur at least 30 days prior to Transplant Surgery.

The following procedures will be performed during these visits:

1) Review of medical and surgical history, medications, and laboratory test results
2) Symptom assessment and ECOG performance status
3) Physical exam including vital signs and measurement of weight
4) Gardasil® 9 will be administered to the participant.
5) Blood draw – A 28 mL blood specimen will be collected from each participant.
6) Self-collection of cervical/vaginal and oral samples for HPV DNA detection.
7) Self-collection of urine for HPV DNA detection from participants who consent to collection of optional urine samples.
8) Collection of eyebrow hairs (collected by research staff) for future viral DNA testing from participants who consent to collection of optional samples for biobanking for future studies

9) Self-collection of male genital samples for future HPV DNA testing from participants who consent to collection of these optional samples for biobanking for future studies
10) Interviewer-administered follow-up questionnaire to obtain information about changes in exposures and behaviors between study visits (Appendix F)
11) Review of inclusion/exclusion criteria and study requirements

Telephone Calls

Research staff will contact study participants by phone 24-72 hours after receiving each vaccine dose throughout the study, including pre-transplant vaccines, post-transplant vaccines, and Additional Study Visit(s). Research staff will ask the participant about potential side effects of the immunization. If the participant reports adverse symptoms there will be a follow-up call on day 7 ± 2 days to assess resolution. Participants will also be contacted 5-7 days before each study visit to confirm the appointment. Contact can be made using site standard procedures and/or mechanisms (i.e. automated or manual phone call, text message, or email) .
The following information with be collected during the telephone calls:

- Concomitant medication review
- Adverse events. Participants will be asked if they have experienced any of the following symptoms to assess adverse events:
    - Pain, swelling, redness, or itching at the vaccine injection site
    - Headache
    - Fever
    - Nausea
    - Signs of a severe allergic reaction: hives, a fast heartbeat, dizziness, weakness, difficulty breathing, or swelling of the face and throat
- Additional symptoms experienced by participants will be recorded to assess adverse events

7.3.4 Transplant Surgery

For participants who receive only one vaccine dose prior to transplant, a blood sample (28 ml) will be obtained for antibody titers before/at transplant surgery. All other participants (who received two or more vaccines prior to transplant) will have no research activity on the day of transplant surgery.

7.4 Evaluation at Completion of Study Intervention

6 Month Post-Transplant Visit

This study visit will occur 6 months (± 2 weeks) after the participant's kidney transplant procedure. The following procedures will be performed during this visit:

1) Review of medical and surgical history, and medications, and laboratory test results
2) Symptom assessment and ECOG performance status
3) Physical exam including vital signs and measurement of weight
4) Blood draw – A 28 mL blood specimen will be collected from each participant.
5) Self-collection of cervical/vaginal and oral samples for HPV DNA detection.
6) Self-collection of urine for HPV DNA detection from participants who consent to collection of optional urine samples.
7) Collection of eyebrow hairs (collected by research staff) for future viral DNA testing from participants who consent to collection of optional samples for biobanking for future studies
8) Self-collection of male genital samples for future HPV DNA testing from participants who consent to collection of these optional samples for biobanking for future studies
9) Interviewer-administered follow-up questionnaire to obtain information about changes in exposures and behaviors between study visits (Appendix F)

10) Review of inclusion/exclusion criteria and study requirements

12 Month Post-Transplant Visit

This study visit will occur 12 months (± 2 weeks) after the participant's kidney transplant procedure. The following procedures will be performed during this visit:

1) Review of medical and surgical history, medications, and laboratory test results
2) Symptom assessment and ECOG performance status
3) Physical exam including vital signs and measurement of weight
4) Pregnancy test (urine or blood) for women who meet both of the following criteria:
    a. Received only one or two vaccines earlier in the study, AND
    b. Are able to become pregnant (women who have had both ovaries removed or a tubal ligation will not be required to have a pregnancy test)

    Women who are pregnant will not receive the Gardasil® 9 HPV vaccine.
5) Participants who have received two vaccine doses prior to transplant will receive the third dose of the vaccine. Participants who have received only one dose of the vaccine prior to transplant will receive the second dose of the vaccine at this visit.
6) Blood draw – A 28 mL blood specimen will be collected from each participant.
7) Self-collection of cervical/vaginal and oral samples for HPV DNA detection.
8) Self-collection of urine for HPV DNA detection from participants who consent to collection of optional urine samples.
9) Self-collection of male genital samples for future HPV DNA testing from participants who consent to collection of these optional samples for biobanking for future studies
10) Collection of eyebrow hairs (collected by research staff) for future viral DNA testing from participants who consent to collection of optional samples for biobanking for future studies
11) Interviewer-administered follow-up questionnaire to obtain information about changes in exposures and behaviors between study visits (Appendix F)
12) Review of inclusion/exclusion criteria and study requirements

7.5 Post-intervention Follow-up Period

13 Month Post-Transplant Visit

If the participant received a vaccine dose at the 12 Month Post-Transplant Visit, the participant will return for a 13 Month Post-Transplant Visit. This visit will occur 1 month (+2 weeks) after the 12 Month Post-Transplant Visit. The following procedures will be performed during this visit:

1) Blood draw – A 10 mL blood specimen will be collected from each participant to measure HPV vaccine-type-specific antibody titers.

7.6 Additional Study Visit(s)

Additional Study Visits will be offered only for the purpose of completing the vaccine series for participants who are unable to receive their second or third vaccine doses in accordance to the proposed schedule of events. These Visits will be offered in the following scenarios:

1. Participants who only received one dose prior to transplant, and their second dose administered at 12 Month Post-Transplant Visit. These participants will receive their third dose at an Additional Study Visit 3 months (+4 weeks) after the 12 Month Post-Transplant Visit.
2. Participants who received two vaccine doses prior to transplant, but their transplant surgery is postponed/rescheduled/cancelled and eventually not scheduled within 12 months of the study enrollment date, will complete their three dose vaccine series at an Additional Study Visit at 12 months (±2 weeks) after Pre-Transplant Vaccine Visit 1. These participants will be considered off-study after the Additional Study Visit is completed, and follow-up calls were made, as

discussed in Section 8.4.

3. Participants who receive one vaccine dose prior to transplant, but their transplant surgery does not occur within 12 months of Pre-Transplant Vaccine Visit 1, will be offered two Additional Study Visits to complete the three dose vaccine series. Additional Study Visit 1 will occur 12 months (±2 weeks) after the Pre-Transplant Vaccine Visit 1. Additional Study Visit 2 will occur 3 months (+4 weeks) after Additional Study Visit 2. These participants will be considered off-study after the Additional Study Visits are completed, and follow-up phone calls were made, as discussed in Section 8.4.

The following procedures will be performed during the Additional Study Visits:

1) The second or third dose of Gardasil® 9 is administered.

7.7 Methods for Clinical Procedures

Administration of Vaccine. The CDC HPV VIS (http://www.immunize.org/vis/hpv.pdf) will be provided to the participant prior to administration of the vaccine. The vaccine will be administered as a 0.5 mL injection in the deltoid region of the upper arm or in the higher anterolateral area of the thigh. Participants will be monitored for adverse reactions to the vaccine for 30 minutes.

Blood specimen. A 28 mL blood specimen will be collected from each participant at the Pre-Transplant Vaccine Visits 1, 2, and 3, at the 6 Month and 12 Month Post-Transplant Visits, and (for participants who do not complete Pre-Transplant Vaccine Visit 2) before/at transplant surgery for measurement of the primary and secondary endpoints for the study. Ten mL of blood will be collected at the 13 Month Post-Transplant Visit to measure the anamnestic response to the booster vaccine dose by assessing HPV vaccine-type-specific titers. The primary biomarker of interest, HPV vaccine-type-specific seroconversion rates, will be measured in peripheral blood that will be drawn by routine venipuncture at the time of mandated blood draws, thus there will be no added risk to the participant.

Collection of cervical/vaginal and oral samples for HPV DNA testing. Cervical/vaginal and oral samples will be self-collected at the Pre-Transplant Vaccine Visits 1, 2, and 3, and at the 6 Month and 12 Month Post-Transplant Visits for HPV DNA testing. Cervical/vaginal samples will be self-collected using the Evalyn Brush® (Rovers Medical Devices B.V., Oss, Netherlands) for female participants only. Oral samples will be self-collected using a mouthwash gargle.

Collection of urine samples for HPV DNA testing. Urine samples will be self-collected at the Pre-Transplant Vaccine Visits 1, 2, and 3, and at the 6 Month and 12 Month Post-Transplant Visits from participants who consent to the collection of optional urine samples. Approximately 20-30 mL of urine will be self-collected at each visit in a sterile urine specimen container. Urine samples will be used for HPV DNA testing.

Collection of eyebrow hair samples for future viral DNA testing. Eyebrow hair samples will be collected at the Pre-Transplant Vaccine Visits 1, 2, and 3, and at the 6 Month and 12 Month Post-Transplant Visits from participants who consent to collection of optional samples for biobanking for future studies. Clinical research staff will collect six eyebrow hairs with the attached follicle from each consenting participant using sterile tweezers. Eyebrow hair samples will be used for future viral DNA testing.

Collection of male genital samples for HPV DNA testing. Male genital samples will be collected using a validated male genital sampler collection protocol [40,46] from participants who consent to the collection of these optional samples for an exploratory analysis of detection of HPV DNA during the course of the study. This analysis is exploratory since there is no FDA-approved HPV sampling or testing protocol in males. Male genital samples will be self-collected by rubbing a dry swab over the entire exterior surface of the penis and placed into a vial. Male genital samples will be self-collected at the Pre-

Transplant Vaccine Visits 1, 2, and 3, and at the 6 Month and 12 Month Post-Transplant Visits and will be used for HPV DNA testing.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

HPV vaccine-type-specific seroconversion rates at 12-months post-transplantation among 18-49 year old kidney transplant recipients who receive ≥ 1 doses of the Gardasil® 9 HPV vaccine ≥ 30 days prior to transplantation.

8.2 Secondary and Exploratory Endpoints

Secondary Endpoint
HPV vaccine-type-specific seroconversion rates at 6- and 12-months post-transplantation stratified by number of doses (1, 2, or 3) of the vaccine given pre-transplant.

Exploratory Endpoints
1) HPV vaccine-type-specific seroconversion rates at 12-months post-transplantation stratified by:
   a) time elapsed between last vaccine dose and the transplant procedure;
   b) variations in doses and types of post-transplant immunosuppressant medications; and interactions with type of transplant surgery (living donor/deceased donor);
   c) differences in Human Leukocyte Antigen (HLA) histocompatibility between donor and recipient;
   d) differences in biological sex (i.e. male vs. female) of the transplant recipient.

2) Stability of HPV vaccine-type-specific geometric mean titers (GMT) at 6- and 12-months post-transplantation and rise in HPV vaccine-type-specific GMT at the 13-month post-transplant visit.

3) Vaccine safety profile and allograft rejection/opportunistic infections stratified by number of vaccine doses and time between the last vaccine dose and the transplant procedure.

4) HPV detection in samples from the cervix/vagina, and oral cavity at baseline (pre-vaccination) and at 6- and 12-months post-vaccination, overall and by number of vaccine doses (1, 2, or 3), sexual behavior, type-specific seroconversion rates, and time elapsed between the last vaccine dose and the transplant procedure.

8.3 Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, AE or serious adverse event (SAE), inadequate agent supply, noncompliance, or medical contraindications. Participants will continue to be followed, if possible, for safety reasons (e.g., telephone contact 24-72 hours after receiving each vaccine dose to ask about potential side effects of the immunization; and a follow-up call on day 7 ± 2 days to assess resolution if the participant reports adverse symptoms). Participants who receive one or two doses of the vaccine in the pre-transplant period and go off-agent due to any reason stated above will be offered the post-transplant study visits at 6-months, 12-months and 13-months to collect endpoint data according to the schedule of events, even though the clinical and/or logistical situation that led to the participant going ‘off-agent’ might not permit giving the remaining vaccine doses at any of these visits.

8.4 Off-Study Criteria

Participants may go ‘off-study’ for the following reasons: the protocol intervention and any protocol-

required follow-up period is completed, AE/SAE, lost to follow-up, non-compliance, medical contraindications, withdraw consent, death, determination of ineligibility (including screen failure), or pregnancy. Participants whose planned transplant surgery does not occur within 12 months of enrollment will be taken 'off-study' after Additional Study Visit(s) and follow-up phone calls (described in Section 7.5.2) are completed, to finish the remaining vaccine doses of the series. All participants who do not receive transplant surgery within 12 months of enrollment will be notified prior to going off study.

8.5 Study Termination

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

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

9.1.1 Vaccine-induced seroconversion: Serum samples obtained at baseline and at follow-up study visits will be assessed for antibodies to HPV VLP types 6/11/16/18/31/33/45/52/58 by competitive Luminex immunoassay (HPV-9 cLIA Version 2.0). For the primary endpoint, a participant will be defined as seroconverted i.e., anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58 positive by Merck's proprietary competitive Luminex Immunoassay (cLIA) assay if the anti-HPV serum level at the 12-months post-transplant visit is ≥30, ≥16, ≥20, ≥24, ≥10, ≥8, ≥8, ≥8, or ≥8 milli Merck units (mMU)/mL, respectively by the cLIA assay [21,23]. The cLIA assay uses a multiplex format with each of the nine virus like particle (VLP)-types in the vaccine fixed to Luminex microspheres with distinct fluorescent properties. Antibody titers are determined in a competitive format, where type-specific phycoerythrin (PE)-labeled, neutralizing monoclonal antibodies (mAbs-PE) compete with an individual's vaccine-induced antibodies in the serum for binding to conformationally-sensitive, neutralizing epitopes on the VLPs [23,24]. There is no specific (minimum) number of serotypes required for classifying someone as seroconverted, since the seroconversion for each vaccine-serotype will be assessed independently. Further, since the cLIA antibody titers to each HPV type are determined using type-specific monoclonal antibodies, it is not possible to make a direct comparison of assay results across HPV types. Given the age of the participants, there is high likelihood of having prior sexual exposure to some, if not all, individual HPV types targeted by the nonavalent HPV vaccine. However, anti-HPV antibodies induced due to such 'natural' infection are usually detected at a much lower titer levels than the aforementioned cutoffs defined for vaccine-induced seropositivity. Type-specific sensitivity analyses, restricted to participants who are seronegative for individual types at baseline, will also be conducted. Assays will be performed at Merck Research Laboratories. If access to cLIA is not feasible due to technical or operational reasons, a 9-valent multiplex HPV assay (based on same principle/framework as the cLIA assay) developed at the NCI Frederick National Laboratory for Cancer Research (FNLCR) will be used for the study.

9.1.2 HPV detection and genotyping: HPV DNA will be extracted from cervical/vaginal (in women), oral, and, optionally, urine samples (in both genders) and male genital samples (in men) by use of commercial reagents (Qiagen, Valencia, CA). A 450 bp region of the L1 HPV genome will be amplified using the PGMY09/11 primer system, a nondegenerate, pooled primer system modified from the original, degenerate MY09/11 primer system [25]. GH20 and PC04 primers will be used to coamplify a 268 bp region of the human β-globin gene as an internal control for sample sufficiency. Specimens positive for the 450- and 268-bp bands of HPV and β-globin, respectively, will be considered positive. Specimens found negative for β-globin on co-amplification will be re-amplified in a single amplification reaction. Those remaining negative for β-globin will be excluded from analysis. HPV DNA-positive specimens will be genotyped using a reverse line-blot detection method for 37 different HPV types [26], including high-risk [oncogenic] types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; possible high-risk types 26, 34, 53, 66, 70, 73, and 82; low-risk [nononcogenic] types 6, 11, 40, 42, 44, 54, 61, 72, 81, and 89; and undetermined-risk types 62, 67, 71, 83, and 84 [27]. HPV-positive specimens that subsequently have negative results in the genotyping assay will be considered to be unclassified HPV-positive specimens.

Urine samples are optional because patients on dialysis may be unable to provide a urine sample. Male genital samples are optional because, unlike female cervical/vaginal HPV testing, there is limited evidence on the ideal methods for HPV testing and the clinical correlates of HPV test positivity results in men.

9.1.3 Eyebrow hair samples for future viral DNA testing. Solid organ transplant recipients are at high risk (30-fold) for non-melanoma skin cancers, most notably squamous cell skin cancer. UV exposure is a major risk factor for these cancers in immunosuppressed and immunocompetent populations. Infections have been hypothesized to play a role in the development of these malignancies, namely genus beta HPVs [28,29]. Studies of skin biopsies indicate that levels of cutaneous HPVs are higher in squamous cell cancers than normal appearing skin, and even higher among those who are immunosuppressed with cancer [30]. Eyebrow hair follicles represent a sun-exposed reservoir for HPV [31]. Compared to the general population, HPV DNA levels in these follicles are higher in those who develop squamous cell skin cancer [32], and even higher in solid organ transplant recipients [31]. There is also growing interest regarding the role of polyomaviruses in squamous cell skin cancer development [33]. Polyomaviruses reside in eyebrow hair follicles [34], and there is recent evidence that polyomavirus DNA in eyebrow hair follicles are associated with squamous cell cancer [35]. Eyebrow hair samples will be collected by research staff at the baseline and follow-up study visits from participants who consent to collection of optional samples for biobanking for future studies. Eyebrow hair samples will be stored for future viral DNA testing.

9.2 Comparable Methods

Proposed methods represent standard technology for HPV detection and genotyping and assessment of HPV antibodies.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

10.1.1 Blood samples for HPV serology will be tested at Merck Research Laboratories through support from the Merck Investigator Studies Program (MISP) and an agreement between Merck and NCI DCP or at the National Cancer Institute's Frederick National Laboratory for Cancer Research (FNLCR).

10.1.2 Laboratory for testing the urine, cervical/vaginal, and oral samples for HPV detection and genotyping will be finalized in consultation with the study sponsor, National Cancer Institute-Division of Cancer Prevention.

10.2 Collection and Handling Procedures

10.2.1 Blood samples. A 28 mL blood specimen will be collected from each participant at the Pre-Transplant Vaccine Visits 1, 2, and 3, at the 6 Month and 12 Month Post-Transplant Visits, and (for participants who do not complete Pre-Transplant Vaccine Visit 2) before/at transplant surgery for measurement of the primary and secondary endpoints for the study. The blood will be collected using four blood collection tubes, including one 10 mL heparin green top tube, two 4 mL EDTA lavender top tubes, and one 10 mL red top tube. A 10 mL blood specimen will be collected at the 13 Month Post-Transplant Visit into one red top tube to measure HPV vaccine-type-specific antibody titers. The blood samples will be processed as specified in the Laboratory Manual and will be separated into plasma, serum, red blood cells, and buffy coat for DNA extraction. These blood components will be transferred to cryovials and will be stored at -80°C. Centrifugation and aliquoting will be done as soon as is feasible (recommended < 2 hours) after the blood draw to allow the samples to be frozen quickly and maintained frozen until thawed and tested. All blood samples will be shipped to CSMC for batch HPV serology at the end of the

study and long-term storage.

10.2.2 Cervical/vaginal and oral samples will be self-collected at the Pre-Transplant Vaccine Visits 1, 2, and 3, and at the 6 Month and 12 Month Post-Transplant Visits for HPV DNA testing. Samples will be collected and processed as specified in the Laboratory Manual. Cervical/vaginal samples will be self-collected using the Evalyn Brush® (Rovers Medical Devices B.V., Oss, Netherlands). Oral samples will be self-collected using a mouthwash gargle. All specimens will be shipped to CSMC as specified in the shipping instructions and will be stored in a -80°C freezer for batch HPV detection and genotyping at the end of the study.

10.2.3 Urine samples will be self-collected at the Pre-Transplant Vaccine Visits 1, 2, and 3, and at the 6 Month and 12 Month Post-Transplant Visits from participants who consent to the collection of optional urine samples. Approximately 20-30 mL of urine (first void catch) will be self-collected at each visit in a sterile urine specimen container. All specimens will be shipped to CSMC as specified in the shipping instructions and will be stored in a -80°C freezer for batch HPV detection and genotyping at the end of the study.

10.2.4 Eyebrow hair samples will be collected at the Pre-Transplant Vaccine Visits 1, 2, and 2, and at the 6 Month and 12 Month Post-Transplant Visits from participants who consent to collection of optional samples for biobanking for future studies. Clinical research staff will collect a total of six eyebrow hairs with the attached follicle from each consenting participant using sterile tweezers and place in a cryovial. Eyebrow hair samples will be shipped to CSMC as specified in the shipping instructions and will be stored in a -80°C freezer for future viral DNA testing.

10.2.5 Male genital samples will be collected at the Pre-Transplant Vaccine Visits 1, 2, and 2, and at the 6 Month and 12 Month Post-Transplant Visits from male participants who consent to collection of these optional samples. Samples will be collected and processed as specified in the Laboratory Manual.

10.3 Shipping Instructions

Samples collected from all study sites will be shipped to the CSMC specimen manager.
Please see the study's Laboratory Manual for the shipping address.

All processed blood and non-blood samples (cervical/vaginal, oral, urine, and eyebrow) will be shipped overnight in dry ice. All samples will be shipped on Monday or Tuesday in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.

10.4 Tissue Banking

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

11. REPORTING ADVERSE EVENTS

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

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance

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

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

Each center has the capacity to link to the electronic medical record enabling study personnel to monitor adverse outcomes. Although there is variability in the frequency of post-transplant follow-up and monitoring at the five participating transplant centers, all centers obtain a metabolic panel (BMP) and urinalysis at 6 months, 1 year, and at 2 years post-transplant, as required by the United Network for Organ Sharing (UNOS). Declining renal function is tracked via creatinine levels and allograft rejection is monitored via biopsy when clinically indicated; although one participating center, UCSF, does perform protocol biopsies post-transplant at 6 months and another biopsy at 1 year if the initial biopsy demonstrates inflammation. Data related to post-transplant infectious (bacterial, viral, and fungal) and rejection episodes will be collected as a part of this study.

Postoperative complications, including biopsy-confirmed graft rejection, recurrent kidney disease, and post-transplant infections, will be monitored by the renal transplant teams. Patients receiving additional immunotherapy to treat graft rejection or experiencing post-transplant infectious complications during the study period will be monitored. Standardized definitions will be developed by the investigative team, including nosocomial infections and common opportunistic viral infections [36].

11.1 Adverse Events

11.1.1 Reportable AEs

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

For all unsolicited AEs not meeting the criteria for "Serious Adverse Events", the following caveats will apply:

a. **AEs in the immediate (up to 14 days) post-vaccination periods:** All unsolicited AEs, including anticipated and unanticipated clinical events, clinically significant laboratory abnormalities, and vaccine-related injection site local reactions (e.g., pain, swelling, erythema, pruritus, induration, warmth, etc.) and vaccine-related systemic side-effects (e.g., headache, oral temperature ≥100 degrees F, nausea, fatigue, dizziness, allergic events, bronchospasm, etc.) will be collected for up to 14 days following vaccine administration (1st, 2nd, and 3rd dose) and reported on AE CRFs.
    i. Note that clinically significant laboratory abnormalities that ***pre-dated*** vaccine administration and ***remain unchanged*** (as per the Site Principal Investigator's judgment) after vaccine-administration should not be reported as AEs

b. AEs outside of the immediate post-vaccination periods (i.e., beyond 14 days):
    i. Anticipated clinically significant laboratory abnormalities, that in the view of either the Site Principal Investigator or the Sponsor, are related to the underlying renal disease, transplant procedure, or post-transplant regimens ***will not*** be collected or reported. **(*exceptions below**)
    ii. Anticipated adverse events, that in the view of either the Site Principal Investigator or the Sponsor, are related to the underlying renal disease, transplant procedure, or post-transplant regimens ***will not*** be collected or reported. **(*exceptions below)**

iii. All other adverse events will be collected and reported on AE CRFs. In situations where multiple AEs relate to a single unifying diagnosis, only the main unifying diagnosis should be reported as an AE on AE CRFs.

Example: In case of pneumonia with leukocytosis and chest pain that only requires outpatient treatment; the diagnosis of pneumonia should be reported as an AE, but leukocytosis and chest pain should not be reported as AEs.

***exceptions:**

- All unsolicited clinical events/laboratory parameters signifying allograft rejection at any time in the study follow-up period and regardless of the need for hospitalization, will be reported as *SAEs*. Rejection events that are required to be reported to UNOS (United Network for Organ Sharing) will be reported simultaneously to DCP using the Adult Kidney Transplant Recipient Follow-Up Worksheet (https://www.transplantpro.org/wp-content/uploads/sites/3/Adult_TRF_Kidney.pdf).
- Clinical events or laboratory investigations (e.g., cross-match change) resulting in cancellation of a planned transplant will be reported as *SAEs*.

11.1.2 AE Data Elements:

The following data elements are required for AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the participant dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the CTCAE version 4.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm [37].

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

CTCAE v4.0 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

ADL
*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.
**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

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

11.1.5 Follow-up of AEs

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

11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) defines an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

All unsolicited clinical events/laboratory parameters signifying allograft rejection at any time in the study follow-up period and regardless of the need for hospitalization, will be reported as SAEs. Rejection events that are required to be reported to UNOS (United Network for Organ Sharing) will be reported simultaneously to DCP using the Adult Kidney Transplant Recipient Follow-Up Worksheet (https://www.transplantpro.org/wp-content/uploads/sites/3/Adult_TRF_Kidney.pdf).

Clinical events or laboratory investigations (e.g., cross-match change) resulting in cancellation of a planned transplant will be reported as SAEs.

11.2.2 Reporting SAEs to DCP

a. All SAEs, including all hospitalizations, during the study period will be reported as per DCP SAE reporting procedures, with the following exception.

i. Hospitalization for planned renal transplant surgery will not be reported. However, if this hospitalization event lasts longer than the usual period at the institution (as determined by the Site Principal Investigator or Sponsor), it will be reportable as an SAE. Adverse events (AEs) relevant to the prolongation of this hospitalization will also be collected and reported on AE CRFs.

b. In situations prompting SAE reporting when multiple abnormalities/associated concurrent/concomitant adverse events are present:

i. The primary/most significant adverse event will be recorded as the SAE. Associated events should be included in the chronology of the case provided in the 'Describe Event' field on the SAE form. Multiple signs and symptoms can be incorporated under a single diagnosis, disease, or condition. These associated events should not be separately reported as AEs on AE CRFs.

Example: pneumonia resulting in hospitalization would be the primary SAE, and concomitant events such as leukocytosis, anemia, fever, etc. can be reported in the 'Describe Event' field on the SAE form but would not be listed separately as AEs on AE CRFs.

ii. Concurrent/concomitant events that prolong hospitalization, or that independently fulfill other serious adverse event reporting criteria (e.g., life-threatening, medically significant), will be reported as separate SAEs.

Example: pneumonia resulting in hospitalization, along with renal failure requiring dialysis, will be reported separately as two SAEs as (i) pneumonia, and (ii) renal failure requiring dialysis.

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

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

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

Include the following information when calling the Medical Monitor:

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

11.2.2.3 The Lead Organization and all Participating Organizations will email written SAE reports to the following within 48 hours of learning of the event using the fillable PDF SAE Report Form.

- DCP's Regulatory Contractor CCS Associates, Inc. (CCSA; phone: 650-691-4400) at safety@ccsainc.com
- NCI DCP Medical Monitor, Dr. Eva Szabo (szaboe@mail.nih.gov)
- Northwestern Cancer Prevention Consortium (ncpc@northwestern.edu)

11.2.2.4 The DCP Medical Monitor and CCSA regulatory and safety staff will determine which SAEs require FDA submission as IND safety reports.

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

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE Report Form in the appropriate format. Follow-up information should be sent to DCP as soon as available. All SAEs will be followed according to standard of care. SAEs possibly, probably, or definitely related to the study agent will be followed until resolved. Serious AEs (SAEs) will be monitored throughout the study regardless of cause by the study physicians and the Data and Safety Monitoring Board (DSMB).

12. STUDY MONITORING

12.1 Data Management

Data will be managed by the study statistician, Dr. Kocherginsky, according to standard operating procedures, which meet the guidelines of DCP Requirements for Data Management and which follow the Data Management Plan that Northwestern University has on file with the Division of Cancer Prevention, NCI. Source data verification will be performed by the Northwestern Cancer Prevention Consortium. The Consortia 2012 Data Management Plan, submitted as part of a contract agreement with the NCI (HHSN261201200035I), was approved.

Clinical data will be reported to the Lurie Cancer Center Clinical Trials Management System (CTMS), which will be the database of record.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRFs) developed from the standard set of DCP Chemoprevention CRF Templates and utilizing NCI-approved Common Data Elements (CDEs). The approved CRFs will be used by Northwestern University to create the electronic CRFs (e-CRFs) screens in the CTMS-RDC application. Site staff will enter data into the e-CRFs for transmission to DCP according to DCP standards and procedures.

All specimen results that are batch analyzed will be collected and stored on excel spreadsheets. The excel spreadsheets will constitute the database of record.

12.3 Source Documents

All source documents will be collected and stored by the research staff at the site of accrual. Any data recorded directly in CTMS that constitute no prior written or electronic record of data, will be specifically identified as source data. Questionnaires completed in person may be completed on paper and entered into CTMS.

12.4 Data and Safety Monitoring Plan

A comprehensive Data Safety and Monitoring Plan has been submitted by Northwestern University, approved by the DCP, and is on file there. Any future changes will be forwarded for review.

This trial is subject to review by the Lurie Cancer Center Data & Safety Monitoring Committee (DSMC). Semi-Annual reports, SAEs, and protocol deviations will be reviewed by the DSMC at bi-weekly meetings. This trial is also subject to possible audits by the Lurie Cancer Center Clinical Trials Audit Committee (CTAC).

12.5 Sponsor or FDA Monitoring

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

12.6 Record Retention

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

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

Not applicable.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

This is a prospective single-arm trial to evaluate if the Gardasil® 9 HPV vaccine induces and sustains an adequate immune response at 12-months post-transplantation among 18-49 year old kidney transplant recipients when ≥ 1 doses of the vaccine are administered prior to transplantation. The study population includes candidates for renal transplant within 12 months of enrollment at five transplant centers in the United States. We anticipate that 96 eligible kidney transplant recipients will ultimately be enrolled and complete follow-up during the study period of 36 months, and 24-28 of them will have received the second vaccine dose before their transplant. For the analytical dataset for the primary endpoint, participants will have received the first dose of Gardasil® 9 nonavalent HPV vaccine at baseline and their post-transplant serology titers are assessed at 12-months post-transplant visit. Kidney transplant candidates who receive one or two doses of the vaccine but do not get transplanted within 12 months of enrollment will be considered off-study after they are offered the remainder of the vaccine doses to complete the three-dose vaccine series.

13.2 Randomization/Stratification

Not applicable.

13.3 Accrual and Feasibility

Sample size: Consent/enrollment = 180; Intervention = 96; Analytic sample = 64 after drop-outs. The expected accrual rate is 10 participants per month across five sites, and the planned recruitment duration is 18 months. We anticipate that all evaluable participants will have completed all study procedures within 36 months.

Initial accrual estimates were calculated based on; 1) the number of kidney transplant candidates aged 18-49 who come forward for kidney transplant who eventually get transplanted; and 2) the number of kidney transplants performed in this age sub-set at the five participating transplant centers in 2017.

After accounting for experiences in recruitment of participants during the years the protocol has been open, as well as the additional accrual and retention challenges encountered due to the COVID-19 pandemic, it was projected that the expected accrual for the study will be in the range of n=24 to 28 participants who will receive one or more vaccine doses pre-transplant and complete the necessary post-transplant follow-up period for the primary endpoint analysis.

13.4 Primary Objective, Endpoint(s), Analysis Plan

The primary objective is to estimate HPV vaccine-type-specific seroconversion rates at 12-months post-transplantation among kidney transplant recipients who receive ≥ 1 doses of the Gardasil® 9 HPV vaccine prior to transplantation,

An estimate of the seroconversion rate will be provided along with exact Clopper-Pearson 95% confidence intervals (CIs).

Originally (until version 3.10), the study was designed with the expectation of at least n=64 evaluable participants for the primary analysis, and the analytic plan was focused on comparisons with pre-specified benchmarks (e.g., 0.75 and 0.90) of the expected seroconversion rate estimate.

In version 3.11, responding to the lower accrual expectations of between n=24 to n=28 evaluable participants in the study, the study's focus was revised to only focus on description of the estimation of the seroconversion rate and the upper limit of its one sided 95% confidence interval, as opposed to any pre-specified comparisons.

Even without pre-specified comparison benchmarks, the revised analysis plan will permit cross-study comparisons with other relevant HPV vaccination studies (e.g., those conducted among individuals undergoing solid organ transplants or other immunosuppressed individuals). The study will generate key preliminary data for testing clinically relevant hypotheses in future larger studies to evaluate the full extent of protection afforded by HPV vaccination administered prior to transplant.

With the study expecting to yield between n=24 to n=28 evaluable participants, Table 3 (below) provides expected upper limits of the one sided 95% CI for the estimates of the seroconversion rates ranging between 0.65 to 0.90.

Table 3. Expected upper limits of one sided 95% CI for seroconversion rates

Expected accrual n=24 evaluable participants	Expected accrual n=28 evaluable participants

Estimate P	One-sided 95%CI Upper Limit	Estimate P	One-sided 95%CI Upper Limit
0.65	0.8088	0.65	0.7977
0.70	0.8480	0.70	0.8380
0.75	0.8851	0.75	0.8763
0.80	0.9197	0.80	0.9123
0.90	0.9776	0.90	0.9739

13.5 Secondary and Exploratory Objectives, Endpoints, Analysis Plans

Secondary Endpoint:
Descriptive statistics, such as probabilities and exact 95% confidence intervals, will be used to summarize HPV vaccine-type-specific seroconversion rates at 6- and 12-months post-transplantation stratified by number of doses (1, 2, or 3) of the vaccine given pre-transplant. Seroconversion probabilities will be compared between dose groups using Fisher's exact test. Armitage trend test will be used to examine whether there is a trend for increased seropositivity across dose groups. Due to the limited sample size, these tests will be sufficiently powered to detect only very large differences and will be considered exploratory.

Exploratory Endpoints:

1) Descriptive statistics, such as probabilities and exact 95% confidence intervals, will be used to summarize probability of seroconversion at 12 months post-transplant for the following groups:

    a) time elapsed between last vaccine dose and the transplant procedure, e.g. <3 months vs. >3 months. Different groupings will be considered based on observed (e.g. median) and clinical considerations. Time will be summarized using descriptive statistics, e.g. median, interquartile range, or range; groups defined by dosing and types of post-transplant immunosuppressant medications, as well as;
    b) type of transplant surgery (living donor/deceased donor);
    c) differences in Human Leukocyte Antigen (HLA) histocompatibility between donor and recipient;
    d) differences by biological sex (i.e., male vs. female) of the transplant recipient.

2) Stability of HPV vaccine-type-specific geometric mean titers (GMT) at 6 and 12- months post-transplantation, and rise in HPV vaccine-type-specific GMT at the 13 month post-transplant visit.
    a) Stability will be evaluated in relation to changes in the type-specific GMTs between the two post-transplant time points (6- and 12-months post-transplant) and reported as follows: (i) decrease: more than 2-fold decrease, (ii) stable: within 2-fold change, and (iii) increase: greater than 2-fold increase.
    b) The magnitude of increase in type-specific GMTs at the 13-month post-transplant visit (i.e., 1 month after the booster dose) will be described in relation to the type-specific GMTs at the other post-transplant visits (6 and 12-months post -transplant). Patterns over time will also be explored using graphical techniques.
    c) Stability, and post-booster dose increase in type-specific GMTs will also be described in relation to the number of vaccine doses (1, 2 or 3) received in the pre-transplant period.

3) Vaccine safety profile and allograft rejection/opportunistic infections will be summarized using descriptive statistics, stratified by number of vaccine doses and time between the last vaccine dose and the transplant procedure.

4) HPV detection in samples from the anogenital, and oral cavity specimens at baseline (pre-vaccination) and at 6- and 12-months post-vaccination, overall and by number of vaccine

doses (1, 2, or 3), sexual behavior, type-specific seroconversion rates, and time elapsed between the last vaccine dose and the transplant procedure. All rates of HPV detection will be specified, overall and stratified by number of doses (1, 2, or 3) and time to transplant.

13.6 Reporting and Exclusions

We anticipate some drop-outs due to transplantation complications, health deterioration, or death. The drop-out rate is expected to be 20%, resulting in a final sample of 24-28 participants who complete the study.

13.7 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of the Gardasil® 9 nonavalent HPV vaccine.

13.8 Evaluation of Response

Vaccine serologic response will be evaluated for all participants who receive at least one dose of Gardasil® 9.

13.9 Interim Analysis

There will be no planned interim analyses.

13.10 Ancillary Studies

Not applicable.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

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

14.2 Other Required Documents

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

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

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

14.2.4 Documentation of training in "Good Clinical Practice (GCP)" for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

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

14.2.6 Signed Investigator's Brochure/Package Insert acknowledgement form

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

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

14.3 Institutional Review Board Approval

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

14.4 Informed Consent

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

Participants will be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. A statement of this option will be included within the informed consent document.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, NCI CIRB, and the IRB at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, NCI CIRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

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

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

Fax: 650-691-4410

E-mail Submissions:
regulatory@ccsainc.com

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

14.6 Other

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

15. FINANCING, EXPENSES, AND/OR INSURANCE

All research related costs associated with participating in this study will be paid for, and will not be the responsibility of the participant. Participants will be reimbursed the cost of parking, at sites where free parking is not provided, in the form of a parking voucher or validation. Participants who drive will have their mileage reimbursed for the entire round trip distance. Participants will receive $150 at the completion of the Consent and Screening Visit, Pre-Transplant Vaccine Visits 1-3, 6 Month Post-Transplant Visit, and 12 Month Post-Transplant Visit. Participants will receive $75 at the completion of the 13 Month Post-Transplant Visit. Participants will not receive compensation for the Additional Study Visit(s), but will receive their Gardasil vaccination at no cost. Participants' compensation will vary depending on which visits they and their research staff decide is feasible, and whether they are able to have their transplant within 12 months of enrollment. Participants may receive up to $750, according to Table 4 below:

Table 4. Participant Compensation

	Participant is able to complete only 1 dose prior to surgery	Participant is able to complete 2 doses prior to surgery	Participant is able to complete 3 doses prior to surgery	Participant completes 1 dose, but transplant does not occur within 12 months of enrollment	Participant completes 2 doses, but transplant does not occur within 12 months of enrollment	Participant completes 3 doses, but transplant does not occur within 12 months of enrollment
Pre-Transplant Vaccine Visit 1	$150	$150	$150	$150	$150	$150
Pre-Transplant Vaccine Visit 2	~~	$150	$150	~~	$150	$150
Pre-Transplant Vaccine Visit 3	~~	~~	$150	~~	~~	$150
Transplant Surgery	$0	$0	$0	~~	~~	~~
6 Month Post-Transplant Visit	$150	$150	$150	~~	~~	~~
12 Month Post-Transplant Visit	$150	$150	$150	~~	~~	~~
13 Month Post-Transplant Visit	$75	$75	~~	~~	~~	~~
Additional Study Visit 1	$0	~~	~~	$0	$0	~~
Additional Study Visit 2	~~	~~	~~	$0	~~	~~
Total	**$525**	**$675**	**$750**	**$150**	**$300**	**$450**

It is possible that a research injury or illness may result from participating in this study. Any expenses incurred as a result of research related injury will be the responsibility of the study participant and/or their insurance carrier.

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CONSENT FORM

(Insert Institution name)

Consent Form

Study Title for Study Participants: Preventive Human Papillomavirus (HPV) Vaccine Trial in Kidney Transplant Recipients

Protocol Title: NWU2015-06-02, Immunogenicity of Nonavalent HPV Vaccine Administered Prior To Renal Transplantation in Adults: A Prospective, Single-Arm, Multi-Center Clinical Trial

Introduction
This is a clinical trial, a type of research study. Your doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part in the research. This document has important information about the reason for the study, what you will do if you choose to be in this research study, and the way we would like to use information about you and your health.

Please take your time to make your decision about volunteering. You may discuss your decision with your friends and family. You can also discuss this study with your health care team. If you have any questions, you can ask your doctor for more of an explanation. You should only agree to participate in this study when you are comfortable enough with the information so that you can make an informed decision about joining.

What is the usual approach to managing infections with human papillomavirus (HPV) among people who receive a kidney transplant?
You are being asked to take part in this research study because you are eligible to receive a kidney transplant procedure. People who receive organ transplants are at increased risk for cancers caused by human papillomavirus (HPV). People who receive kidney transplants at increased risk for cancer are followed closely by their doctor to watch for the development of cancer. The Centers for Disease Control and Prevention (CDC) and American Society of Transplantation recommend that immunosuppressed individuals, including transplant candidates, receive the same HPV vaccines according to the same schedule as individuals in the general population. Currently the vaccine is approved by the FDA for individuals between ages 9 through 45 years.

What are my other choices if I do not take part in this study?
- You may choose to have the usual approach described above;
- You may choose to receive the HPV vaccine outside of this study if you are between 18-45 years of age;
- You may choose to take part in a different study, if one is available; or
- You may choose to do nothing.

Why is this study being done?
Nearly all sexually active men and women will be exposed to HPV in their lifetime. About 14 million Americans get infected every year. Most individuals are able to clear HPV infections, but

in a small proportion of people, HPV infection can lead to development of several cancers, including cervical cancer, vulvar cancer, vaginal cancer, anal cancer, and cancer of the mouth and throat region.

Gardasil® 9 is a vaccine approved by the Food and Drug Administration (FDA) to guard against many strains of HPV infection. The vaccine protects males and females from getting certain strains of HPV and is not meant for treatment of a previously established HPV infection. It is unknown how Gardasil® 9 affects the immune system of individuals who have received a transplant, so the side effects of getting this vaccination will also be evaluated in this study. It is also unknown how the immune system responds to vaccine among individuals between ages 27-49, who are older than the age group for whom the vaccine is currently approved.

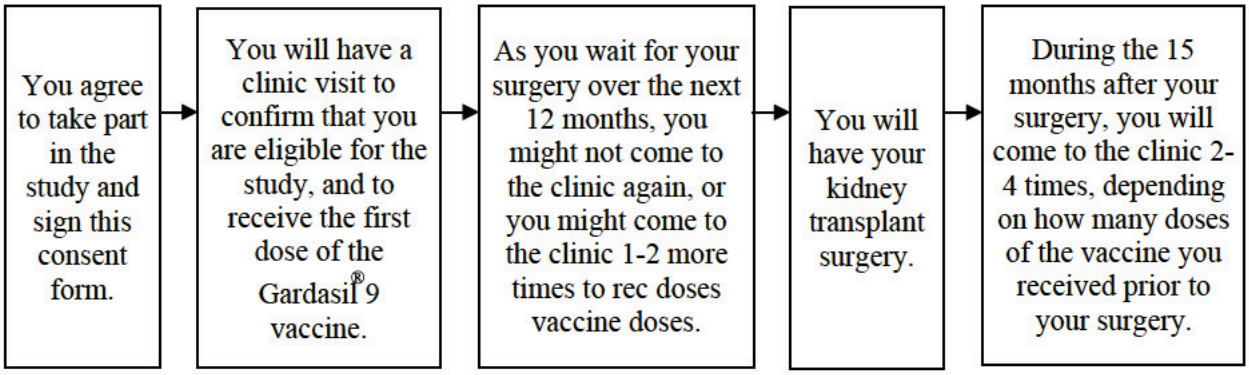
People who receive organ transplants are at greater risk for cancers linked to HPV. The purpose of this study is to learn whether individuals who receive the Gardasil® 9 vaccine prior to undergoing a kidney transplant produce a strong immune response against HPV infection during the post-transplant period. The use of Gardasil® 9 in this study is experimental in nature, and the vaccination schedule being administered in this study is different from the FDA-approved vaccination schedule.

There will be about 180 kidney transplant candidates taking part in this study at Cedars-Sinai Medical Center; Northwestern University Feinberg School of Medicine; the University of California, San Francisco Medical Center; the University of Alabama at Birmingham and the University of North Carolina at Chapel Hill.

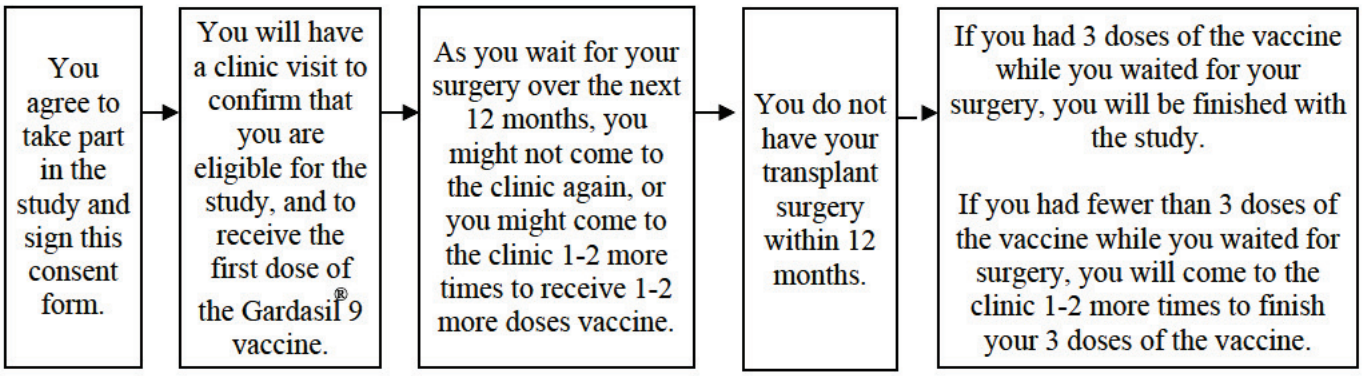
How long will I be in this study?
The amount of time you are in the study depends on how soon your transplant surgery is scheduled. The total time you could be involved in the study is up to 12 months before the transplant, and then up to 15 months after the transplant. Your doctor and your research team do not know exactly when you may have your surgery and cannot control when it might happen. The timing of your transplant surgery will not change if you take part in this study.

What are the study groups?
This study has one group: adults who are expected to receive a kidney transplant within 12 months after you start the study. There will be 180 participants in the group. All participants in this study will receive three doses of the Gardasil® 9 vaccine.

Within this one study group, there are a few different schedules you might follow. You, your doctor, and your research team will decide which schedule works best for you. Your schedule will depend on when you have your transplant surgery, and on how many times you are able to come to the clinic before your surgery. If you have your transplant surgery within 12 months after you start the study, your schedule will look like this:



Some participants may not have their transplant surgery within 12 months after they start the study. If this happens, the research team will make sure you can still receive all three doses of the vaccine. If you do not have your transplant within 12 months after you start the study, your schedule will look like this:



What extra tests and procedures will I have if I take part in this study?

If you agree to participate in this study, you will be required to sign this consent form before you have any tests or procedures that are done only for this study. Most of the tests and procedures you will have are part of the usual approach for your condition. However, there are some extra tests and procedures that you will need to have if you take part in this study, including review of your medical history and medications; pregnancy tests (only for women who are able to become pregnant); blood tests; three doses of the Gardasil® 9 vaccine; collection of cervical/vaginal (for women only), and mouth specimens; and completion of questionnaires. Blood samples will be collected to measure your immune response to the HPV vaccine. Cervical/vaginal (for women only) and mouth samples will be collected to look for HPV infection (you will be instructed on how to self-collect these samples). The cervix, vagina, and mouth are areas of the body where cancer related to HPV can occur. These extra tests and procedures are described in further detail below.

The study will involve the following parts:

Consent and Screening
During this period you will be offered information about the study and your risks and benefits of participating in it. After you sign the consent form, the following tests and procedures will be done to determine if you are eligible to participate in the study:

- Your doctor will review your medical history and medications, and evaluate the study inclusion and exclusion criteria as they apply to you
- Confirmation that you have not previously received a preventive HPV vaccine
- Pregnancy test (for women who are able to become pregnant). Your pregnancy test could be a urine test or a blood test.

If you are pregnant or you have previously received a preventive HPV vaccination, you will not be eligible for the study.

Before Your Transplant
If the Screening exams and tests show that you can take part in the study, and you choose to, then you will be enrolled in the study. As you wait for your transplant surgery, you will be asked to participate in at least one, but up to three study visits. You will receive one dose of the Gardasil® 9 vaccine at each visit. *Research staff will contact you by phone 24-72 hours each time after you receive the Gardasil® 9 vaccine* to ask you if you are experiencing any potential side effects from the vaccine and to answer any questions you may have. These phone calls will last approximately 10 minutes.

- *Pre-Transplant Vaccine Visit 1* – The study visit will take place at *(site specific clinic and address)* may occur the same day as the Consent and Screening visit if all of your information is obtained for eligibility. This study visit will last approximately 3 hours, and include the following tests or procedures:
    - Review of your medical history, medications, and laboratory test results
    - Review of your symptoms and current activity level and limitations
    - Physical exam including blood pressure, heart rate, temperature, and weight
    - Collection of a blood sample to measure your immune response to the HPV vaccine. About 5½ teaspoons of your blood will be collected. Your blood will drawn by a person who is trained to collect blood.
    - Self-collection of cervical/vaginal (for women only) and mouth samples for HPV testing. The cervical/vaginal samples (for women only) from your genital tract will be self-collected using a specially made brush. The mouth sample will be self-collected using a saliva collection kit.
    - Completion of a 30-minute questionnaire that asks about your background (race, education, marital status), reproductive history, sexual history, and tobacco and alcohol use. The questionnaire will be administered by a research staff person.
    - Gardasil® 9 HPV vaccination. The vaccine will be given in your shoulder muscle or in the side of your thigh.

- *Pre-Transplant Vaccine Visit 2* – If there is enough time before your transplant surgery, you will be asked to come to *(site specific clinic and address)* around 30 days after your

Vaccine Visit 1. This study visit will last approximately 2 hours. If you and your study doctor agree that you are unable to complete this visit prior to your transplant surgery, this visit may be skipped, and you will have blood drawn on the day of your transplant surgery. This visit will include the following tests or procedures:

- Review of your medical history, medications, and laboratory test results
- Review of your symptoms and current activity level and limitations
- Physical exam
- Gardasil® 9 HPV vaccination
- Collection of a blood sample (about 5½ teaspoons)
- Self-collection of cervical/vaginal (for women only) and mouth samples
- Completion of a 15-minute questionnaire.

- *Pre-Transplant Vaccine Visit 3* – If there is enough time before your transplant surgery, you will be asked to come to *(site specific clinic and address)* for a third study visit. If you and your study doctor agree that you are unable to complete this visit prior to your transplant surgery, this visit may be skipped. This will be at least 3 months after Vaccine Visit 2, and at least 5 months after Vaccine Visit 1. This study visit will last approximately 2 hours and include the same tests and procedures as Vaccine Visit 2.

- *Transplant Surgery* – If you completed only one dose of the vaccine before your surgery, you will have a blood sample collected before your surgery (about 5½ teaspoons). If you complete two or three doses of the vaccine before your surgery, you will have no study procedures on the day of your surgery.

After Your Transplant

After your transplant surgery, you will be asked to participate in two to four study visits over the next 12 to 15 months. If you received fewer than 3 doses of the vaccine before your transplant surgery, you will receive the remaining doses of the Gardasil® 9 vaccine.

- *6 Month Post-Transplant Visit* – You will need to come to *(site specific clinic and address)* for this study visit 6 months after you have your kidney transplant. This study visit will last approximately 2 hours and include the following tests and procedures:
  - Review of your medical history, medications, and laboratory test results
  - Review of your symptoms and current activity level and limitations
  - Physical exam
  - Collection of a blood sample (about 5½ teaspoons)
  - Self-collection cervical/vaginal (for women only) and mouth samples
  - Completion of a 15-minute questionnaire.

- *12 Month Post-Transplant Visit* – This study visit will take place at *(site specific clinic and address)* 12 months after you have your kidney transplant procedure. This study visit will last approximately 2 hours and will include the following tests and procedures:
  - Review of your medical history, medications, and laboratory test results
  - Review of your symptoms and current activity level and limitations
  - Physical exam

  - If you had only one or two doses of the vaccine before your transplant, and you are able to become pregnant, you will receive a pregnancy test
  - If you had only one or two doses of the vaccine before your transplant, you will receive a Gardasil® 9 HPV vaccination
  - Collection of a blood sample (about 5½ teaspoons)
  - Self-collection of cervical/vaginal (for women only) and mouth samples
  - Completion of a 15-minute questionnaire.

- *13 Month Post-Transplant Visit* – If you received a vaccine dose at the 12 Month Post-Transplant Visit, you will be asked to come to *(site specific clinic and address)* 13 months after you have your kidney transplant procedure. If you did not receive a vaccine dose at the 12 Month Post-Transplant Visit, you will skip this visit. This study visit will last approximately 30 minutes and will include the following tests and procedures:
  - Collection of a blood sample (about 2 teaspoons)

Additional Study Visits
If you received only one dose of the Gardasil® 9 vaccine before your transplant surgery, and your received your second dose at your 12 Month Post-Transplant Visit, you will have an Additional Study Visit at *(site specific clinic and address)* 15 months after your transplant surgery to receive the third dose of Gardasil® 9 vaccine.

If you received one or two doses of the Gardasil® 9 vaccine, but your transplant surgery does not occur within 12 months after you start the study, you will be offered one or two Additional Study Visits. These visits will be offered at 12-months and 15-months after you began the study and you will receive the remaining doses of the Gardasil® 9 vaccine.

What possible risks can I expect from taking part in this study?
Your involvement in this study may involve the following risks:

Risks associated with Gardasil® 9 vaccine
The Gardasil® 9 HPV vaccine has been found to be very safe, and effective at preventing several types of HPV infections that cause cancer and genital warts. Vaccines, like any medicine, can have side effects. Many people who get the Gardasil® 9 HPV vaccine have no side effects at all. Some people report having very mild side effects, like a sore arm from the shot. The most common side effects are usually mild and temporary.

Here are important points about side effects:
- Doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may be serious and may even result in death

Here are important points about how you and your doctor can make side effects less of a problem:
- Tell your doctor if you notice or feel anything different so they can see if you are having a side effect.

- Your doctor may be able to treat some side effects.

The table below shows the most common side effects that we know about the Gardasil® 9 HPV vaccine, some of which may be serious. There might be other side effects that we do not yet know about. If important new side effects are found, your doctor will discuss these with you.

COMMON (out of every 100 people receiving the Gardasil® 9 vaccine, more than 20 may experience)	**OCCASIONAL** (out of every 100 people receiving the Gardasil® 9 vaccine, 4 to 20 may experience)	**RARE, SOME MAY BE SERIOUS** (out of every 100 people receiving the Gardasil® 9 vaccine, 3 or fewer may experience)
• Pain, swelling, redness, or itching in the arm where the injection was given • Headache	• Fever • Nausea • Feeling tired	• Fever over 102°F • Dizziness • Fainting/passing out and related symptoms (such as jerking movements) • Allergic reaction (symptoms: swelling of the face, tongue, lips, and/or throat that may cause difficulty in breathing or swallowing; wheezing; hives; a fast heartbeat; weakness; severe headache; itching) • Possibility of developing a new autoimmune disease

You will be watched for 30 minutes following vaccination with Gardasil® 9 for fainting and allergic reactions.

Reproductive risks

The Gardasil® 9 HPV vaccine is not recommended for pregnant women. The safety and effectiveness of Gardasil® 9 have not been established in pregnant women, and women who receive the Gardasil® 9 vaccination should not breastfeed a baby. For this reason and because there have been no adequate and well-controlled studies of Gardasil® 9 in pregnant women, women who are able to become pregnant will be required to have a pregnancy test before the study, and must agree to use adequate birth control (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Women who are pregnant, attempting to become pregnant, or who are breastfeeding may not participate in the study. Let your doctor know immediately if you believe you might be pregnant.

Currently, there are no reproductive risks for men that have been documented in either the product label or literature.

Blood Collection

There may be pain, swelling, or bruising around the vein where your blood is collected. You may feel faint. There is a small risk of infection at the place on your body from which the blood is collected. The blood will be drawn by a person trained to collect blood using sterile (clean) equipment, and a very small needle will be used for drawing your blood to minimize discomfort.

Questionnaires
You may feel uncomfortable answering some of the questions you will be asked. If you feel uncomfortable answering any question, you can choose not to answer it.

Unknown Risks
There may be risks of the study that are not yet known.

Incidental Findings
You will be informed of significant new findings developed during the course of the research which may relate to your willingness to continue in the study.

What possible benefits can I expect from taking part in this study?
While you may not directly benefit from taking part in the study, we hope that studying your samples and data may, in the future, help to decrease or prevent HPV-associated cancers in people who receive transplants.

Can I stop taking part in this study?
Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study for the following reasons:
- If you develop a dangerous side effect;
- If you become pregnant;
- If your health changes;
- If the study is no longer in your best interest;
- If new information becomes available;
- If you do not follow the study rules;
- If the study is stopped early for any reason by the sponsor, the National Cancer Institute (NCI); the Central Institutional Review Board (CIRB) of the National Cancer Institute; or the Food and Drug Administration (FDA).

What are my rights in this study?
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the *(Insert institution name and Institutional Review Board or other site specific entity)* at *(insert phone number)* or contact them by email at *(insert email address)*.

What are the costs of taking part in this study?
The Gardasil® 9 vaccine will be supplied at no charge while you take part in this study. The cost of study-specific exams, tests, and any other procedures will be paid for by the study. Some costs associated with your care may be considered standard of care, and will be billed to you or your insurance company. You will have to pay for any costs (including deductibles and co-payments) not covered by your health insurer. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

Will I receive payment for taking part in this study?
You will receive payment at the completion of certain study visits to reimburse you for your time, transportation, parking, and other expenses related to the study, as summarized in the table below. For your travel, you will be provided with parking validation or a parking voucher if you incur any costs related to parking. Additionally, a mileage reimbursement will provided for the entire, round trip distance driven from your home address, to *(site specific clinic(s) and address(es))*, and back to your home address. The amount reimbursed for mileage will be calculated using the current IRS standard mileage rate at the time of your consenting. The total amount you will receive if you complete all of your study visits is $675-$750, depending on when you have your transplant. If you do not complete the entire research study, you will only be paid for those visits you do complete. Finishing the visit means that you complete all of the following study procedures: get the Gardasil® 9 vaccination, and collection of blood, cervical/vaginal (for women only) and mouth samples.

Study Visit	**Covered** (done for research purposes at no cost to you)	**Payment** (if you complete this visit)
Consent and Screening Visit	Pregnancy test	You will not be paid for this visit.
Pre-Transplant Vaccine Visit 1	Medical history, medications, and laboratory test results review; physical exam; blood draw; Gardasil® 9 vaccination; collection cervical /vaginal (for women only) and mouth samples; questionnaire	$150
Pre-Transplant Vaccine Visits 2 and Vaccine Visit 3	Medical history, medications, and laboratory test results review; physical exam; blood draw; Gardasil® 9 vaccination; collection cervical / vaginal (for women only) and mouth samples; questionnaire	$150 for each visit
6 Month Post-Transplant Visit	Medical history, medications, and laboratory test results review; physical exam; blood draw; collection of cervical / vaginal (for women only) and mouth samples; questionnaire	$150
12 Month Post-Transplant Visit	Medical history, medications, and laboratory test results review; physical exam; blood draw; pregnancy test; Gardasil® 9 vaccination; collection of cervical / vaginal (for women only) and mouth samples; questionnaire	$150
13 Month Post-	Blood draw	$75

Transplant Visit		
Additional Study Visit(s) (if needed)	Gardasil® 9 vaccination	You will not be paid for these visits.

Financial Interest in the Research
The Principal Investigator and institution have no potential financial conflict of interest with respect to this study.

What happens if I am injured or hurt because I took part in this study?
If you feel you have been injured or hurt as a result of taking part in the study, it is important that you tell the study doctor immediately: *(Insert site specific study doctor's name and telephone number)*. You will get medical treatment if you are injured or hurt as a result of taking part in this research study.

The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance coverage, you would be responsible for any costs. Even though you are in a study, you keep all of your legal rights to receive payment for injury caused by medical errors.

Who will see my medical information?
Your privacy is very important to us and we will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, we will do our best to make sure that any information that is released will not be able to identify you. Some of your health information, and information about your specimens, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

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

- The study sponsor, the National Cancer Institute (NCI)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the US, and similar organizations if other countries are involved in the study.
- The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285

Where can I get more information?
You may visit the NCI website at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor *(insert name of site specific study doctor(s))* at *(insert telephone number)*.

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

Optional Sample Collections for Biobanking for Possible Future Studies

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, and you or your study doctor may not know the results. You will not be billed for these optional studies.

You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Researchers are trying to learn more about cancer and other health problems. Much of this research is done using samples from your biopsies, blood, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems. Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

The researchers would like to ask your permission to store left over samples and health information obtained during your participation in this study for future medical research. Storing samples for future studies is called biobanking. The Biobank is being run by Cedars-Sinai Medical Center and supported by the National Cancer Institute. If you agree, the blood and tissue samples, and information collected about you during the study, will be coded and kept at Cedars-Sinai Medical Center until the end of the study, when they may be transferred to the National Institutes of Health. Your samples and information will be labeled with a unique study number (code), not with your name or other information that may identify you.

We would also like your permission to collect urine samples at several study visits to look for HPV infection in your body. If you agree, you will provide a small cup of urine during each indicated visit.

For male participants, we would like your permission to collect genital samples at several study visits to look for HPV infection in your body. If you agree, you will provide a specimen collection kit during each indicated visit.

Lastly, we would like your permission to collect samples of your eyebrow hairs at several study visits for future viral DNA testing. Several types of viruses have been found in eyebrow hairs, including beta-papillomavirus (beta-HPV) and polyomaviruses. Virus infections may play a role in causing skin cancers, and people who receive organ transplants are at high risk for several types of skin cancers. If you agree, the clinical research staff will collect six eyebrow hairs at each study visit. Your eyebrow hair samples will be stored for future viral DNA testing.

The research that may be done is unknown at this time. Future research may include: 1) studies to identify genes and/or biomarkers and proteins that influence a risk of cancer in people who receive transplants; 2) studies to identify specific pathways and mechanisms that promote cancer; 3) studies to investigate viral DNA infection and cancer. A biomarker is a biological molecule found in blood, other body fluids, or tissues that may be a sign of a condition or disease.

What is involved?
Your samples and related information may be stored in the NCI Biobank, along with samples and information from other people who take part. The samples will be stored at *(insert name of institution storing samples during study)* and Cedars Sinai Medical Center until the end of the study, when they may be transferred to the National Institutes of Health.

Qualified researchers can submit a request to use the materials stored in the NCI Biobank. A research committee will review each request. There will also be an ethics review to ensure that the request is necessary and proper. All samples and information sent to approved researchers will be coded with your unique study number to protect your privacy and confidentiality. Researchers will not be given your name or any other information that could directly identify you. You will not be notified if/when research is conducted using your samples.

What are the possible risks?

1) There is a risk that an unauthorized person could obtain the personal information in your medical records or other information we have stored about you.
2) There is a potential risk that someone could trace genetic information about you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. There are laws against the misuse of genetic information, but they may not give full protection. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

How will information about me be kept private?
Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name or birth date) will be sent. Samples will be identified by a unique study code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any NCI Biobank and Cedars-Sinai Medical Center staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom Cedars-Sinai Medical Center sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) The results from research on your samples will not be put in your medical record.
6) If research results are published, your name and other personal information will not be used.

What are the possible benefits?
While you may not directly benefit from taking part in the study, we hope that studying your samples and data may, in the future, help to decrease or prevent HPV-associated cancers in people who receive transplants.

Are there any costs or payments?
There will be no cost to you or your insurance company for storage of your samples. Your blood and tissue samples will be used only for research and will not be sold. You will not be paid for allowing your leftover samples to be used in research. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?
If you decide you no longer want your samples to be used, you can call Dr. Marc T. Goodman at (310) 423-6188, who will let the researchers know. Then, any samples that remain in the bank will be destroyed. Samples or related information that have already been given to or used by researchers will not be returned.

What if I have more questions?
If you have questions about the use of your samples for research, contact the principal investigator, Dr. Marc T. Goodman, at (310) 423-6188.

Urine sample to look for HPV infection
I agree to provide a small cup of urine at the indicated study visits and agree that my samples maybe used to look for HPV infection in my body.

Please circle one: YES NO

Eyebrow hair samples for future viral DNA testing
I agree to have samples of my eyebrow hairs collected at the indicated study visits and agree that my samples may be used for detecting HPV in my body.

Please circle one: YES NO

Male genital samples for future HPV testing
I agree to provide self-collected samples at the indicated study visits and agree that my samples may be used for detecting HPV in my body.

Please circle one: YES NO N/A

Samples for future research studies
Please circle your answer to show whether or not you would like to take part in each option.

My samples and related information may be kept in the NCI Biobank for use in future health research.

Please circle one: YES NO

I agree that the researchers, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

Please circle one: YES NO

Access to unused samples
The researchers would like your permission to access unused samples collected for clinical purposes as part of your usual care, such as leftover tissue from Pap smears, biopsies, pathology slides, and tissue blocks. Please circle your answer to show whether or not you give permission.

I agree that the researchers, or their representative, may have to access to my unused samples.

Please circle one: YES NO

Follow-up and future contact
There may be other important questions about you that have not been answered during the course of this research study. In order to answer these questions, we may need to contact you in the future.

I agree that the researchers, or their representative, may contact me in the future if they have additional questions.

Please circle one: YES NO

I provide permission to my study doctor, or their representatives, to contact me once the entire study has been completed for the purposes of sending study results when they become available

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature	Date of Signature
Signature of person(s) conducting the informed consent discussion	Date of Signature

APPENDIX A
Performance Status Criteria

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Karnofsky Performance Scale

Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B
Timeline and Schedule for Study Coordinators

	Participant is able to complete only 1 dose prior to surgery	Participant is able to complete 2 doses prior to surgery	Participant is able to complete 3 doses prior to surgery	Participant completes 1 dose, but transplant does not occur within 12 months of enrollment	Participant completes 2 doses, but transplant does not occur within 12 months of enrollment	Participant completes 3 doses, but transplant does not occur within 12 months of enrollment
Consent and Screening Visit	• Occurs for all participants					
Pre-Transplant Vaccine Visit 1	**Vaccine #1** • ≤ 28 days after negative pregnancy test (for women able to become pregnant) • ≥30 days prior to Transplant Surgery	**Vaccine #1** • ≤ 28 days after negative pregnancy test (for women able to become pregnant) • ≥30 days prior to Transplant Surgery	**Vaccine #1** • ≤ 28 days after negative pregnancy test (for women able to become pregnant) • ≥30 days prior to Transplant Surgery	**Vaccine #1** • ≤ 28 days after negative pregnancy test (for women able to become pregnant)	**Vaccine #1** • ≤ 28 days after negative pregnancy test (for women able to become pregnant)	**Vaccine #1** • ≤ 28 days after negative pregnancy test (for women able to become pregnant)
Pre-Transplant Vaccine Visit 2	~~	**Vaccine #2** •≥30 days after to Pre-Transplant Vaccine Visit 1 • If possible (but not required): ≥30 days prior to Transplant Surgery	**Vaccine #2** •≥30 days after to Pre-Transplant Vaccine Visit 1	~~	**Vaccine #2** •≥30 days after to Pre-Transplant Vaccine Visit 1	**Vaccine #2** •≥30 days after to Pre-Transplant Vaccine Visit 1
Pre-Transplant Vaccine Visit 3	~~		**Vaccine #3** • ≥5 months after Pre-Transplant Vaccine Visit 1 • ≥3 months after Pre-Transplant Vaccine Visit 2 • If possible (but not required): ≥30 days prior to Transplant Surgery	~~		**Vaccine #3** • ≥5 months after Pre-Transplant Vaccine Visit 1 • ≥3 months after Pre-Transplant Vaccine Visit 2
Transplant Surgery	• ≥30 days after Pre-Transplant Vaccine Visit 1 • ≤12 months after enrollment	• ≤12 months after enrollment	• ≤12 months after enrollment	~~		
6 Months Post-Transplant Visit	•6 months (±2 weeks) after Transplant Surgery	• 6 months (±2 weeks) after Transplant Surgery	• 6 months (±2 weeks) after Transplant Surgery	~~		
12 Months Post-Transplant Visit	**Vaccine #2** • 12 months (±2 weeks) after Transplant Surgery	**Vaccine #3** • 12 months (±2 weeks) after Transplant Surgery	• 12 months (±2 weeks) after Transplant Surgery	~~		
13 Months Post-Transplant Visit	• 1 month (+2 weeks) after 12 Months Post-Transplant Visit	• 1 month (+2 weeks) after 12 Months Post-Transplant Visit	~~	~~		
Additional Study Visit 1	**Vaccine #3** • 3 months (+4 weeks) after 12 Months Post-Transplant Visit	~~		**Vaccine #2** • 12 months (±2 weeks) after Pre-Transplant Vaccine Visit 1	**Vaccine #3** • 12 months (±2 weeks) after Pre-Transplant Vaccine Visit 1	N/A, participant is notified 12 months (±2 weeks) after Pre-Transplant Vaccine Visit 1 that they are off study
Additional Study Visit 2	~~			**Vaccine #3** • 3 months (+4 weeks) after Additional Study Visit 1	~~	

APPENDIX C
Study Procedures for Potential Participants

Remember, the visits you complete will depend on the timing of your transplant surgery. You will complete only some of the visits below. Your research team will let you know which visits you may complete.

Study Procedures	Consent and Screening	Pre-Transplant Vaccine Visit 1	Pre-Transplant Vaccine Visits 2 and 3	6 Month Post-Transplant Visit	12 Month Post-Transplant Visit	13 Month Post-Transplant Visit	Additional Study Visit(s) (if needed)
Pregnancy test	X				X		
Review of your medical history, medications, and laboratory test results		X	X	X	X		
Review of your symptoms and current activity level and limitations		X	X	X	X		
Physical exam including blood pressure, heart rate, temperature, and weight		X	X	X	X		
Gardasil® 9 HPV vaccination		X	X		X		X
Collection of a blood sample to measure your immune response to the HPV vaccine		X	X	X	X	X	
Collection of self-collected cervical/vaginal and mouth samples for HPV testing		X	X	X	X		
Completion of a questionnaire that asks about your background (race, education, marital status), reproductive history, sexual history, and tobacco and alcohol use		X	X	X	X		

APPENDIX D
Study Schedule and Compensation for Potential Participants

	You are able to complete only one vaccine before your surgery	You are able to complete two vaccines before your surgery	You are able to complete three vaccines before your surgery	You complete one vaccine, but your surgery does not occur within 12 months of starting the study	You complete two vaccines, but your surgery does not occur within 12 months of starting the study	You complete three vaccines, but your surgery does not occur within 12 months of starting the study
Pre-Transplant Vaccine Visit 1 -Physical exam & questionnaire -Collect blood, cervical/vaginal, and mouth samples -Vaccine	$150	$150	$150	$150	$150	$150
Pre-Transplant Vaccine Visit 2 -Physical exam & questionnaire -Collect blood, cervical/vaginal, and mouth samples -Vaccine	~~	$150	$150	~~	$150	$150
Pre-Transplant Vaccine Visit 3 -Physical exam & questionnaire -Collect blood, cervical/vaginal, and mouth samples -Vaccine	~~	~~	$150	~~	~~	$150
Transplant Surgery -You might have blood collected	$0	$0	$0	~~	~~	~~
6 Month Post-Transplant Visit -Physical exam & questionnaire -Collect blood, cervical/vaginal, and mouth samples	$150	$150	$150	~~	~~	~~
12 Month Post-Transplant Visit -Physical exam & questionnaire -Collect blood, cervical/vaginal, and mouth samples -You might have a vaccine and a pregnancy test	$150	$150	$150	~~	~~	~~
13 Month Post-Transplant Visit -Collect blood	$75	$75	~~	~~	~~	~~
Additional Study Visit 1 -Vaccine	$0	~~	~~	$0	$0	~~
Additional Study Visit 2 -Vaccine	~~	~~	~~	$0	~~	~~
Total Payment	**$525**	**$675**	**$750**	**$150**	**$300**	**$450**

APPENDIX E

Participant ID: _____

Date: _____

Preventive Human Papillomavirus (HPV) Vaccine Trial in Kidney Transplant Recipients

Baseline Questionnaire

We appreciate the time you are taking to complete this interview. We will be asking you questions about factors and behaviors that we believe may contribute to an individual's risk of disease. Please try to answer each question as completely as you can, even if you are unsure about the answer. If you feel uncomfortable answering any question, you can choose not to answer it. All answers will be kept confidential.

DEMOGRAPHICS

The first questions ask about your personal background.

1. What is your racial background? *Check all boxes that apply.*

- [1] ☐ White or Caucasian
- [2] ☐ African-American or Black
- [3] ☐ American Indian or Alaska Native
- [4] ☐ Chinese or Taiwanese
- [5] ☐ Japanese or Okinawan
- [6] ☐ Filipino
- [7] ☐ Korean
- [8] ☐ Vietnamese
- [9] ☐ Other Asian _____
- [10] ☐ Native Hawaiian
- [11] ☐ Samoan
- [12] ☐ Other Pacific Islander _____
- [13] ☐ Asian Indian
- [14] ☐ Iranian
- [15] ☐ Armenian
- [16] ☐ Israeli
- [17] ☐ Egyptian
- [18] ☐ Other race _____

2. Are you of Hispanic or Latino/a ancestry?

[1] ☐ Yes [0] ☐ No

a. Which group best represents your Hispanic origin or ancestry? *Check all boxes that apply.*

- [1] ☐ Mexican, Mexican American, Chicano
- [2] ☐ Caribbean
- [3] ☐ Central American
- [4] ☐ South American
- [5] ☐ Other Hispanic (please describe) _____

3. What is the **highest** grade or level of schooling you have completed? *Check one box only.*

- [1] ☐ No formal education
- [2] ☐ 8th grade or less
- [3] ☐ Some high school (9th -11th grade)
- [4] ☐ High school graduate or GED
- [5] ☐ Technical or vocational school
- [6] ☐ Associate degree or some college
- [7] ☐ Bachelor's degree
- [8] ☐ Advanced degree (Master's or Doctoral degree)

4. Are you currently employed (including self-employed)?

[1] ☐ Yes [0] ☐ No

a. On average, how many hours do you work each week? *Check one box only.*

[1] ☐ 1-29 hours [2] ☐ 30-44 hours [3] ☐ 45-54 hours [4] ☐ 55+ hours

5. What is your current marital status? *Check one box only.*

- [1] ☐ Single (never married)
- [2] ☐ Married
- [3] ☐ Living with partner
- [4] ☐ Separated
- [5] ☐ Divorced
- [6] ☐ Widowed

6. With whom do you currently live? *Check all boxes that apply.*

- [1] ☐ Spouse/partner
- [2] ☐ Children
- [3] ☐ Parent(s)
- [4] ☐ Parent(s)-in-law
- [5] ☐ Other relative(s)
- [6] ☐ Friend(s)
- [7] ☐ I live alone
- [8] ☐ Other (please describe) _____

PHYSICAL HEALTH AND FRAILTY

The next questions ask about your physical health.

1. How tall are you? _____Feet _____Inches

<< The next 5 questions are Components of the FRAIL AAH Questionnaire >>

2. How much do you **currently** weigh with your clothes on but without shoes?_____Pounds

3. **One year ago** in (___/____Month/Year), how much did you weigh with your clothes on but without shoes? _____ Pounds

4. How much of the time during the **past 4 weeks** did you feel tired? Please select one answer only.

[1] ☐ All of the time [2] ☐ Most of the time [3] ☐ Some of the time [4] ☐ A little of the time [5] ☐ None of the time

5. By yourself and not using aids, do you have any difficulty **walking up 10 steps without resting**?

[1] ☐ Yes [0] ☐ No

6. By yourself and not using aids, do you have any difficulty **walking several hundred yards**?

[1] ☐ Yes [0] ☐ No

SF-12® HEALTH SURVEY

This set of questions asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Answer every question by selecting one answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is (please select one answer only):
   1 ☐ Excellent 2 ☐ Very Good 3 ☐ Good 4 ☐ Fair 5 ☐ Poor

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1☐	2☐	3☐
b. Climbing several flights of stairs	1☐	2☐	3☐

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a. Accomplished less than you would like	1☐	2☐
b. Were limited in the kind of work or other activities	1☐	2☐

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a. Accomplished less than you would like	1☐	2☐
b. Did work or activities less carefully than usual	1☐	2☐

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? Please select one answer only.
   1 ☐ Not at all 2 ☐ A little bit 3 ☐ Moderately 4 ☐ Quite a bit 5 ☐ Extremely

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks:	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	1☐	2☐	3☐	4☐	5☐	6☐
b. Did you have a lot of energy?	1☐	2☐	3☐	4☐	5☐	6☐
c. Have you felt downhearted and blue?	1☐	2☐	3☐	4☐	5☐	6☐

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? Please select one answer only.
   1 ☐ All of the time 2 ☐ Most of the time 3 ☐ Some of the time 4 ☐ A little of the time 5 ☐ None of the time

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SKIN TYPE, SUN EXPOSURE, AND SUN PROTECTION

The next questions ask about your skin type, sun exposure, and sun protection.

1. What is your natural eye color?
   0 ☐ Light Blue, Gray, or Green 1 ☐ Blue, Gray, or Green 2 ☐ Dark Blue or Hazel
   3 ☐ Dark Brown 4 ☐ Brownish Black

2. What is the natural color of your hair?
   0 ☐ Sandy Red 1 ☐ Blonde 2 ☐ Chestnut or Dark Blonde 3 ☐ Dark Brown 4 ☐ Black

3. What is the color of your skin in unexposed areas (areas with no sun exposure)?
   0 ☐ Reddish 1 ☐ Very Pale 2 ☐ Pale with Beige Tint 3 ☐ Light Brown 4 ☐ Dark Brown

4. Do you have freckles on unexposed areas?
   0 ☐ Many 1 ☐ Several 2 ☐ Few 3 ☐ Hardly any 4 ☐ None

5. What happens when you stay in the sun too long?
   0 ☐ Painful redness, blistering, peeling 1 ☐ Blister then peel
   2 ☐ Burn sometimes followed by peeling 3 ☐ Rarely burn 4 ☐ Never burn

6. Do you turn brown within several hours after sun exposure?
   0 ☐ Never 1 ☐ Hardly ever 2 ☐ Sometimes 3 ☐ Often 4 ☐ Always

7. To what degree do you turn brown?
   0 ☐ Hardly or not at all 1 ☐ Lightly 2 ☐ Moderately 3 ☐ Deeply 4 ☐ My skin is naturally dark

8. How does your face react to the sun?
   0 ☐ Very sensitive 1 ☐ Sensitive 2 ☐ Normal 3 ☐ Very resistant 4 ☐ Never had a problem

9. About how many times have you had a severe sunburn that blistered? Please estimate as best you can.
   0 ☐ 0 1 ☐ 1-2 2 ☐ 3-5 3 ☐ 6-10 4 ☐ More than 10

10. How many moles do you have on your body that are larger than a pencil eraser (1/4 inch)?
    0 ☐ 0 1 ☐ 1-2 2 ☐ 3-5 3 ☐ 6-10 4 ☐ More than 10

11. Where did you live during most of your childhood (until age 18)?
    State_____ OR Country _____

12. Have you ever had a full body skin exam by a dermatologist?
    1 ☐ Yes 0 ☐ No
    a. When was your **most recent** full body skin exam?_____/_____(Month/Year)

13. Has a doctor or health care provider ever told you that you had (skin condition)?

If YES, ask age at first diagnosis, location, and treatment received.	Yes	No	Age at first diagnosis	Location	Treatment Received *(If none enter None)*
a. Atypical moles	1☐	0☐	_____	_____	_____
b. Benign skin lesions	1☐	0☐	_____	_____	_____
c. Skin cancer (*If YES, ask question # 14)*	1☐	0☐	_____	_____	_____

14. *If Question # 13c is Yes, ask:* What type of skin cancer?
    1 ☐ Basal 2 ☐ Squamous 3 ☐ Melanoma 4 ☐ Hemangioma 9 ☐ Don't know

15. For the following questions, think about what you do when you are outside during a typical sunny day.

Select one response for each question.	Never	Rarely	Sometimes	Often	Always
a. How often do you wear SUNSCREEN?	0☐	1☐	2☐	3☐	4☐
b. How often do you wear a SHIRT WITH SLEEVES that covers your shoulders?	0☐	1☐	2☐	3☐	4☐
c. How often do you wear a HAT?	0☐	1☐	2☐	3☐	4☐
d. How often do you stay in the SHADE or UNDER AN UMBRELLA?	0☐	1☐	2☐	3☐	4☐
e. How often do you wear SUNGLASSES?	0☐	1☐	2☐	3☐	4☐

16. In **the past month**, how many times did you have skin irritation including anytime that even a small part of your skin was irritated for more than 12 hours? *Select one answer only.*

0	1	2	3	4	5 or more
0☐	1☐	2☐	3☐	4☐	5☐

MEDICAL HISTORY

The following questions ask about your medical history. Please answer the best you can.

*There are two types of dialysis, **hemodialysis** and **peritoneal dialysis**. In **hemodialysis**, blood is pumped out of your body to an artificial kidney machine, and returned to your body by tubes that connect you to the machine. Treatment usually takes place in a hemodialysis unit, which is a special building equipped with machines that perform the dialysis treatment. Patients generally go to the dialysis unit three times a week for treatment.*

1. Have you ever been on **hemodialysis**?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 2*
   a. At what age did you **first start** hemodialysis?_____years old
   b. What is the **most often** you have done hemodialysis?_____times per week
   c. Are you currently on hemodialysis? [1] ☐ Yes [0] ☐ No
   If NO, ask: d. At what age did you **stop** hemodialysis?_____years old

***Peritoneal dialysis** uses a fluid that is placed into the patient's abdominal cavity through a special plastic tube to remove excess waste products and fluid from the body. In peritoneal dialysis, wastes are taken out by means of a cleansing fluid, which is washed in and out of your belly in cycles. There are two kinds of peritoneal dialysis. Continuous Ambulatory Peritoneal Dialysis (CAPD) is machine-free and is done while you go about your normal activities. This process usually is done three, four, or five times in a 24-hour period while you are awake during normal activities. With Automated Peritoneal Dialysis (APD), a machine (cycler) delivers and then drains the cleansing fluid for you. The treatment usually is done at night while you sleep.*

2. Have you ever been on **peritoneal dialysis**?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 3 (Pap smear)*
   a. At what age did you **first start** peritoneal dialysis?_____years old
   b. What is the **most often** you have done peritoneal dialysis?_____times per day
   c. Are you currently on peritoneal dialysis? [1] ☐ Yes [0] ☐ No
   If NO, ask: d. At what age did you **stop** peritoneal dialysis?_____years old
   e. What type of peritoneal dialysis do/did you do? *Check all boxes that apply*
   [1] ☐ Continuous Ambulatory Peritoneal Dialysis (CAPD) [2] ☐ Automated Peritoneal Dialysis (APD)

Females only:

3. Have you ever had a Pap smear?
   [1] ☐ Yes [0] ☐ No → *If NO skip to question # 4 (human papillomavirus (HPV) infection)*
   a. When was your **most recent** Pap smear?_____/_____(Month/Year)
   b. How many Pap smears have you had during the past 10 years? *Please give your best estimate.* _____
   c. How many of your Pap smears during the past 10 years were abnormal? *If none enter 0.* _____

4. Has a doctor or health care provider ever told you that you had a human papillomavirus (HPV) infection?
   [1] ☐ Yes [0] ☐ No

Females only:

5. Have you ever had any of the following medical procedures?

If Yes, ask date of medical procedure.	Yes	No	Don't know	When did you have [medical procedure]? (Month/Year)
a. Repeat/follow-up Pap smear	1☐	0☐	9☐	_____/_____
b. Colposcopy	1☐	0☐	9☐	_____/_____
c. Freezing or cryotherapy of the cervix	1☐	0☐	9☐	_____/_____
d. Burning or laser therapy of the cervix	1☐	0☐	9☐	_____/_____
e. Biopsy of the cervix (*If YES, also ask question # 6)*	1☐	0☐	9☐	_____/_____
f. Surgery of the cervix (including conization or LEEP)	1☐	0☐	9☐	_____/_____
g. D & C (Dilation and Curettage)	1☐	0☐	9☐	_____/_____
h. Hysterectomy (removal of your uterus)	1☐	0☐	9☐	_____/_____
i. Other cervical/vaginal medical procedure (Describe)	1☐	0☐	9☐	_____/_____

Females only:

6. *If question # 5e (biopsy of the cervix) is YES, ask:* Why did you have the biopsy of your cervix?
   1☐ A follow-up to an abnormal Pap smear or pelvic exam
   2☐ Some other reason (please describe): _____
   9☐ I don't know

Females only:

7. Have you ever been pregnant?
   1☐ Yes 0☐ No
   a. How many full-term births (≥ 28 weeks or 7 months), including live births and still births, have you had?
   ____ full-term births

ALCOHOL AND TOBACCO USE

The next questions ask about your use of alcohol and tobacco.

1. How often do you have a drink containing alcohol? *If NEVER skip to question # 4 (cigarette smoking)*
   0☐ Never 1☐ Monthly or less 2☐ 2-4 times a month 3☐ 2-3 times a week 4☐ 4 or more times a week

2. How many standard drinks containing alcohol do you have on a typical day? A standard drink is a 12-ounce bottle or can of beer, a 4-ounce glass of wine, a shot of liquor, or a mixed drink._____drinks

3. How often do you have **six or more drinks** on one occasion?
   0☐ Never 1☐ Less than monthly 2☐ Monthly 3☐ Weekly 4☐ Daily or almost daily

4. Have you ever smoked **at least one cigarette a day** for **6 months or longer**?
   1☐ Yes 0☐ No → *If NO skip to next section – SEXUAL HISTORY*

5. How old were you when you first started smoking cigarettes **daily**?_____years old

6. During the time you smoked, how many cigarettes did you usually smoke **each day**?_____cigarettes per day

7. How many years have you (or did you use) smoke **at least one cigarette a day**?_____years

8. Do you smoke cigarettes now? 1☐ Yes 0☐ No
   <<IF NO>> a. How old were you when you **quit smoking cigarettes**?_____years old

---

SEXUAL ACTIVITY

The last questions ask about your sexual activity. We ask you these questions because human papillomavirus (HPV) is spread primarily through sexual contact. You can skip any questions you feel uncomfortable answering.

1. Have you been sexually active during the **past 6 months?**

[1] ☐ Yes [0] ☐ No → ***If NO the interview is completed***

a. With how many partners have you been sexually active during the **past 6 months?**_____partners

Females only:

2. Have you had sexual (vaginal) intercourse with a male partner during the **past 6 months?**

[1] ☐ Yes [0] ☐ No → *If NO skip to question # 3*

a. How often have you had sexual intercourse during the **past 6 months?** *Interviewer: probe for frequency.*

[1] ☐ 1-2 times in past 6 months [2] ☐ 3-5 times in past 6 months [3] ☐ Once per month
[4] ☐ 2-3 times per month [5] ☐ 1 or more times per week

Females only:

3. Have you had oral sex with a male partner during the **past 6 months?**

[1] ☐ Yes [0] ☐ No → ***If NO the interview is completed***

a. How often have you had oral sex during the **past 6 months?** *Interviewer: probe for frequency.*

[1] ☐ 1-2 times in past 6 months [2] ☐ 3-5 times in past 6 months [3] ☐ Once per month
[4] ☐ 2-3 times per month [5] ☐ 1 or more times per week

Males Only:

2. Have you had sexual intercourse during the **past 6 months?**

[1] ☐ Yes [0] ☐ No → *If NO skip to question # 3*

a. How often have you had sexual intercourse during the **past 6 months?** *Interviewer: probe for frequency.*

[1] ☐ 1-2 times in past 6 months [2] ☐ 3-5 times in past 6 months [3] ☐ Once per month
[4] ☐ 2-3 times per month [5] ☐ 1 or more times per week

Males Only:

3. Have you had oral sex during the **past 6 months?**

[1] ☐ Yes [0] ☐ No → ***If NO the interview is completed***

a. How often have you had oral sex during the **past 6 months?** *Interviewer: probe for frequency.*

[1] ☐ 1-2 times in past 6 months [2] ☐ 3-5 times in past 6 months [3] ☐ Once per month
[4] ☐ 2-3 times per month [5] ☐ 1 or more times per week

END OF INTERVIEWER-ADMINISTERED QUESTIONNAIRE

Thank you for taking the time to complete the interview. This information is vitally important to our study and we greatly appreciate your contributions.

INTERVIEWER'S REMARKS

1. Participant ID _____

2. Interviewer ___ ___ (Initials)

3. Participant's date of birth Month_____Day_____Year_____ (*Current Age*:_____)

4. Date of Interview Month_____Day_____Year _____

5. Interview Start Time _____:_____(Hour: Minutes [24-hour time])

6. Interview End Time _____:_____(Hour: Minutes [24-hour time])

7. The interview included: *(Check all boxes that apply.)*
   1 ☐ The participant only
   2 ☐ A spouse or partner
   3 ☐ Another family member
   4 ☐ Another person (please specify) _____

8. The participant's cooperation was: *(Check one box only.)*
   1 ☐ Excellent 2 ☐ Very Good 3 ☐ Good 4 ☐ Fair 5 ☐ Poor

9. The quality of the interview is: *(Check one box only.)*
   1 ☐ Excellent 2 ☐ Generally reliable 3 ☐ Questionable 4 ☐ Unreliable

APPENDIX F

Participant ID: _____

Date: _____

Preventive Human Papillomavirus (HPV) Vaccine Trial in Kidney Transplant Recipients

Follow-Up Questionnaire

We appreciate the time you are taking to complete this interview. We will be asking you questions that focus on any changes that may have occurred since your last research visit for this study on__ (date of last study visit). Please try to answer each question as completely as you can, even if you are unsure about the answer. If you feel uncomfortable answering any question, you can choose not to answer it. All answers will be kept confidential.

PHYSICAL HEALTH AND FRAILTY

The first questions ask about your physical health. << Components of the FRAIL AAH Questionnaire >>

1. How much do you **currently** weigh with your clothes on but without shoes?_____Pounds

2. How much of the time during the **past 4 weeks** did you feel tired? Please select one answer only.
   1 ☐ All of the time 2 ☐ Most of the time 3 ☐ Some of the time 4 ☐ A little of the time 5 ☐ None of the time

3. By yourself and not using aids, do you have any difficulty **walking up 10 steps without resting**?
   1 ☐ Yes 0 ☐ No

4. By yourself and not using aids, do you have any difficulty **walking several hundred yards**? 1 ☐ Yes 0 ☐ No

SF-12® HEALTH SURVEY

This set of questions asks for your views about your health since your last research study visit on_____(date of last study visit). If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your current health is (please select one answer only):
   1 ☐ Excellent 2 ☐ Very Good 3 ☐ Good 4 ☐ Fair 5 ☐ Poor

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1☐	2☐	3☐
b. Climbing several flights of stairs	1☐	2☐	3☐

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a. Accomplished less than you would like	1☐	2☐
b. Were limited in the kind of work or other activities	1☐	2☐

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a. Accomplished less than you would like	1☐	2☐
b. Did work or activities less carefully than usual	1☐	2☐

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? Please select one answer only.
   1 ☐ Not at all 2 ☐ A little bit 3 ☐ Moderately 4 ☐ Quite a bit 5 ☐ Extremely

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks:	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	1☐	2☐	3☐	4☐	5☐	6☐
b. Did you have a lot of energy?	1☐	2☐	3☐	4☐	5☐	6☐
c. Have you felt downhearted and blue?	1☐	2☐	3☐	4☐	5☐	6☐

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? Please select one answer only.
   1 ☐ All of the time 2 ☐ Most of the time 3 ☐ Some of the time 4 ☐ A little of the time 5 ☐ None of the time

SKIN TYPE, SUN EXPOSURE, AND SUN PROTECTION

The next questions ask about your skin, sun exposure, and sun protection since your last research study visit.

1. Since your last research study visit on_____, have you had a full body skin exam by a dermatologist?
   1 ☐ Yes 0 ☐ No
   a. When was your **most recent** full bodyskin exam?_____(Month/Day/Year)

2. Since your last study visit, has a doctor or health care provider told you that you had (skincondition)?

If YES, ask date of diagnosis, location, and treatment received.	Yes	No	Diagnosis date (Mon/Day/Yr)	Location	Treatment Received *(If none enter None)*
a. Atypical moles	1☐	0☐	___/___/____	_____	_____
b. Benign skin lesions	1☐	0☐	___/___/____	_____	_____
c. Skin cancer (*If YES, ask question # 3)*	1☐	0☐	___/___/____	_____	_____

3. *If Question # 2c is Yes, ask:* What type of skin cancer?
   1 ☐ Basal 2 ☐ Squamous 3 ☐ Melanoma 4 ☐ Hemangioma 9 ☐ Don't know

4. For the following questions, think about what you do when you are outside during a typical sunny day.

Select one response for each question.	Never	Rarely	Sometimes	Often	Always
a. How often do you wear SUNSCREEN?	0☐	1☐	2☐	3☐	4☐
b. How often do you wear a SHIRT WITH SLEEVES that covers your shoulders?	0☐	1☐	2☐	3☐	4☐
c. How often do you wear a HAT?	0☐	1☐	2☐	3☐	4☐
d. How often do you stay in the SHADE or UNDER AN UMBRELLA?	0☐	1☐	2☐	3☐	4☐
e. How often do you wear SUNGLASSES?	0☐	1☐	2☐	3☐	4☐

5. In **the past month**, how many times did you have skin irritation including anytime that even a small part of your skin was irritated for more than 12 hours? *Select one answer only.*

0	1	2	3	4	5 or more
0☐	1☐	2☐	3☐	4☐	5☐

6. Please indicate whether you agree or disagree with each of the following statements.

	Agree	Disagree
a. People with a kidney transplant take medicine that may make their skin sensitive to the sun.	1☐	2☐
b. Only people with a kidney transplant that have sun sensitive skin, who freckle and sunburn easily, have to worry about getting a skin cancer.	1☐	2☐
c. Applying sunscreen after being out in the sun is enough protection.	1☐	2☐
d. When the sun is high in the sky, seek shade to avoid the strong rays of the sun.	1☐	2☐
e. Clothing does not protect the skin from the sun.	1☐	2☐
f. Sunglasses protect the delicate skin around the eyes.	1☐	2☐
g. It takes about a teaspoon of sunscreen to cover the skin of the whole body.	1☐	2☐
h. A baseball cap is a good hat for sun protection	1☐	2☐
i. Walking outside at noon for an hour is not enough time outside to need sun protective gear.	1☐	2☐

7. Please indicate your level of agreement with each of the following statements.

Select one answer for each statement.	Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
a. I am at risk of developing skin cancer.	1☐	2☐	3☐	4☐	5☐
b. Skin cancer does not kill people.	1☐	2☐	3☐	4☐	5☐
c. Regular use of sun protection helps to prevent skin cancer.	1☐	2☐	3☐	4☐	5☐
d. The transplant doctors and nurses seem to feel that I should use sun protection.	1☐	2☐	3☐	4☐	5☐
e. It is important to my partner that I use sun protection.	1☐	2☐	3☐	4☐	5☐
f. I look better with a tan.	1☐	2☐	3☐	4☐	5☐
g. I look healthier with a tan.	1☐	2☐	3☐	4☐	5☐

MEDICAL HISTORY

The following questions ask about your medical history since your last research study visit.

Females only:

1. Since your last research study visit on_____(date of last study visit), have you had a Pap smear?
   1☐ Yes 0☐ No → *If NO skip to question # 2 (medical procedures)*
   a. When was your **most recent** Pap smear?_____(Month/Day/Year)
   b. Was your most recent Pap smear abnormal? 1☐ Yes 0☐ No

Females only:

2. Since your last research study visit on_____, have you had any of the following medical procedures?

If Yes, ask date of medical procedure.	Yes	No	Don't know	When did you have [medical procedure]? (Month/Year)
a. Repeat/follow-up Pap smear	1☐	0☐	9☐	____/____
b. Colposcopy	1☐	0☐	9☐	____/____
c. Freezing or cryotherapy of the cervix	1☐	0☐	9☐	____/____
d. Burning or laser therapy of the cervix	1☐	0☐	9☐	____/____
e. Biopsy of the cervix (*If YES, also ask question # 3)*	1☐	0☐	9☐	____/____
f. Surgery of the cervix (including conization or LEEP)	1☐	0☐	9☐	____/____
g. D & C (Dilation and Curettage)	1☐	0☐	9☐	____/____
h. Hysterectomy (removal of your uterus)	1☐	0☐	9☐	____/____
i. Other cervical/vaginal medical procedure (Describe)	1☐	0☐	9☐	____/____

Females only:

3. *If question # 2e (biopsy of the cervix) is YES, ask:* Why did you have the biopsy of your cervix?
   1☐ A follow-up to an abnormal Pap smear or pelvic exam
   2☐ Some other reason (please describe): _____
   9☐ I don't know

ALCOHOL AND TOBACCO USE

The next questions ask about your use of alcohol and tobacco since your last research study visit.

1. How often do you have a drink containing alcohol? *If NEVER skip to question # 4 (cigarette smoking)*
   0 ☐ Never 1 ☐ Monthly or less 2 ☐ 2-4 times a month 3 ☐ 2-3 times a week 4 ☐ 4 or more times a week
2. How many standard drinks containing alcohol do you have on a typical day? A standard drink is a 12-ounce bottle or can of beer, a 4-ounce glass of wine, a shot of liquor, or a mixed drink._____drinks
3. How often do you have **six or more drinks** on one occasion?
   0 ☐ Never 1 ☐ Less than monthly 2 ☐ Monthly 3 ☐ Weekly 4 ☐ Daily or almost daily
4. Since your last research study visit on_____(date of last study visit)**,** have you smoked cigarettes?
   1 ☐ Yes 0 ☐ No → *If NO skip to next section – SEXUAL HISTORY*
5. When did you **last smoke** a cigarette? _____ (Month/Day/Year)
6. How many cigarettes do you usually smoke **each day**? ____ cigarettes per day

SEXUAL ACTIVITY

The last questions ask about your sexual activity since your last research study visit on_____(date of last visit). We ask you these questions because human papillomavirus (HPV) is spread primarily through sexual contact. You can skip any questions you feel uncomfortable answering.

1. Have you been sexually active since your last research study visit on_____?
   1 ☐ Yes 0 ☐ No → ***If NO the interview is completed***
   a. With how many partners have you been sexually active since your last study visit?_____partners

Females only:

2. Since your last research study visit, have you had sexual (vaginal) intercourse with a male partner?
   1 ☐ Yes 0 ☐ No → *If NO skip to question # 3*
   a. How often have you had sexual intercourse since your last study visit? *Interviewer: probe for frequency.*
   1 ☐ 1-2 times since last visit 2 ☐ 3-5 times since last visit 3 ☐ Once per month
   4 ☐ 2-3 times per month 5 ☐ 1 or more times per week

Females only:

3. Since your last study visit, have you had oral sex with a male partner?
   1 ☐ Yes 0 ☐ No → ***If NO the interview is completed***
   a. How often have you had oral sex since your last study visit? *Interviewer: probe for frequency.*
   1 ☐ 1-2 times since last visit 2 ☐ 3-5 times since last visit 3 ☐ Once per month
   4 ☐ 2-3 times per month 5 ☐ 1 or more times per week

Males only:

2. Since your last research study visit, have you had sexual intercourse?
   1 ☐ Yes 0 ☐ No → *If NO skip to question # 3*
   a. How often have you had sexual intercourse since your last study visit? *Interviewer: probe for frequency.*
   1 ☐ 1-2 times since last visit 2 ☐ 3-5 times since last visit 3 ☐ Once per month
   4 ☐ 2-3 times per month 5 ☐ 1 or more times per week

Males only:

3. Since your last study visit, have you had oral sex?

1 ☐ Yes 0 ☐ No → ***If NO the interview is completed***

a. How often have you had oral sex since your last study visit? *Interviewer: probe for frequency.*

1 ☐ 1-2 times since last visit 2 ☐ 3-5 times since last visit 3 ☐ Once per month

4 ☐ 2-3 times per month 5 ☐ 1 or more times per week

END OF INTERVIEWER-ADMINISTERED QUESTIONNAIRE

Thank you for taking the time to complete the interview. This information is vitally important to our study and we greatly appreciate your contributions.

INTERVIEWER'S REMARKS

1. Participant ID _____

2. Study Visit Number [2] ☐ Second [3] ☐ Third [4] ☐ Fourth

3. Date of This Study Visit Month_____Day_____Year _____

4. Date of Last Study Visit Month_____Day_____Year _____

5. Interviewer _____(Initials)

6. Interview Start Time _____:_____(Hour: Minutes [24-hour time])

7. Interview End Time _____:_____(Hour: Minutes [24-hour time])

8. The interview included: *(Check all boxes that apply.)*
   [1] ☐ The participant only
   [2] ☐ A spouse or partner
   [3] ☐ Another family member
   [4] ☐ Another person (please specify) _____

9. The participant's cooperation was: *(Check one box only.)*
   [1] ☐ Excellent [2] ☐ Very Good [3] ☐ Good [4] ☐ Fair [5] ☐ Poor

10. The quality of the interview is: *(Check one box only.)*
   [1] ☐ Excellent [2] ☐ Generally reliable [3] ☐ Questionable [4] ☐ Unreliable

APPENDIX G

COVID-19 Contingency Plan

Background: In response to the public health emergency due to the COVID-19 pandemic, several adaptations have been included to ensure that the protocol will be able to meet its primary endpoint. This Appendix lists the specific modifications to the protocol that may be permitted to be undertaken in the context of the COVID-19 Contingency plans.

1. **Remote Specimen Collection:** Considering the closure of several study clinics to non-emergency study visits due to the COVID-19 crisis and concerns about SARS-COV2 transmission, an alternative plan for remote specimen collection will be offered to eligible and affected participants. This includes an at-home self-collection of a cervical/vaginal specimen that is described in the protocol and would also be self-collected in clinic. In addition, we include an at-home finger stick capillary blood collection of a dried blood spot via a novel sample collection device (Neoteryx Mitra cartridge). This device is based on volumetric absorptive microsampling (VAMS) technique that has been previously evaluated in measuring vaccine antibody responses and other biomarkers (See references below). Incorporating this device will allow the possibility of measurement of HPV antibody responses closer to the original/protocol-specified visit time points when COVID-19-related concerns preclude the possibility of in-person clinic visits. The procedures for remote specimen collection includes an addendum consent (APPENDIX H) for an at-home finger-stick capillary blood collection (dried blood spot) via a special collection device and return shipment of the specimen, along with phone calls to review medical and surgical history, medications, symptom assessment, determination of ECOG performance status and administration of study questionnaire.

   Applicable visits:

   - 6-months post-transplant visit
   - 12-months post-transplant visit
   - 13-months post-transplant visit (to be conducted only if, and 1-month after, any original scheduled or rescheduled in-person 12-month post-transplant visit is conducted).

   Procedures:

   1. Study staff will identify appropriate participants affected by the cancellation/deferral of regularly scheduled study visits.
   2. Eligible participants will be contacted by phone and procedures will be explained by the study investigators and staff.
   3. Participants will be administered the remote consent as per COVID-19 remote consent procedures approved by the CIRB. (see '**Appendix H**')
   4. Staff will interview the participants for review of medical and surgical history, medications, symptom assessment, determination of ECOG performance status, and follow-up questionnaire for the 6-months and 12-months visits.
   5. Participants will be sent an Evalyn cervical/vaginal specimen collection kit, and a Neoteryx Mitra sampling cartridge. All collection kits will have standardized instructions and study specific information sheets (see '**Finger Stick Participant Information material**' and '**Vaginal Self-Collection Instructions**'). All devices and return collection kits will have barcoded labels that confidentially link back to the participant record without any identifying information (participant name, other contact details, etc.).
   6. Participants will self-collect a personal cervical/vaginal specimen and a finger stick blood specimen and will return to the Cedars Sinai biorepository using pre-labeled, pre-paid packages that will be picked up by a courier at the participant's home or pre-arranged location.

2. **Expansion of window for 12-months post-transplant visit for specimen collection for primary endpoint:** The visit for specimen collection for the primary endpoint (12-months post-transplantation time point) is regularly scheduled at 12-months +/- 2 weeks after the transplant surgery. The +/- 2 weeks window will now be extended to ***up to +/- 6 months*** to permit maximum operational flexibility due to the scheduling challenges due to COVID-19, and may be rescheduled to a convenient date and time once it is considered safe to resume study activities.

3. **6-months post-transplant study visits:** The rescheduled 12-month post-transplant visit (for the primary endpoint) now includes a very broad/expanded window (+/- 6 months) that may overlap with the original 6-month post-transplant visit timeframe. The 6-month post-transplant visit will therefore be considered an optional one due to the COVID-19-related scheduling challenges.

4. **13-months post-transplant study visits**: This visit will also be considered an optional one and can now be rescheduled to occur one month (+/- 2 weeks) after the rescheduled 12-month post-transplant visit, only for participants who have received the booster injection.

5. **Visit procedures:** All procedures in Section 7 "CLINICAL EVALUATIONS AND PROCEDURES" corresponding to the rescheduled visits will be conducted as outlined. In addition, cervical/vaginal, and blood specimens may occur for eligible and consenting participants for the 6-months, 12-months, and 13-months (finger stick only) post-transplant visits.

6. **Specimen Management:** The finger-prick collection method will yield dried blood spot collection that will be stored in the biorepository at Cedars Sinai Medical Center for future analysis for the HPV serological analysis for the primary and secondary endpoints. The cervical/vaginal specimens will be used per protocol for analysis of secondary aims.

7. **Participant reimbursement**: For participants seen under the COVID-19 Contingency Plan compensation will be per protocol.

References:

i. Wang et al. Application of VAMS to measure multidimensional anti-influenza IgG antibodies by the mPlex-Flu assay *J Clin Transl Sci* 2019;3(6):332-34)
ii. Shufelt et al. A Protocol Integrating Remote Patient Monitoring Patient Reported Outcomes and Cardiovascular Biomarkers. *NPJ Digit Med* 2019 Sep 3;2:84

APPENDIX H

Consent Form Addendum

This form is an Addendum to the Informed Consent for study entitled "Immunogenicity of Nonavalent HPV Vaccine Administered Prior To Renal Transplantation in Adults: A Prospective, Single-Arm, Multi-Center Clinical Trial" for participants whose post-transplant study visits are delayed during the COVID-19 pandemic.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Immunogenicity of Nonavalent HPV Vaccine Administered Prior To Renal Transplantation in Adults: A Prospective, Single-Arm, Multi-Center Clinical Trial

How long will I be in this study?
Under regular circumstances, the total time you would be involved in this study would be no more than 13 months after your transplant. However, if you are not able to come into the clinic for your 6-month, 12-month, or 13-month post-transplant study visit during the time of the COVID-19 pandemic, we will ask you to come in to the clinic at a later date. This may extend the period of participation in the study by about six additional months.

What extra tests and procedures will I have if I take part in this study?
Because you cannot come into clinic in person, there will be some changes to study related tests and procedures. Instead of your 6-month or 12-month post-transplant in-person visit, you will receive a phone call. You will be asked about your medical history, medications, symptoms, and current activity level and limitations. You will go through the questionnaire you would have done in the clinic as well. Instead of the blood that would normally be drawn at your 6-month, 12-month, or 13-month post-transplant study visit, a new method for at-home finger stick sampling is being proposed in this study. The at-home finger-stick device has been used in several studies previously, and given the challenges in scheduling in-person clinic visits during the COVID-19 pandemic, it will provide an opportunity for collection of key information for this HPV vaccine study even though study visits do not occur at their original scheduled time. You will receive a blood collection kit in the mail around the time of these visits to collect a blood sample at home and send it back. A brochure included in the kit will instruct you how to collect a few drops of blood from your finger using a disposable lancet (a small medical tool used to puncture your skin to obtain blood sample, often used by persons with diabetes) and collect it on the special collection device provided in the kit. For female participants, you will also be offered the opportunity for self-collection of a cervical/vaginal specimen. Instructions for collection and returning the sample will be included with the specimen collection kits sent to you. Your missed visits (at 6-, 12-, and 13-months post-transplant) may be rescheduled to a convenient date and time once it is considered safe to resume study activities. The procedures in the rescheduled study visits will be the same as you would have done originally in the study. These visits will take place at the same clinic you have visited for this study before. If the study physician determines that these visits are not useful for the study goals, they may be cancelled, and you will be informed accordingly.

What possible risks can I expect from the addendum participation?
If used correctly there are minimal risks to utilizing an at home lancet device. You may feel slight pain when you prick your finger with the testing device. Your fingertip may be sore for a short time and you could have a small bruise. Your privacy remains very important and we will make every effort to protect it. Your specimens will be confidentially identified with a barcode (not your name or other contact information) for return shipment to the clinical research facility.

What are the costs of taking part in this study?

For the home-based specimen collection and phone visits, you will receive compensation for your time and effort. The amount of compensation will be $150 for the 6-month Post-Transplant Study Visit, $150 for the 12-month Post-Transplant Study Visit, and $75 for the 13-Month Post-Transplant Visit. If and when you are able to come into clinic to make up the missed in person visits at a later date, you will be compensated for expenses associated with study participation for that visit, such as travel expenses, time missed from work or other. The amount of compensation for in person visits remains unchanged ($150 for the 6-month, $150 for the 12-month Post-Transplant Study Visits, and $75 for the 13-Month Post-Transplant Visit).

My Signature Agreeing to extend study participation

I have read this consent addendum, or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to the changes discussed in this addendum.

Participant's signature	Date of Signature
Signature of person(s) conducting the informed consent discussion	Date of Signature
Participant witness signature	Date of Signature