THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., WHITEHOUSE STATION, NJ, U.S.A.

THIS PROTOCOL REPLACES THE ORIGINAL PROTOCOL AND ANY SUBSEQUENT AMENDMENTS AND SHOULD BE SIGNED BY ALL INVESTIGATORS SIGNING THE ORIGINAL PROTOCOL

SPONSOR:

Merck Sharp & Dohme Corp. (hereafter referred to as the **SPONSOR**)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ, 08889-0100, U.S.A.

TITLE:

Post-Licensure Observational Study of the Safety of GARDASIL™ in Males

PRINCIPAL INVESTIGATOR:

PPD

SITE:

PPD

INSTITUTIONAL REVIEW BOARD/ETHICAL REVIEW COMMITTEE:

PPD will seek IRB approval from the PPD

SUMMARY OF CHANGES FOR AMENDMENT 1

Protocol Section	Change
Cover Page	Study Principal Investigators, Site, and Institutional Review Board changed to reflect change in study site to PPD
1.3 Study Setting; 3.1 Study Setting; elsewhere, as needed	Study site changed to PPD
2.3 Hypotheses	Added clarifying statement that no formal hypotheses will be tested.
Figure 3-1: Vaccinated Cohorts	Clarified that for Regimen Initiators and Autoimmune Cohorts, males must be health plan members at time of vaccination with GARDASIL™.
3.4.1 General Safety Cohorts: Regimen Initiators and Regimen Completers	Clarified continuous enrollment membership criterion for Regimen Completers cohort. Removed statement regarding the analyses to be conducted on each cohort (replaced with more comprehensive table added to Section 4.1.2).
3.4.3 General Safety and Autoimmune Cohort Exclusion Criteria	For Regimen Completers cohort, deleted post-vaccination self-comparison membership exclusion criterion. Males will be censored when membership expires.
3.5 Accrual of Study Subjects and Accrual Timelines	Removed study vaccine provisioning language as it is no longer relevant for this study setting.
3.6.1 General Safety Endpoints and Risk Periods	Clarified that all health outcomes resulting in emergency room visit or hospitalization will be evaluated in this study, including venous embolism and thrombosis.
3.6.1 General Safety Endpoints and Risk Periods	Clarified how health outcomes will be identified within the PPD database.
3.6.1 General Safety Endpoints and Risk Periods	Clarified that for sub-analyses in which pre-existing chronic conditions are excluded, decision rules and methods will be described in the study's Data Analysis Plan.
3.6.1 General Safety Endpoints and Risk Periods	For clarity, removed sentence regarding self-comparison periods. Self-comparison periods are described in detail in Section 3.7.1
3.6.1 General Safety Endpoints and Risk Periods	Clarified rationale for limiting Day 0 events to pre-specified outcomes of interest.

SUMMARY OF CHANGES FOR AMENDMENT 1 (CONT.)

Protocol Section	Change
3.6.2 Identification of Pre-specified, New-Onset Autoimmune Endpoints	To be consistent with one-year membership criterion for Autoimmune Cohort, exclusion of pre-existing conditions identified from codes in the PPD database will be limited to one year (rather than two years) prior to a subject's first dose of GARDASIL™.
3.6.2 Identification of Pre-specified, New-Onset Autoimmune Endpoints	To allow for a thorough review of pre-existing symptoms and diagnoses, medical records (when available) of potential cases in the Autoimmune Cohort will be reviewed from at least 2 years (rather than 1 year) prior to a subject's first dose of GARDASIL™.
3.6.2 Identification of Pre-specified, New-Onset Autoimmune Endpoints	Clarified that Case Review SOP will specify procedures for reconciling disagreements between the case reviewers with respect to the diagnosis or date of symptom onset. Removed statement that procedure will be majority rule; consensus or other approach may be preferable. (Final approach will be agreed upon by Case Review Committees and Safety Review Committee.)
3.7.1 General Safety Comparison Population	Added statement clarifying the value of using self-comparison approach.
3.7.1 General Safety Comparison Population and Figure 3-2 Footnote	For analyses using Day 1-60 risk periods, post-vaccination self-comparison person-time accrual will begin after a 60-day risk period and 30-day washout period after any dose (not limited only to last dose).
3.7.1 General Safety Comparison Population	Clarified that post-vaccination self-comparison periods for Day 0 and Day 1-14 analyses will require a health care visit day as much as possible, and that self-comparison period for Day 1-14 analyses will be 14 days in length.
3.7.2 Autoimmune Comparison Population	Added potential use of propensity score matching for autoimmune background cohort comparison (to help limit confounding).
3.7.2 Autoimmune Comparison Population; 4.2 Autoimmune Study Population Analysis	Deleted use of post-vaccination self-comparison for Autoimmune Cohort, after further evaluation of logistical feasibility. Deleted Figure 3-3 (Autoimmune Self-Comparison figure). Added statement to Section 4.2 that autoimmune post-vaccination self-comparison approach could be one of many options the Safety Review Committee can recommend if further evaluation of autoimmune conditions is needed after background rate comparison is undertaken.

SUMMARY OF CHANGES FOR AMENDMENT 1 (CONT.)

Protocol Section	Change
4.1.2 Relative Risks	Added Table 4-1 to summarize the analyses to be conducted in the study. Added separate analysis of each dose for Regimen Completer cohort, to assist in evaluating dose-specific safety. Removed redundant analyses from Regimen Completer cohort that are already planned for Regimen Initiator cohort (completers are a subset of initiators).
Global	"Incidence rates" replaced with "incidence" to reflect the possibility that for some analyses with limited person-time, risk ratios (based on number of events per number of subjects) may be used rather than rate ratios.
Global	Minor editorial revisions for clarification purposes.

TABLE OF CONTENTS

PAGE

TABLE OF CONTENTS (CONT.)

PAGE

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ADEM	Acute disseminated encephalomyelitis
AHA	Autoimmune hemolytic anemia
AS	Ankylosing spondylitis
CDC	Centers for Disease Control
CI	Confidence interval
CIOMS V	Council for International Organization of Medical Sciences
CPT	Current Procedural Terminology
CRC	Case Review Committee
EMEA	European Medicines Agency
FDA	Food and Drug Administration
GBS	Guillain-Barre syndrome
HCFA	Healthcare Financing Agency
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability & Accountability Act
HPV	Human papillomavirus
HCUP	Healthcare Cost and Utilization Project
IEC	Independent Ethics Committee
IRB	Institutional review board
ITP	Immune thrombocytopenia
JRA	Juvenile rheumatoid arthritis
MS	Multiple sclerosis
NDC	National Drug Code
RA	Rheumatoid arthritis
RR	Relative risk
SAE	Serious Adverse Event
SLE	Systemic lupus erythematosus
SOP	Standard operating procedures
SRC	Safety Review Committee
US	United States

SPONSOR CONTACT INFORMATION

PPD
PPD
P.O. Box 1000, UG1D-60
North Wales, PA 19454-1099
Telephone – Office: PPD
FAX No.: PPD

PPD
PPD
P.O. Box 1000, UG1D-60
North Wales, PA 19454-1099
Telephone – Office: PPD
FAX No.: PPD

PPD
P.O. Box 1000, UG1D-60
North Wales, PA 19454-1099
Telephone – Office: PPD
FAX No.: PPD

SYNOPSIS

Background and Rationale: GARDASIL™ is Merck's (the SPONSOR's) quadrivalent human papillomavirus (HPV) vaccine. The vaccine was approved in 2006 by the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the prevention of several diseases caused by HPV types 6, 11, 16, and 18 in females. In October 2009, the US FDA approved GARDASIL™ for use in boys and men, 9 through 26 years of age, for the prevention of external genital warts (condyloma acuminata) caused by HPV types 6 and 11. In December 2010, the US FDA approved GARDASIL™ for use in males and females, 9 through 26 years of age, for the prevention of anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16, and 18, and for the prevention of anal cancer caused by HPV types 16 and 18. This observational study of the safety of GARDASIL in males is a post-licensure regulatory commitment after the October 2009 approval of GARDASIL™ in males.

Study Setting: The study will be conducted in collaboration with PPD The study population will be drawn from a proprietary research database containing eligibility, pharmacy claims, and medical claims data from a large US health plan affiliated with PPD The study protocol will be submitted to an Institutional Review Board (IRB) for review and approval. The SPONSOR will not have access to any individual patient's medical information. The data will be analyzed by the study investigators and only aggregated data with no personal identifiers will be provided to the SPONSOR.

Objectives: The primary objective of this study is to describe the general safety of GARDASIL™ among males within 60 days following the administration of *each dose* of the vaccine by estimating: a) the incidence of health outcomes resulting in emergency room visits or hospitalizations occurring in combined 60-day risk periods after each dose of GARDASIL™; and b) the relative risk of such health outcomes as compared to incidence in a post-vaccination self-comparison reference period.

The three secondary objectives are:

1) To describe the general safety of a *first dose* of GARDASIL™ in males;

2) To provide descriptive epidemiology of 20 pre-specified new-onset conditions (collectively termed "autoimmune conditions" for the purposes of this protocol) for a period of 6 months after each dose of GARDASIL™, including comparison of incidence of these conditions to background incidence within the PPD male population of similar age distribution; and

3) To describe the general safety of GARDASIL™ on the day of vaccination in males.

Hypotheses: This is a descriptive observational study designed to provide data on the safety of GARDASIL™ in young males in the course of routine clinical practice. No formal hypotheses will be tested.

Committees: Study results will be provided for review and interpretation to the Safety Review Committee (SRC), an independent committee of experts, external to PPD and the SPONSOR, in charge of monitoring the safety data emerging from the study. In addition, several Case Review Committees (CRCs) will be comprised of independent, expert physicians, whose role will be to review redacted medical records to confirm potential diagnoses of the pre-specified autoimmune conditions of interest identified from the PPD database.

Study Subjects and Accrual: There will be no active enrollment of study subjects. Study subjects will receive GARDASIL™ as part of their routine medical care. Recipients of GARDASIL™ will be identified in PPD database. General safety will be monitored in two cohorts:

1) Regimen Initiators (any male health plan member with at least one dose of GARDASIL);

2) Regimen Completers (any male health plan member between the ages of 9 and 26 years at first dose, who completed the 3-dose vaccination regimen within a pre-specified period of time).

Pre-specified autoimmune conditions will be monitored within the Autoimmune Cohort, which is a subset of the Regimen Initiators cohort with at least one year of health plan membership prior to their first dose (to help identify pre-existing conditions).

Accrual of study participants will continue until the earliest of:

1) accrual of 135,000 males in the general safety Regimen Initiators cohort;

2) accrual of 44,000 males in the general safety Regimen Completers cohort; or

3) six years after study start date. Interim annual and final reports are planned.

Study Endpoints: The general safety endpoints are all health outcomes resulting in an emergency room visit or hospitalization in each of the following time periods immediately after vaccination (referred to as "risk periods") as follows: Days 1-60, Days 1-14, and Day 0 (for the conditions identified in secondary objective 3). These health outcomes will be grouped into pre-defined categories, using the Healthcare Cost and Utilization Project (HCUP) coding structure. HCUP is a comprehensive and well-established grouping structure that offers a pre-specified hierarchical grouping of all ICD-9 diagnosis codes into a manageable number of clinically meaningful categories.

For the autoimmune analysis (secondary objective 2), all pre-specified new onset conditions occurring within 180 days after any dose, as identified from outpatient, emergency room visits, or hospitalizations, will be evaluated.

Comparison Groups: For the analysis of general safety, the recipients of GARDASIL™ will serve as their own "controls" for any health outcome identified from emergency room visits and hospitalizations. For each general safety health outcome, the incidence rate of the health outcome observed during a post-vaccination self-comparison period will serve as a background rate to which the incidence rate observed in the risk periods immediately following vaccination will be compared. For the Day 1-14 and Day 0 risk period analyses, the post-vaccination self-comparison period will include a health care visit during that period to the extent possible.

For the autoimmune analysis, the comparison group will be an age-matched population of males from the health plan, not vaccinated with GARDASIL™ within the time period during which the autoimmune cases were vaccinated.

Data Analysis: For the general safety and autoimmune cohorts, descriptive statistics will be summarized in the study reports. When either the Regimen Initiator or Regimen Completer cohort accrues at least 22,000 males, incidence and relative risks will also be calculated. A multiplicity adjustment will be applied to take into account the large number of comparisons being made. However, all results (adjusted and unadjusted) will be included in study reports.

For the autoimmune analysis, incidence and relative risks will also be calculated. Propensity score matching is expected to be used for the background autoimmune comparison cohort.

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND

GARDASIL™ is Merck's quadrivalent human papillomavirus (HPV) vaccine. The vaccine was approved in 2006 by the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMEA) for the prevention of several diseases caused by HPV types 6, 11, 16, and 18 in females. In October 2009, the US FDA approved GARDASIL™ for use in boys and men, 9 through 26 years of age, for the prevention of external genital warts (condyloma acuminata) caused by HPV types 6 and 11. In December 2010, the US FDA approved GARDASIL™ for use in males and females, 9 through 26 years of age, for the prevention of anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16, and 18, and for the prevention of anal cancer caused by HPV types 16 and 18.

GARDASIL™ is an aluminum adjuvanted recombinant protein particulate (virus-like particle [VLP]) vaccine that contains 20 μg HPV 6 L1 VLP, 40 μg HPV 11 L1 VLP, 40 μg HPV 16 L1 VLP, and 20 μg HPV 18 L1 VLP, along with 225 μg of amorphous aluminum hydroxyphosphate sulfate [1]. GARDASIL™ is administered intramuscularly as a 0.5-mL dose according to the following schedule: 0, 2 and 6 months.

Human papillomavirus (HPV) is a family of small DNA viruses and is the most commonly detected sexually transmitted virus in men and women [2]. In men, HPV anogenital infection can result in anogenital diseases, including condyloma acuminata or anogenital warts, intraepithelial neoplasia, and carcinoma of the penis and anus [2]. These diseases are associated with substantial morbidity and mortality [3]. In females, persistent genital HPV infection can cause cervical cancer, other types of anogenital cancers and genital warts [2].

This study intends to build on the large body of safety experience from the administration of GARDASIL™ to females, including a large post-licensure observational safety study. In clinical trials involving the administration of GARDASIL™ to young males, the vaccine was generally well tolerated. No serious adverse events have been identified to be associated with GARDASIL™ in the randomized clinical trials involving over 3,000 young male recipients of GARDASIL™.

1.2 STUDY RATIONALE

This observational study is being conducted as a post-licensure regulatory commitment after the October 2009 approval of GARDASIL™ in males. This study will include males vaccinated with GARDASIL™ in a large US health plan. The objective of the study is to assess the safety of GARDASIL™ in the general population of males for whom the vaccine is approved.

1.3 STUDY SETTING

The study will be conducted in collaboration with PPD The study population will be drawn from a proprietary research database containing eligibility, pharmacy claims, and medical claims data from a large US health plan affiliated with PPD This study in males includes features that are methodologically similar to those used for the safety study of GARDASIL™ in females.

All of the statistical analyses will be performed by PPD Study results will be provided for review and interpretation to the Safety Review Committee (SRC), an independent committee of experts, external to PPD and the SPONSOR, in charge of monitoring the safety data emerging from the study.

2. OBJECTIVES AND HYPOTHESES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to describe the general safety of GARDASIL™ among males within 60 days following the administration of *each dose* of the vaccine by estimating: a) the incidence of health outcomes resulting in emergency room visits or hospitalizations occurring in combined 60-day risk periods after each dose of GARDASIL™; and b) the relative risk of such health outcomes as compared to incidence rates in a post-vaccination self-comparison reference period.

2.2 SECONDARY OBJECTIVES

The three secondary objectives of this study are:

1. To describe the general safety of a *first dose* of GARDASIL™ in males by estimating: a) the incidence of health outcomes resulting in emergency room visits or hospitalizations in the 60-day risk period following the first dose of GARDASIL™; and b) the relative risk of such health outcomes as compared to incidence rates in a post-vaccination self-comparison reference period.

2. To provide descriptive epidemiology of the following pre-specified new-onset conditions for a period of 6 months after each dose of GARDASIL™, including comparison of incidence of these new-onset conditions, identified from the outpatient, emergency room, and hospital setting, to background incidence within the PPD male population of similar age distribution. These pre-specified conditions are considered conditions of interest, although no safety signals have been found in the GARDASIL™ trials or in postmarketing surveillance. For ease and clarity of reference, these conditions will collectively be referred to as "autoimmune conditions" hereafter in this protocol, though it is acknowledged that they are actually a broader group of conditions.

    - Rheumatologic/autoimmune disorders: immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AHA), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), psoriatic arthritis, ankylosing spondylitis (AS), reactive arthritis, Crohn's disease, and ulcerative colitis;
    - Autoimmune endocrine conditions: type 1 diabetes, Hashimoto's disease, Graves' disease;
    - Autoimmune neurologic and ophthalmic conditions: multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), other demyelinating diseases of the nervous system, Guillain-Barré syndrome (GBS), neuromyelitis optica, optic neuritis, and uveitis.

3. To describe the general safety of GARDASIL™ on the day of vaccination (i.e., Day 0) among young males by estimating the incidence of the following health outcomes on the day of vaccination, and estimating relative risk of these health outcomes as compared to incidence rates in a post-vaccination self-comparison period:

    - Syncope, convulsive syncope;
    - Epilepsy, convulsions;
    - Head trauma;
    - Allergic reactions.

2.3 HYPOTHESES

This is a descriptive observational study designed to provide data on the safety of GARDASIL™ in young males in the course of routine clinical practice. No formal hypotheses will be tested.

3. PROTOCOL DETAILS

3.1 STUDY SETTING

This descriptive observational database study will be conducted at PPD The patients included in this study will be drawn from a proprietary research database containing eligibility, pharmacy claims, and medical claims data from a large US health plan affiliated with PPD The PPD database contains claims and enrollment data dating back to 1993. For 2008, there were approximately 14 million individuals within the database for whom both medical and pharmacy benefit coverage was available. The patient population in the database is geographically diverse across the US and fairly representative of the US population. Underlying information is updated frequently.

Within the PPD database, encounters with the health plan are associated with a combination of provider and procedure codes distinguishing hospitalizations and emergency room visits. For hospitalizations, claims associated with the health outcomes are identified between the beginning and end dates of a hospitalization. Each facility service record contains information on up to nine International Classification of Diseases Ninth Revision (ICD-9) diagnosis codes, with the primary diagnosis listed in the first position, and up to six procedures recorded with ICD-9-CM procedure codes, current procedural terminology (CPT) codes, or Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS) codes. The facility transactions contain each service category that the facility (e.g., hospital) listed on its claim for reimbursement, such as surgeries, radiologic procedures, laboratory tests, room and board charges, or other billed items.

The database provides the opportunity to link patient and physician survey data to pharmacy and medical claims, medical record data, socioeconomic measures, and clinical laboratory results. PPD research activities utilize de-identified data from the research database except in limited instances where applicable law allows the use of patient identifiable data.

The research database affords distinct research advantages. An important advantage is the large number of subjects that can be studied because the data are routinely collected and maintained in computerized data files. The completeness of the data allows PPD to investigate and link any number of patient, physician, and treatment attributes, while maintaining the de-identified nature of the data. The database also captures a longitudinal record of medical services, irrespective of treatment site.

3.2 INFORMED CONSENT

There will be no active enrollment or active follow-up of the study subjects, and no data will be collected directly from the study subjects. The study protocol will be submitted to an Institutional Review Board (IRB) by PPD for review and approval.

The SPONSOR will not have access to any individual patient's medical information except as part of an audit of the data. Procedures for data audits will be determined. The data will be analyzed by the study investigators and only aggregated data with no personal identifiers will be provided to the SPONSOR.

3.3 SAFETY REVIEW COMMITTEE (SRC)

An SRC that is external to the study will consist of independent experts in various relevant areas such as vaccine safety, immunology, pharmacoepidemiology, rheumatology, neurology, pediatric infectious diseases, or adolescent medicine. As much as possible, the SRC will consist of an odd number of voting members to avoid a tie in voting. In case of a tie, where the SRC consists of an even number of members, the SRC chair's vote will prevail. One of the SRC members will be selected as the chairperson in the first SRC meeting and will facilitate the subsequent meetings. The SRC chairperson will be selected by consensus among the SRC members.

The SRC will meet annually (or more often, if deemed necessary) to review data compiled by PPD in preparation for the annual interim reports and the final study report, and to assess any evidence that may be indicative of a potential signal. The assessment of safety will be made based on a process that is pre-specified in the SRC Standard Operating Procedures (SOP). **The possible relationship of an event to GARDASIL™ will be assessed by the SRC based on statistical and clinical judgment of a range of information elements, including biological plausibility, clinical relevance, statistical strength, adjustment for false discovery rate due to multiple comparisons, temporal relationship, and time distribution of the event after vaccination (i.e., the existence of a cluster or not).**

If the SRC determines that the data suggest a potential safety signal, further investigations may be conducted, as requested by the SRC. The investigation can include, but may not be limited to, assessment of the existence of a cluster, additional exploratory data analysis (such as SaTSCAN analysis), or medical record review (for example, to determine if a condition was pre-existing prior to vaccination with GARDASIL™ or to determine the nature of the condition resulting in a specific diagnosis code). In addition, the SRC may request case review or adjudication of diagnosis in the general safety portion of the analysis, if it identifies the need for additional information on certain general safety outcomes.

Annual interim study reports will be prepared subsequent to these meetings. The study investigators and the SPONSOR representative(s) will attend the SRC meetings as non-voting, observing members to provide information requested by the SRC and to answer questions that the SRC has about the study. An SOP adapted from that of the

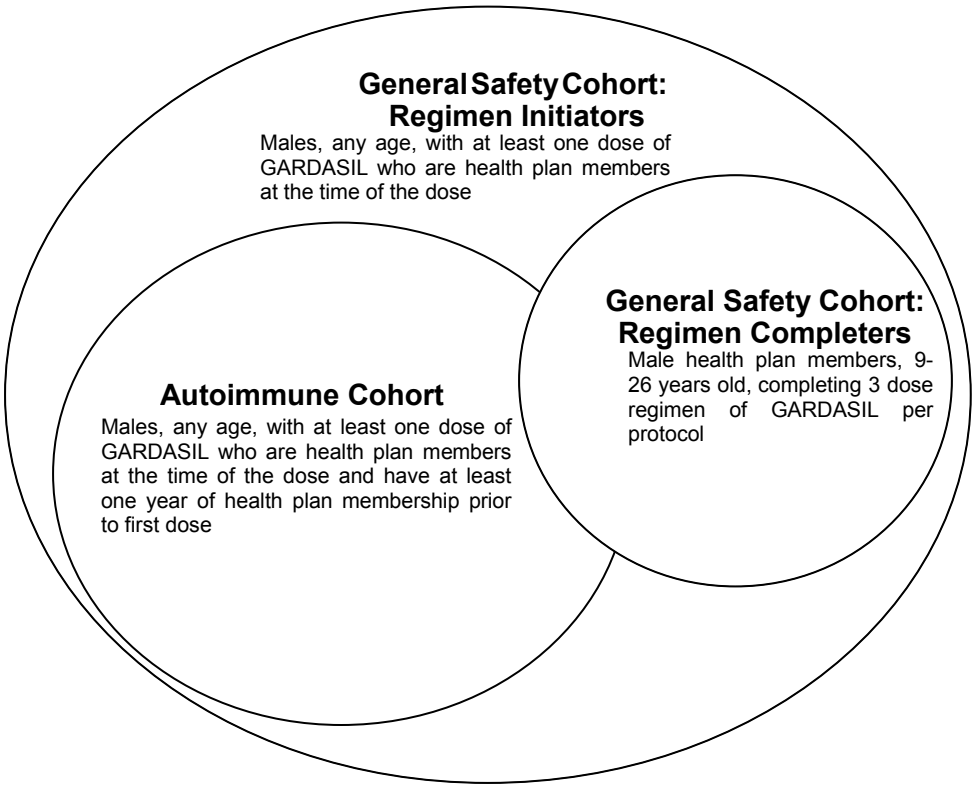
GARDASIL female post-licensure safety study will be developed for this study. The SOP will provide details regarding the assembly of the SRC, its roles and responsibilities, and voting procedures. The SOP will incorporate elements of the SPONSOR's Data Safety Monitoring Board Charter, as appropriate. This SOP will be written collaboratively by PPD and the SPONSOR, and approved by the SRC. The SOP will be finalized prior to the first meeting of the SRC, in advance of any review of data analysis undertaken for the study.

3.4 COHORT DEFINITIONS

There will be 2 general safety cohorts and one autoimmune cohort (not mutually exclusive) of males who received GARDASIL™, as described below (Figure 3-1).

Figure 3-1

Males in the PPD Database Vaccinated with GARDASIL™: Study Populations for the Post-licensure Observational Study of the Safety of GARDASIL™ in Males



3.4.1 General Safety Cohorts: Regimen Initiators and Regimen Completers

For monitoring general safety, there will be two cohorts:

1) **Regimen Initiators:** Males who received at least one GARDASIL™ vaccination administered after FDA licensure for males (October 2009). Males in this cohort will be required to be members of the health plan affiliated with PPD (hereafter referred to as "the health plan") at the time of GARDASIL™ receipt.

2) **Regimen Completers:** Male health plan members who received exactly 3 doses of GARDASIL™ after FDA licensure for males (October 2009). This cohort will be limited to subjects who received GARDASIL™ per protocol (male, 9-26 years of age at time of the first dose, the first and third dose administered within 12 months with intervals of at least 28 days between dose 1 and dose 2, 12 weeks between dose 2 and dose 3, and 24 weeks between dose 1 and dose 3). With the exception of the allowance of a 12-month interval between the first and third doses, this is the administration regimen recommended by the CDC Advisory Committee on Immunization Practices (ACIP) [4]. ACIP specifies a 6-month interval for regimen completion. A 12-month interval was selected for this study to provide sufficient flexibility for accrual within the Regimen Completers cohort, as not all 3-dose completers will adhere exactly to a 6-month completion regimen. Males in this cohort will be required to be continuously enrolled into the health plan (with allowance for standard grace periods that account for brief lapses in membership) through the receipt of all three GARDASIL™ doses.

3.4.2 Autoimmune Cohort

For evaluation of pre-specified, new-onset autoimmune conditions, the cohort will be the same as the general safety cohort of Regimen Initiators (at least one dose of GARDASIL™), except that the cohort will include only males who were members of the health plan during the 12-month period prior to their first dose of GARDASIL™. This membership criterion will assist in determining whether a condition is new-onset after receipt of GARDASIL™ or considered as pre-existing. A description of the autoimmune comparison population of male in the health plan who were not vaccinated with GARDASIL™ is provided in Section 3.7.2.

3.4.3 General Safety and Autoimmune Cohort Exclusion Criteria

As a general rule, all males vaccinated with at least one dose of GARDASIL™ after the approval of the male indication in the US will be included in the study.

For the general safety cohorts, the following exclusion criteria will apply:

- any females;
- males vaccinated prior to the FDA date of licensure of GARDASIL™ for males for the prevention of external genital warts (October 2009); and/or
- males who received all doses of GARDASIL™ outside of the health plan.

Specific to the Regimen Completers cohort, the following additional exclusion criteria will also apply:

- any male outside the 9-26 year old age range at first dose;
- males who were not health plan members at each GARDASIL™ dose;
- males who completed the 3-dose regimen of GARDASIL™ over a period greater than 12 months;
- males who had less than a 28-day interval between the first and second dose;
- males who had less than 12 weeks between the second and third dose; and/or
- males who had less than 24 weeks between the first and third dose.

For the autoimmune cohort of males vaccinated with GARDASIL™, the following exclusion criteria will apply (i.e., same as for general safety plus requirement of 12 months of health plan membership prior to vaccination):

- any females;
- males vaccinated prior to the FDA date of licensure of GARDASIL™ for males for the prevention of external genital warts (October 2009);
- males who received all doses of GARDASIL™ outside of the health plan; and/or
- males with less than 12 months of health plan membership prior to their first dose of GARDASIL™.

3.5 ACCRUAL OF STUDY SUBJECTS AND ACCRUAL TIMELINES

As specified by the FDA, accrual of study participants will continue until the earliest of:

1) accrual of 135,000 males in the general safety Regimen Initiators cohort;

2) accrual of 44,000 males in the general safety Regimen Completers cohort; or

3) six years after study start date (as further described in Section 3.9).

There will be no active enrollment of study subjects. Study subjects will receive GARDASIL™ as part of their routine medical care.

Recipients of GARDASIL™ will be identified in PPD database. Vaccination details, such as date of vaccination, are available in the electronic claims records.

3.6 STUDY ENDPOINTS

3.6.1 General Safety Endpoints and Risk Periods

The general safety endpoints for the Regimen Initiator and/or Completer cohorts are all health outcomes resulting in an emergency room visit or hospitalization in each of the three following time periods of interest, referred to as "risk periods":

1) on the date of vaccination (i.e., Day 0; *Note that Day 0 health outcomes are limited to pre-specified conditions, as further described below*);

2) on Days 1-14 after vaccination (starting at the first day after vaccination); and

3) on Days 1-60 after vaccination (starting at the first day after vaccination). An example of the Day 1-60 risk periods is shown in Figure 3-2.

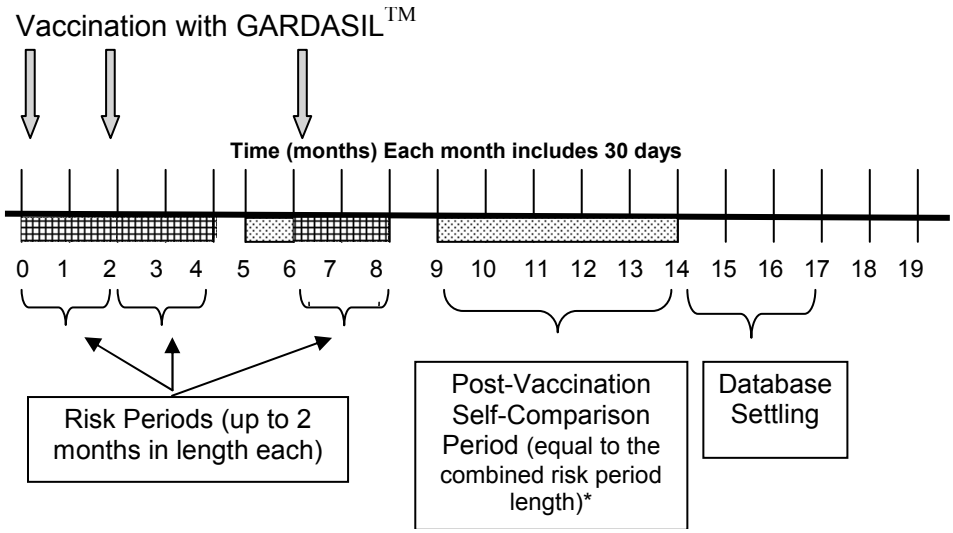
All health outcomes resulting in an emergency room visit or hospitalization will be evaluated, including venous embolism and thrombosis. This study will assess the incidence of the health outcome as defined by the first occurrence of the health outcome in the risk period of interest for a given subject. As a result, recurrences of health outcomes in the emergency room or hospital setting with the same diagnosis within this risk period will not be addressed (see Section 4.1.1 for further details). Also, if a subject receives his next dose of GARDASIL™ prior to the end of a risk period associated with a previous dose, the risk period associated with the previous dose will be truncated on the day prior to receipt of the next dose, to avoid overlapping risk periods.

Health outcome codes reported for an emergency room visit or a hospitalization during the risk (and self-comparison) periods will be identified using claims associated with the appropriate ICD-9 diagnosis codes. Within the claims database, site of medical care encounters may be identified by a combination of corresponding procedure codes and codes for site of care. For hospitalizations, claims associated with the health outcomes will be identified between the beginning and end dates of a hospitalization. ICD-9 codes associated with an emergency room encounter will also be evaluated.

Figure 3-2

General Safety Cohorts:
Example of Risk Periods and Post-Vaccination Self-Comparison Periods

(Length and timing of actual periods will vary according to number of doses received and vaccination schedule of each study subject)



*Post-vaccination self-comparison person-time will begin 91 days after each dose, thus allowing a 60-day risk window and 30-day "washout" period after each dose. In this example, the post-vaccination self-comparison time is the combined time of month 5-6 and 9-14.

ICD-9 diagnosis codes listed in any position (primary or secondary) in the database for an emergency room visit or a hospitalization occurring during the risk (or self-comparison) periods will be included in the general safety analysis, irrespective of whether it is a new diagnosis code for the patient or corresponds to a pre-existing condition or a prior episode of the health outcome. In addition, to provide interpretation context for the SRC for the primary general safety objective, the analysis will be re-run excluding chronic pre-existing conditions. The methods and decision rules for identifying and excluding chronic pre-existing conditions will be described in the study's Data Analysis Plan. The subject would still be included in analyses of all other health outcomes for which he does not have a pre-existing condition.

To facilitate the analysis and interpretation of results, all ICD-9 diagnosis codes listed for emergency room visits and hospitalizations occurring during the risk or self-comparison periods will be grouped into pre-defined health outcome categories, using the Healthcare Cost and Utilization Project (HCUP) coding structure [5]. HCUP is a comprehensive and well-established grouping structure that offers a pre-specified hierarchical grouping of all

ICD-9 diagnosis codes into a manageable number of clinically meaningful categories. The specific HCUP categories and subcategories of interest for this study will be pre-specified before any analysis is performed, with concurrence from the SRC.

For events occurring on the date of vaccination (Day 0), emergency room visits and hospitalization health outcomes of interest will be limited to pre-specified, syncope, convulsive syncope; epilepsy, convulsions; head trauma; and allergic reactions. These Day 0 health outcomes of interest were pre-specified based on consideration of temporal and biological plausibility for an association with an injection or vaccination.

Death among any study subject will also be identified for the period starting at the date of their first vaccination with GARDASIL™ and ending 60 days after their last vaccination. A short narrative will be prepared by PPD investigators, after appropriate approvals, summarizing relevant information from the subject's medical history, the cause of death as available in the PPD database, death certificate information (as available through the National Death Index), or other sources as available. This information will then be reviewed by an independent physician (i.e., not part of the study research team) to determine the cause of death. Given the lag time of up to two years in the state and national death registries, a complete accounting of deaths may require a supplemental report after the study end, to be delivered after the final study report.

3.6.2 Identification of Pre-specified, New-Onset Autoimmune Endpoints

Although there was no indication of an autoimmune safety signal in the clinical program or post-licensure safety data of GARDASIL™, new onset of the following conditions within 6 months after receipt of any dose of GARDASIL™ will be monitored:

(1) Rheumatologic: immune thrombocytopenia, autoimmune hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis and juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, reactive arthritis, Crohn's disease and ulcerative colitis.

(2) Endocrine: type 1 diabetes, Hashimoto's and Graves' disease.

(3) Neurologic/Ophthalmologic: multiple sclerosis, acute disseminated encephalomyelitis (ADEM), other demyelinating diseases of the nervous system, Guillain-Barré syndrome, neuromyelitis optica, optic neuritis, and uveitis.

Identification of potential new-onset cases

Potential cases will be identified from a pre-specified list of ICD-9 diagnosis codes for each of these conditions, using all possible medical encounters, including outpatient visits (since these conditions are often handled on an outpatient basis), emergency room visits, and hospitalization records. When appropriate, an expanded set of ICD-9 codes, CPT codes, laboratory codes, and/or pharmacy codes potentially indicative of these conditions will be used to increase detection sensitivity. Accounting of all potential cases will be reported. Subjects with a similar autoimmune condition identified from codes in the PPD databases within a 1-year period prior to their first dose of GARDASIL[1]

will be flagged, as their condition is likely a pre-existing condition, and not a new onset. Medical records from at least 2 years (when available) prior to the first dose of GARDASIL™ of all suspected new-onset cases will then be retrieved for review to confirm the diagnosis of the condition and the date of disease onset. If there is clear indication in the medical record that the condition was diagnosed before the first dose of GARDASIL™, that potential case will not be included for case review. In the event that a large number of potential cases of a particular condition are identified from this algorithm, a random sample of cases may be selected for review to facilitate the case review logistics.

Case review of potential new-onset cases

Potential new-onset cases will be reviewed by the Case Review Committees (CRC). There will be three CRCs: (1) Rheumatology; (2) Endocrinology; and (3) Neurology/Ophthalmology. The CRCs will be composed of independent physicians, masked to the GARDASIL™ vaccination status of each patient. The primary responsibility of the CRCs is to review redacted medical records of suspected cases of new-onset autoimmune conditions that occur in study subjects receiving GARDASIL™ during the timeframe of accrual of the general safety cohorts. The study investigators at PPD will select the CRC members for the study. The CRC members will be physicians with expertise in the particular conditions of interest, but will be independent of the study (i.e., they will not be part of the research team running the study).

Within each of the 3 CRCs, the reviews will be conducted independently by each of the 3 reviewers. The Case Review SOP will specify procedures for reconciling disagreements between the case reviewers with respect to the diagnosis or date of symptom onset. The CRC will determine the onset date of the condition (i.e., first symptoms suggestive of the condition), based on clinical manifestations and the time sequence of medical events and diagnoses. The roles and responsibilities of the CRC, and the procedures for case review and administrative procedures of the case review process will be pre-specified in an SOP.

Based on vaccination date (unavailable to the CRC), the PPD research study team will determine if the disease onset date assigned by the CRC precedes the first dose of GARDASIL™. Subjects who are confirmed as having an onset date of an autoimmune condition before receiving their first dose of GARDASIL™ will not be considered a post-vaccination new onset of that condition for this study.

3.7 COMPARISON POPULATIONS

3.7.1 General Safety Self-Comparison Period

For the analysis of general safety, the recipients of GARDASIL™ will serve as their own "controls" for any health outcome (HCUP code category) resulting in an emergency room visit or hospitalization. For each health outcome, the incidence rate of the health outcome observed during the self-comparison period will serve as a background rate to which the incidence rate observed in the risk periods immediately following vaccination can be compared. Use of a self-comparison group reduces the potential confounding

relative to an external comparison cohort since all group members will have received the vaccine. This means that whatever characteristics (both measured and unmeasured) are associated with receipt of the vaccine will be evenly distributed among the exposed and unexposed groups.

The post-vaccination self-comparison period will start 91 days after each dose of GARDASIL™. Figure 3-2 for an example in which the ACIP vaccination schedule is followed. This allows for a 60-day risk period and a 30-day "washout" period prior to the start of up to 3 self-comparison periods, each up to 60 days in length. Details of this approached will be included in the data analysis plan.

For analyses associated with Day 0 (Secondary Objective 3) and Day 1-14 health outcomes (a sub-analysis for the Primary Objective and Secondary Objective 1), a self-comparison period of 180 days in length would create an extremely uneven length of follow-up between the risk and comparison period and is expected to result in an imbalance of chance significant findings (i.e., more chance findings suggesting an increased risk following GARDASIL™) [6]. Therefore, an attempt will be made to balance the length of the risk periods in the analysis in the Day 0 and Day 1-14 analyses. The opportunity to have had a healthcare visit during the post-vaccination self-comparison period will be taken into consideration. For example, a day on which a doctor visit occurred during the self-comparison period will be used for outcome assessment for Day 0 analyses. Similarly, for the Day 1-14 analyses, the self-comparison period will be 14 days following the date associated with a physician visit if such visit occurred in the relevant time period. This approach will be further detailed in the study's Data Analysis Plan and may include use of simulations or developing similar length comparison periods. The methods will be finalized prior to undertaking any statistical analysis of the data.

3.7.2 Autoimmune Comparison Populations

To provide context for interpreting data on autoimmune cases identified in the risk periods, the rates of the pre-specified, new-onset autoimmune conditions will be estimated in a general cohort of age-matched males not vaccinated with GARDASIL™ (background rates). Propensity score matching is expected to be used for the comparison cohort analysis.

Background rates in the general population: Background rates of the autoimmune conditions will be estimated within an age-matched population of males, from the health plan, not vaccinated with GARDASIL™ within the time period during which the autoimmune cases from the vaccinated cohort were vaccinated. A sample of potential cases from the background population will be selected for case review to further refine the true incidence of each autoimmune condition in the background population. These potential background cases will be selected using similar methods as used for the autoimmune cohort (described in Section 3.6.2).

3.8 REPORTING OF SERIOUS ADVERSE EXPERIENCES

No reporting of individual cases to regulatory agencies is planned as part of this retrospective observational database study. This is consistent with the Council for International Organization of Medical Sciences (CIOMS V), which states that for epidemiological studies, individual case reporting is generally not appropriate unless there is specific attribution of an individual case (i.e., within the medical record). The study results will be included in a report at the end of study. Interim reports may be provided on an annual basis to the regulatory agencies until completion of the study. Aggregate reports may be provided to regulatory agencies in the Periodic Safety Update Reports (PSUR) as soon as available.

However, since the study specifies procedures for the case review of medical records for specific health outcomes of interest, there are certain circumstances in which serious adverse experiences (SAEs), if identified, will be reported. Specifically, for cases whose medical records are reviewed, if there is written notation in the medical record indicating that a health care provider attributed a serious adverse experience to any Merck product, then PPD would complete a serious adverse experience (SAE) report form (Attachment) and submit it within 24 hours to the Merck SPONSOR Contact by Fax or e-mail. (Note: the SAE form will not include identifying information such as names or phone numbers.) Merck Sponsor Contact will submit the SAE form to Merck Global Safety within 2 business days of receipt for reporting to worldwide regulatory agencies as appropriate.

For reference, an SAE is any adverse experience occurring at any dose that:

- †Results in death; or
- †Is life threatening (places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred; or
- †Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or
- †Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or
- †Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or
- Is a cancer; or
- Is an overdose (whether accidental or intentional).

ALSO: Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed

previously (designated above by a †). Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

3.9 STUDY START AND END DATES

The official study start date will be the date of IRB approval at PPD targeted to be no later than 2 months after the FDA has reviewed and approved the final protocol. The study end date will be when either the targeted sample size of 135,000 Regimen Initiators or 44,000 Regimen Completers in the general safety cohort is achieved. If this sample size is not achieved within 6 years of the official study start date, the study will be ended, with the end date being the sixth anniversary of the study start date.

3.10 REPORT TIMELINES AND CONTENTS

3.10.1 Annual Interim Reports

A series of annual interim reports will be developed. The annual interim reports will include information generated from the study for the time period starting at the date of FDA approval for use of GARDASIL™ in males (October 2009) and ending at a pre-specified cut-off date. For each annual interim report, the cut-off date will be the most recent one-year anniversary of the official study start date. Each annual interim report will be submitted within six months after the most recent annual cut-off date.

Each annual interim report will include:

- the number of males accrued in the general safety and autoimmune cohorts;
- a description of the demographic, health care use and general characteristics of vaccinees, put into perspective with the general male population of the same age at PPD by age categories;
- the numbers of events for each general safety health outcome observed within the risk windows with any available follow-up time prior to the cut-off date;
- the number of electronically identified potential new-onset autoimmune cases; and
- the number of new-onset autoimmune cases that were confirmed by the CRC prior to the cut-off date.

When 22,000 males in the general safety cohort of Regimen Initiators (i.e., at least one dose of GARDASIL™) are accrued at least 3 months in advance of any interim annual report cut-off date, the annual interim reports will also include:

- incidence and 95% confidence intervals for general safety events (emergency room visits or hospitalizations) in the risk and self-comparison periods; and
- relative risks and 95% confidence intervals for general safety events occurring in the risk periods relative to the self-comparison periods.

The 3-month lag time is required to allow sufficient analysis time. The accrual point of 22,000 males with at least one dose was selected to provide a preliminary assessment of general safety in a manner somewhat similar to the GARDASIL™ safety study for females. For females, an interim report was written after accrual and follow-up time was available for 22,000 females with 3 doses per protocol. The male population of 22,000 Regimen Initiators (rather than Regimen Completers with complete follow-up time) was selected to allow preliminary results to be presented sooner.

When 22,000 males in the Regimen Completers cohort are accrued at least 3 months in advance of any interim annual report cut-off date, preliminary results, including incidence and relative risks for this cohort will also be provided in the annual interim report, using an approach analogous to the Regimen Initiator approach described above. Once provided in an interim annual report, updated preliminary results on the Regimen Initiators and/or Regimen Completers will be provided in subsequent annual interim reports until the final report.

3.10.2 Final Report

A final report will be written and will include incidence and relative risk estimates for the final number of participants in the general safety and autoimmune cohorts as of the study end date. To allow for complete follow-up for general safety, database settling, and analysis time, the final report will be submitted within 24 months of the study end date, which will occur upon attainment of the target sample size or at study year 6, whichever occurs first. It is possible that a supplemental report may be needed after the final report to achieve full follow-up for deaths and/or the autoimmune population. The final report will replace the last interim report if the cut-off time for the final report is estimated to be less than 12 months apart from the cut-off time for the last interim report.

4. DATA ANALYSIS

The methods for data analysis will be detailed in the study's Data Analysis Plan. The Data Analysis Plan will describe statistical methods, data management and programming procedures and quality assurance/quality control procedures. The Data Analysis Plan will be finalized prior to undertaking any data analyses. An overview of the data analysis approach is presented in this section.

4.1 DATA ANALYSIS FOR GENERAL SAFETY COHORTS

4.1.1 Incidence

The incidence of all health outcomes that result in a hospitalization or emergency room visit during the risk and self-comparison periods will be described. Incidence will be calculated separately for health outcomes associated with hospitalizations and emergency room visits, as well as for hospitalizations and emergency room visits combined. For the analysis using combined hospitalizations and emergency room visits, if an emergency room visit results in a hospitalization for the same health care event, the event will be counted once to avoid duplication.

For each subject, the incidence of a health outcome in a given risk or self-comparison period will be defined as the first occurrence in the database of a code of the health outcome HCUP category, if any, during this study period. For each health outcome category, the incidence in both the risk and the post-vaccination self-comparison periods will be calculated as the number of first occurrences of the health outcome divided by the total person-time accrued from the study subjects under observation. For each event, accrued person-time for an individual will be calculated as the total number of days from the beginning of the risk or self-comparison period and ending at the earliest of: the end of the period, receipt of a subsequent dose of GARDASIL^{TM}, termination of membership in the health plan, occurrence of the health outcome of interest, death, or, for interim annual reports only, attainment of the pre-specified cut-off date for the report. A subject can have partially-missing risk or self-comparison periods and still be part of the analysis.

For analyses in which subjects may have more than one dose, each subject can contribute only once for each specific health outcome throughout the combined risk periods (i.e., maximum of one occurrence of each health outcome taken into account for each study subject). The denominator will be the combined at risk person-time accrued throughout the number of risk periods (or corresponding self-comparison periods) available for a given individual (censored upon occurrence of the outcome), which will depend on the number of doses received.

4.1.2 Relative Risks

Relative risks (RRs) will be calculated as the ratio of the incidence of the health outcome in the risk and self-comparison periods. Confidence intervals (CIs) will be calculated

using the mid-probability exact method. Consistent with the primary and secondary objectives, RRs and CIs (along with number of events and incidence) will be calculated for the analyses shown in Table 4-1.

For health outcomes occurring in the risk period but not in the self-comparison period (or vice versa), incidence for the period with one or more events will be calculated but relative risks will not be provided. Number of events will be displayed for all pre-specified HCUP categories of interest, even if no events occurred.

4.1.3 Multiplicity

To take into account the very large number of comparisons being undertaken in this study, a multiplicity adjustment will be applied to help interpret the safety findings. Details of the adjustment will be provided in the study's Data Analysis Plan. Both unadjusted and multiplicity-adjusted results will be presented to the SRC for review, and included in study report tables.

4.1.4 Deaths

As described previously, deaths among any study subject will be identified for the period starting at the date of their first vaccination and ending 60 days after their last vaccination. A short narrative will be prepared by PPD investigators, after appropriate approvals, summarizing relevant information from medical history, the cause of death as available in the PPD database, death certificate (as available through the National Death Index), or other sources as available. This information will then be reviewed by an independent physician (i.e., not part of the study research team) to determine the cause of death. A tabulation of information pertaining to the cause of death and timing of death with respect to vaccination with GARDASIL™ will be provided to the SRC. The SRC will review this information to determine if there is a potential safety association with GARDASIL™. No formal comparison will be made because of the anticipated small number of deaths.

Given the lag time of up to two years in the state and national death registries, a complete accounting of deaths may require a supplemental report after the study end, to be delivered after the final study report.

4.1.5 Sample Size and Power Calculations

Table 4-2 outlines the approximate power to detect increases in risks for health outcomes with a two-sided α=0.05 for a range of background incidence rates from 1 per 2,000 to 1 per 20,000. For a sample size of 132,000 males (or 44,000 males receiving 3 doses), the study will have 50% and 92% power to detect a relative risk of 2 and 3, respectively, for medical events with a known background incidence of 1 per 12,000 doses.

Table 4-1

Summary of Analyses to be Conducted for Study of Safety of GARDASIL in Males

Cohort	Comparator	Doses	Risk Period Length (after each dose)	Report*
Regimen Initiator	Self-comparison	All doses combined	Days 1-60 Days 1-14 Day 0 Sub-analysis screening out chronic pre-existing conditions (among HCUP codes with elevated relative risks): Days 1-60 Days 1-14	All interim annual reports with more than 22,000 regimen initiators accrued. Final report
Regimen Initiator	Self-comparison	Dose 1	Days 1-60 Days 1-14 Day 0 Sub-analysis screening out chronic pre-existing conditions (among HCUP codes with elevated relative risks): Days 1-60 Days 1-14	All interim annual reports with more than 22,000 regimen initiators accrued. Final report
Regimen Completers	Self-comparison	Dose 1, 2, 3 (each separate)	Days 1-60 Day 1-14	Final report
Autoimmune Cohort	Background cohort not vaccinated with GARDASIL	All doses combined	Days 1-180	All interim annual reports with more than 22,000 regimen initiators accrued. Final report

* Prior to accrual of 22,000 study subjects, descriptive analyses will be provided in Interim Annual Reports.

Table 4-2

Estimation of Statistical Power to Detect an Increased Risk of Medical Events in 132,000 Doses*

	Relative Risk			
Background Incidence per Dose**	**2**	**3**	**4**	**5**
1/2,000	100	100	100	100
1/5,000	90	100	100	100
1/10,000	60	97	100	100
1/12,000	50	92	99	100
1/15,000	38	81	96	99
1/20,000	31	72	92	98

* PASS 2008 Poisson Regression routine used; Relative Risks based on a 180 day window
** Background risk within a 2 month window

4.2 AUTOIMMUNE STUDY POPULATION ANALYSIS

The risk period for the autoimmune population begins the day after a GARDASIL™ dose and ends 180 days thereafter (Table 4-1). If more than one dose is administered to an individual in the autoimmune population during the time of accrual of the general safety cohort, the risk period associated with each dose will be evaluated for the autoimmune conditions. If there is less than 6 months between these doses, the risk period associated with a dose will be truncated at the subsequent dose. For calculation of person-time, the overlapped period will be counted only once.

The approach for comparing new-onset autoimmune conditions in the risk periods following vaccination to a non-vaccinated age-matched cohort will be detailed in the study's Data Analysis Plan.

In addition to evaluating rates of new-onset autoimmune conditions in the background comparison cohort, spatial/temporal techniques to assess the existence of clusters, analyses with a self-comparison cohort, or other analyses may be requested by the Safety Review Committee if an imbalance (which will be independently defined by the Safety Review Committee) is noted among the study groups for any of the pre-specified autoimmune events, even if not statistically significant.

5. ADMINISTRATIVE AND REGULATORY DETAILS

5.1 CONFIDENTIALITY

5.1.1 Confidentiality of Data

For Studies Conducted in the U.S.

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

By signing this protocol, the investigator affirms to the SPONSOR that information furnished to the investigator by the SPONSOR will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethics Review Committee, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section in the study agreement.

5.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; all identifying information will be masked prior to transmission to the SPONSOR.

For Studies Conducted in the U.S.

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time. ("HIPAA").

5.1.3 Confidentiality of Investigator Information

For All Studies

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site

personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the SPONSOR, and subsidiaries, affiliates and agents of the SPONSOR, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

For Multicenter Studies

In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

5.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review, and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects/patients, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the SPONSOR.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study, provide all data, and upon completion or termination of the clinical study submit any other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives

of the SPONSOR or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the SPONSOR as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) recommend that the investigator inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this SPONSOR's studies. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the SPONSOR prematurely terminates a particular trial site, the SPONSOR will promptly notify that site's IRB/IEC.

5.3 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

6. LIST OF REFERENCES

1. Bryan JT. Developing an HPV vaccine to prevent cervical cancer and genital warts. Vaccine 2007;25(16):3001-6.

2. World Health Organization. IARC monographs on the evaluation of carcinogenic risks to humans: volume 90, human papillomaviruses, 2007.

3. Palefsky JM. HPV infection in men. Dis Markers 2007;23:261-72.

4. Centers for Disease Control and Prevention. ACIP Provisional recommendations for HPV vaccine. Date of ACIP vote: October 21, 2009. Date of posting of provisional recommendations: December 1, 2009 [web-based report], 2009. http://www.cdc.gov/vaccines/recs/provisional/downloads/hpv-vac-dec2009-508.pdf

5. Agency for healthcare research and quality. HCUP.net Healthcare cost and utilization project (HCUP) 1993-2003 [homepage on the Internet], Rockville (MD), 2009. http://hcupnet.ahrq.gov/ [accessed 24-Mar-2010].

6. Li X, Chan ISF, Fireman BH, Gould LA, Maiese E, Baxter R, et al. Length of follow-up periods in safety studies can affect chance findings [Abstract]. Pharmacoepidemiol Drug Saf 2009;18:483.