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

Fifth Annual Interim Report

Data Accrual Period: 16-October-2009 through 31-December-2015
with Follow-up through 29-February-2016

Final Report Date: 09-December-2016

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1. LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ADEM	Acute disseminated encephalomyelitis
AHA	Autoimmune hemolytic anemia
AHFS	American Hospital Formulary Service
AHRQ	Agency for Healthcare Research and Quality
AIN	Anal intraepithelial neoplasia
AS	Ankylosing spondylitis
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CPT	Current procedural terminology
CRC	Case Review Committee
DAP	Data analysis plan
DFDR	Double False Discovery Rate
DMF	Death Master File
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
EMA	European Medicines Agency
ER	Emergency room
HCFA	Health Care Financing Agency
HCPCS	Healthcare Common Procedure Coding System
HCUP	Healthcare Cost and Utilization Project
HICL	Hierarchical ingredient code list
HIPAA	Health insurance Portability and Accountability Act
HPV	Human papillomavirus
ICD-9	International Classification of Diseases, Ninth Revision
ICD-9CM	International Classification of Diseases, Ninth Revision Clinical Modification
ICD-10	International Classification of Diseases, Tenth Revision
ICD-10CM	International Classification of Diseases, Tenth Revision Clinical Modification
ITP	Immune thrombocytopenia
IR	Incidence rate
JRA	Juvenile rheumatoid arthritis
KM	Kaplan-Meier
MMWR	Morbidity and Mortality Weekly Report
MRR	Medical Record Review
MS	Multiple sclerosis
NDC	National drug code
NDI	National Death Index
PPD	PPD
PPD	PPD Research Database
PHI	Protected health information
RA	Rheumatoid arthritis
RR	Relative rate
SLE	Systemic lupus erythematosus
SOP	Standard Operating Procedure
SRC	Safety Review Committee
SSA	Social Security Administration
TherSpec	First Databank Specific Therapeutic Class
UHC	United HealthCare
US	United States

VAERS	Vaccine Adverse Event Reporting System
VTE	Venous thromboembolism

2. EXECUTIVE SUMMARY

Background: GARDASIL® is a quadrivalent human papillomavirus (HPV) vaccine licensed by Merck. 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 an additional indication for GARDASIL®: use in boys and men, ages 9 through 26 years, for the prevention of external genital warts (condyloma acuminata) caused by HPV types 6 and 11. A further indication for GARDASIL® was approved by the US FDA in December 2010: 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.

On 21-October-2009, the Advisory Committee on Immunization Practices (ACIP) provided guidance that GARDASIL® may be given to males 9 through 26 years of age to prevent acquisition of genital warts, but the vaccine was not included in the routine immunization schedule for males.[1] Subsequently, on 25-October-2011, ACIP recommended routine use of GARDASIL® in males aged 11 to 12 years, and recommended vaccination among males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series; males aged 22 through 26 years may be vaccinated (reiterating the permissive vaccination recommendation for this age group). This recommendation was published 23-December-2011 in Morbidity and Mortality Weekly Report (MMWR).[2]

Merck received approval from the US FDA to market GARDASIL®9 (a 9-valent HPV vaccine) on 10-December-2014, for use in females (ages 9-26 years) and males (ages 9-15 years) for prevention of a range of conditions caused by HPV. This vaccine was subsequently recommended for routine use by ACIP (27-March-2015) in females and males (at ages 11 or 12 years) and may be started as young as 9 years or as old as 26 years (females) or 21 years (males). The impact of GARDASIL®9 availability on GARDASIL® use remains to be seen, but a transition from one vaccine to the other is likely to occur as existing stock of GARDASIL® is used and replaced by GARDASIL®9.

This is the 5th Annual Interim Report of an observational study of the safety of GARDASIL® in males conducted by PPD (Merck Protocol V501-070-01), which is a post-licensure regulatory commitment to the US FDA following the October 2009 approval for the use of GARDASIL® in males. This cohort study includes males who received GARDASIL® in the course of routine clinical care from 16-October-2009 through 31-December-2015 and were followed for study outcomes through 29-February-2016 (i.e., approximately 2 months from the last potential accrual date).

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 (ER) visits or hospitalizations occurring in the combined 60-day risk periods after each dose of GARDASIL®; and b) the rates of such health outcomes as compared to rates in a post-vaccination self-comparison reference period (relative rate).

The 3 secondary objectives of this study are:

1. To describe the general safety of a *first dose* of GARDASIL® in males;
2. To provide descriptive epidemiology of new onset of 20 pre-specified autoimmune conditions for a period of 6 months after each dose of GARDASIL®, including comparison of incidence of these conditions to background incidence within the male population; and
3. To describe the general safety of GARDASIL® on the day of vaccination (i.e., Day 0).

Data Source: Patients were drawn from a proprietary research database containing eligibility, pharmacy, and medical claims data from a large US health plan affiliated with PPD The PPD Research Database PPD contains claims and enrollment data dating back to 1993, capturing a longitudinal record of covered medical services, irrespective of treatment site.

IRB: The protocol and data analysis plan (DAP) for this study were approved by the PPD A Waiver of Patient Authorization to access medical records for abstraction purposes was obtained from The Privacy Board of the PPD

Review Committees: An external Safety Review Committee (SRC) comprised of 4 experts in adolescent medicine, vaccine safety, autoimmune conditions, and pharmacoepidemiology was established prior to the start of the study. The SRC's primary responsibility is to review and evaluate the safety data emerging from the study. Separate from the SRC, the Case Review Committees (CRCs) are independent committees of clinicians with expertise relevant to the autoimmune conditions being evaluated. The CRCs review medical records of suspected new onset cases of autoimmune conditions and, blinded to the vaccination status, determine the case's diagnosis and onset date according to the study's pre-specified adjudication procedure.

Methods:

Study Populations:

General safety outcomes were evaluated in the regimen initiator cohort, comprised of any male identified in the research database with at least one dose of GARDASIL® while enrolled in the health plan between 16-October-2009 and 31-December-2015. The Day 0 analyses were also conducted in the regimen initiator cohort. Autoimmune conditions were monitored in the autoimmune cohort, which is a subset of the regimen initiator cohort having at least 12 months of health plan membership prior to their first dose of GARDASIL®.

General Safety Outcomes:

General safety outcomes were identified by claims corresponding to an ER visit or hospitalization and the associated International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes. All of the specific diagnosis codes from these claims were grouped according to hierarchical, clinically meaningful categories developed by the Healthcare Cost Utilization Project (HCUP).[3] Four levels exist in the multi-level HCUP classification system, with increasing specificity in the higher levels: level one categories are the most broad, second-level categories are more specific than first-level categories, third-level categories are more specific than second-level categories, and fourth-level categories are more specific than third-level categories. Because the HCUP classification is hierarchical, health outcomes included in an HCUP level 4 category are also included in the corresponding levels 3, 2, and 1. On 01-October-2015, ICD-10CM replaced ICD-9CM as the recognized coding system for claims submitted to US insurers. Mapping of ICD-10 codes into HCUP categories has been conducted by the Agency for Healthcare Research and Quality (AHRQ), and is used in this study for data collected beyond 01-October-2015. The ICD-10 mapping by AHRQ was performed only for levels 1 and 2 of the HCUP hierarchy (mapping ICD-10 to level 3 and 4 categories was not conducted by the AHRQ, due to the increased specificity of ICD-10 and the changes in the ICD-9 and ICD-10 coding structures). In this Annual Interim Report, general safety analyses were conducted with all level 1 and 2 HCUP categories, and 3 selected level 3 and 4 categories that were custom mapped to ICD-10 codes by PPD 'otitis media and related conditions' (HCUP 6.8.1); 'cellulitis and abscess of arm' (HCUP 12.1.1.3); and 'concussion' (HCUP 16.4.1). These outcomes were selected because they had shown some elevation in at least one of the previous Annual Interim Reports. The general safety outcomes were identified in specific windows of time,

referred to as risk periods, that occur on Days 1-60 and Days 1-14 following each dose of the vaccine regimen (there is also a subset analysis following Dose 1 only). Each male contributing at least one risk period may also contribute post-vaccination self-comparison periods that are used for the Day 1-60 and Day 1-14 comparative analyses. Self-comparison periods consist of a time period following vaccination during which males are followed, and outcomes are tabulated for comparison to those observed in the risk period.

For general safety analyses among the regimen initiators, incidence rates (IRs) and associated 95% confidence intervals (CIs) were calculated for each outcome (i.e., HCUP category) as the number of first occurrences of the health outcome across the combined risk periods for each individual divided by the sum of the person-time accrued throughout the risk periods, for Days 1-60 and Days 1-14. The IRs and CIs were also calculated for the first occurrences of each health outcome during the post-vaccination self-comparison period. Relative Rates (RRs) were calculated as the ratio of the incidence rates (events divided by person-time) of the health outcome in the risk and self-comparison periods. Analyses were conducted after combining risk periods for doses 1-3 for each patient and separately after restricting to the risk period following the first dose.

Because the general safety analyses used outcomes identified by diagnosis codes that could represent pre-existing conditions or follow-up for health outcomes that occurred before vaccination, the analyses were repeated after excluding males with claims for the same HCUP category before or on the date of the first vaccine dose (referred to as “no prior codes cohort”). Specifically, males with codes for the same HCUP category up to 12 months prior to the first vaccination in any healthcare setting (outpatient visit, ER, or hospitalization) were excluded from the analysis for that HCUP category for the all doses combined in Days 1-60 and Days 1-14 analysis, and for Dose 1 in Days 1-60 and Days 1-14 analysis.

Unadjusted general safety results for Days 1-60 and Days 1-14 (including the general safety analyses excluding prior health outcomes) are presented along with adjustment for multiple comparisons. No adjustment for potential confounding variables is made since the risk and comparison periods arise from the same males, at times that differ by only a few months so that the change in age across compared time periods is unlikely to result in appreciable confounding.

Venous Thromboembolism (VTE) Outcomes:

VTE was identified among the general safety cohorts using ICD-9 and ICD-10 codes associated with an outpatient visit, ER visit, or hospitalization. Outpatient visits were included for this general safety outcome for consistency with the FDA’s Mini-Sentinel approach. VTE outcomes were evaluated in categories grouped by ICD-9 and ICD-10 codes rather than the less specific HCUP codes for VTE. Analyses for VTE included the post-vaccination risk periods: Day 1-60 and Day 1-14, for all doses combined. A post-vaccination self-comparison period was used similar to the general safety analysis. Medical records associated with VTE outcomes are being reviewed and adjudicated by clinical reviewers with relevant expertise.

Day 0 Outcomes:

Counts of pre-specified events (syncope, convulsive syncope, epilepsy/convulsions, head trauma, and allergic events) that occurred on Day 0 (the day of vaccination) were identified by ICD-9 and ICD-10 diagnosis codes associated with an outpatient visit, ER visit, or hospitalization corresponding to the diagnosis. These counts were assessed in contrast to a concurrent matched comparison cohort of males with a physician office visit for administration of another vaccine (Td/Tdap, meningococcal, or influenza (injectable)). Other Day 0 comparison groups were also used and results provided in an appendix. Analyses were repeated after excluding from each outcome category (syncope/convulsive syncope, epilepsy/convulsions, head trauma, and allergic

reactions) those patients who have codes for the same HCUP category in the 30 days prior to day of vaccination.

New-onset Autoimmune Condition Outcomes:
The occurrence of 20 autoimmune conditions was evaluated within 6 months after each dose of the vaccine among the autoimmune cohort and among a propensity-matched comparison group comprised of males of similar age to the autoimmune cohort matched at the time of a physician visit and who had not received a dose of GARDASIL® prior to the time of the matching. Autoimmune conditions were identified by ICD-9 and ICD-10 codes associated with an outpatient visit, ER visit, or hospitalization. Medical records of the suspected cases of autoimmune condition outcomes will be reviewed and adjudicated by the CRCs.

Death Outcomes:
Potential deaths among vaccinated males in the regimen initiator cohort were identified (by patient discharge status codes, ICD-9 and ICD-10 diagnosis codes, and using the Death Master File (DMF) from the Social Security Administration (SSA) from the date of first vaccination with GARDASIL® through 60 days after the last vaccine dose. Medical records associated with potential deaths are being reviewed by a clinician to identify date and cause of death. As requested by the SRC, an out-of-sequence National Death Index (NDI) search (NDI approval #2016-0018) was conducted to determine facts, date and cause of death for a regimen initiator who had a claim for death in 2014 and a claim for CPT 90649 (GARDASIL®) on the same day. This was implemented as a broader NDI search for all GARDASIL® recipients who disenrolled from the healthplan. A final NDI search will be conducted at the end of the study and summarized in the Final Report.

Results:
General Safety:
Given the increasing use of GARDASIL®9 since the end of 2014, the study may not meet either of its numerical stopping points (135,000 regimen initiators or 44,000 regimen completers) before its planned time-based stopping point (6 years from start in June 2011). However, the study has already accrued more GARDASIL® doses than assumed in the protocol power calculation (132,000). Between 16-October-2009 and 31-December-2015, a total of 189,892 doses of GARDASIL® were administered to the regimen initiator cohort of 106,110 males (an average of 1.8 doses each).

Eight HCUP categories had significantly elevated RRs (as assessed by the lower bound of the 95% CI of the RRs >1.00) and, of those, 4 HCUP categories were level 2 or higher categories embedded within a more general HCUP category that was also identified (see Summary Table 1). The Summary Table includes HCUP categories with at least one significantly elevated RR (denoted by bolding and/or shading); all related comparisons (including both risk periods, analysis in “no prior codes cohort”, and Dose 1 and all doses analyses) are shown for each HCUP category to provide context. There were no consistent elevations in RRs or trends observed in HCUP categories by risk period or dose (i.e., Dose 1 or all doses combined).

The 8 HCUP categories with significantly elevated RRs corresponded to ‘coma; stupor; and brain damage’ (HCUP 6.6); ‘ear conditions’ (HCUP 6.8); ‘otitis media and related conditions’ (HCUP 6.8.1); ‘skin and subcutaneous tissue infections’ (HCUP 12.1); ‘cellulitis and abscess of arm’ (HCUP 12.1.1.3); ‘injury and poisoning’ (HCUP 16); ‘concussion’ (HCUP 16.4.1); and ‘sprains and strains’ (HCUP 16.7). Following multiple-comparison adjustment, 4 HCUP categories remained statistically significant in the Days 1-60 for all doses combined analysis: ‘ear conditions’ (HCUP 6.8) (RR 1.32; 95% CI 1.05-1.67); ‘otitis media and related conditions’ (HCUP 6.8.1) (RR 1.55; 95% CI 1.03-2.35); ‘cellulitis and abscess of arm’ (HCUP 12.1.1.3) (RR 1.97 (1.02-4.02); and ‘concussion’ (HCUP

16.4.1) (RR 1.24; 95% CI 1.00-1.54). In last year's report there were 8 HCUP categories with at least one significantly elevated RR; 6 of the 8 HCUP categories in the current report had significantly elevated RRs in the last annual report.

Twenty-six HCUP categories had significantly decreased RRs, and 12 of those were embedded within a more general HCUP category that was also identified; 4 HCUP categories had RRs that remained significant after multiple comparisons adjustment: 'mental illness' (HCUP 5) (RR 0.74; 95% CI 0.63-0.87); 'diseases of musculoskeletal system and connective tissue' (HCUP 13) (RR 0.84; 95% CI 0.76-0.92); 'intracranial injury' (HCUP 16.4) (RR 0.45; 95% CI 0.24-0.82); 'concussion' (HCUP 16.4.1) (RR 0.35; 95% CI 0.17-0.67). In last year's 4th Annual Interim Report, there were 32 HCUP categories with decreased RRs; of those, 18 HCUP categories had significantly decreased RRs also in the current report.

VTE:

Through 31-December-2015, a total of 31 potential VTE cases in any risk period and 16 potential cases in any self-comparison period were identified, representing 21 and 10 unique males, respectively. Medical record review was conducted on the potential cases of VTE identified through 31-December-2014. Through 2014, a total of 21 potential VTE outcomes representing 20 unique males were identified in any risk or self-comparison period. Medical records were requested for all 21 potential cases and were obtained for 17 cases. Of these 17 potential cases, 11 VTE diagnoses were confirmed: 5 in the Day 1-60 risk period (1 of these outcomes occurred in the Day 1-14 risk period); 2 in the Day 1-60 self-comparison period; 2 in follow-up time that was neither a risk nor self-comparison period; and 2 that occurred prior to the first dose. Claims-profile review and medical record review continue to be conducted for new claims-based VTE outcomes identified. Results will be presented in future reports.

Day 0:

Doses of GARDASIL® among the regimen initiators were matched to a comparison cohort of male recipients of vaccines other than GARDASIL® (Td/Tdap, meningococcal, or influenza (injectable)) during a physician office visit (80% of doses were able to be matched). Among the GARDASIL® recipients (n=152,814 doses), there were 597 pre-specified emergent Day 0 outcomes (83 syncope, 76 epilepsy/convulsions, 121 head trauma, and 316 allergic reactions) for all doses combined, almost all of which (95%) occurred in the outpatient setting (as opposed to the ER or hospital setting). In the matched comparison cohort (n=152,814 vaccine visits), the count of Day 0 emergent outcomes was slightly higher (n=633): 101 syncope, 122 epilepsy/convulsions, 152 head trauma, and 252 allergic reactions. However, for the subset of Day 0 events that occurred on the day of dose 1, the total number of emergent outcomes among GARDASIL® recipients (460) was higher than among the comparison cohort (328); in particular, syncope, head trauma, and allergic reactions were more frequent among recipients of a first dose of GARDASIL® than among recipients of another vaccine (any dose) (syncope 77 vs. 56; head trauma 105 vs. 98; allergic reactions 221 vs. 107).

New-onset Autoimmune Conditions:

A total of 62,615 vaccinated males were eligible for the autoimmune cohort, accounting for 59% (62,615 of 106,110) of the initiator cohort. Of those, 52,679 males (84%) were propensity-score matched to an equal number of comparators with a physician visit (n=52,679). Overall, 214 potential new-onset autoimmune diagnoses were identified among the matched GARDASIL® vaccinated autoimmune cohort (n=52,679), and 279 were identified among the matched comparison cohort (n=52,679). Claims-profile review and medical record review and adjudication will continue for potential autoimmune outcomes. Results will be presented in future reports.

Deaths:
Nine potential deaths were identified among males vaccinated with GARDASIL® through this year's report. Among those, 3 deaths were confirmed by medical record review, 3 deaths were not confirmed because there was no indication of death in the available medical records, for one death outcome the medical chart was unavailable because the provider refused to release it, and medical records will be sought for the 2 potential deaths identified in this new report. An NDI Plus search was conducted at the request of the study SRC for the 7 potential deaths identified up to and including last year's report. This NDI search was broadened to all eligible regimen initiators who were accrued through 31-December-2014 and who were no longer enrolled in the health plan during the time period from 31-December-2014 through 29-February-2016 (n=34,166). Of the 7 potential deaths, the NDI search indicated a low probability of death for one outcome, and high likelihood matches for 5 claims-based deaths; one death identified in the claims database was ineligible for the NDI search because the patient was now covered by a healthplan that does not allow use of protected health information, and this potential death is still being investigated. For context, the expected number of deaths among the regimen initiator cohort in this year's report was calculated based on age-, sex-, and race-specific mortality rates from the US National Vital Statistics Report and on the person-time follow-up in the regimen initiator cohort. The results suggest that 9 deaths were to be expected, identical to the number of potential claims-based deaths observed among the GARDASIL® recipients. Medical record ascertainment is ongoing and results will be presented in future reports.

SRC Evaluation: The SRC reviewed this report's data at several meetings in the second half of 2016, issued requests for additional information and recommendations, and reviewed the final version of this Annual Interim Report. Overall, the SRC concluded that it had identified no safety concerns related to GARDASIL® through the results generated by this study.

Conclusion: This observational GARDASIL® safety study continues to accrue patients and doses as well as identify outcomes among the vaccine recipients and comparators. Study accrual and conduct has been consistent with the protocol. However, projections of future accrual based on current accrual rates may not materialize due to the increasing use of GARDASIL®9, a 9-valent HPV vaccine licensed to Merck by the US FDA at the end of 2014. Although this means that this study may not meet either of its numerical stopping points (135,000 regimen initiators or 44,000 regimen completers) before its planned time-based stopping point (6 years from start), the study has already accrued more GARDASIL® doses (189,892) than assumed in the protocol power calculation (132,000). The general safety outcome analyses suggest only chance findings or the consequences of vaccine timing relative to other healthcare services. The small elevations observed in the RRs for the general safety outcomes could be attributed to uncontrollable artifacts or other possible explanations, such as seasonality (e.g., timing of the risk period relative to the self-control period with respect to the increased number of injuries during the summer), chance, or pre-existing conditions. The observed decreased RRs for the general safety analyses may represent delayed workup for possible conditions identified at the vaccine visit, or the healthy vaccinee effect, or may be due to chance or uncontrollable artifacts. The VTE and autoimmune analyses are ongoing, pending case review and/or adjudication of study outcomes. The study data overall do not suggest an alteration in the existing safety profile of GARDASIL®.

Summary Table 1. Incidence Rates and Increased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Combined Potential ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
6.6	Coma; stupor; and brain damage	All Doses	9	1.25	3	0.47	2.64	(0.75-12.10)	29	0.97	11	0.44	**2.23**	**(1.13-4.64)**
		All Doses, no prior codes cohort[f] (N=106,028)	9	1.25	3	0.47	2.64	(0.75-12.10)	28	0.94	11	0.44	**2.15**	**(1.09-4.50)**
		Dose 1	7	1.74	2	0.55	3.15	(0.70-22.16)	18	1.07	7	0.46	2.30	(0.98-5.91)
		Dose 1, no prior codes cohort[f] (N=106,028)	7	1.74	2	0.55	3.15	(0.70-22.16)	17	1.01	7	0.46	2.17	(0.92-5.62)
6.8	Ear conditions	All Doses	44	6.12	28	4.42	1.38	(0.86-2.25)	188	6.31	120	4.76	**1.32**	**(1.05-1.67)**
		All Doses, no prior codes cohort[f] (N=93,749)	31	4.32	22	3.48	1.24	(0.72-2.17)	141	4.74	97	3.86	1.23	(0.95-1.59)
		Dose 1	25	6.20	20	5.50	1.13	(0.62-2.05)	110	6.53	84	5.57	1.17	(0.88-1.56)
		Dose 1, no prior codes cohort[f] (N=93,749)	17	4.22	16	4.41	0.96	(0.48-1.92)	80	4.75	70	4.65	1.02	(0.74-1.41)
6.8.1	Otitis media and related conditions	All Doses	16	2.22	7	1.10	2.01	(0.84-5.24)	64	2.15	35	1.39	**1.55**	**(1.03-2.35)**
		All Doses, no prior codes cohort[f] (N=100,444)	11	1.53	6	0.95	1.61	(0.60-4.72)	50	1.68	27	1.07	1.56	(0.98-2.53)
		Dose 1	9	2.23	5	1.38	1.62	(0.54-5.34)	39	2.31	21	1.39	1.66	(0.98-2.87)
		Dose 1, no prior codes cohort[f] (N=100,444)	5	1.24	4	1.10	1.13	(0.29-4.72)	29	1.72	19	1.26	1.37	(0.77-2.48)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and Utilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age with at least one dose of Gardasil.

[c]Only HCUP categories with at least one increased RR (lower confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false-discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males with codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) were excluded from the analysis for that HCUP category.

Summary Table 1. Incidence Rates and Increased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Combined Potential ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
12.1.	Skin and subcutaneous tissue infections	All Doses	37	5.14	25	3.95	1.30	(0.79-2.19)	132	4.43	97	3.85	1.15	(0.89-1.50)
		All Doses, no prior codes cohort[f] (N=102,270)	25	3.48	23	3.63	0.96	(0.54-1.70)	110	3.69	83	3.30	1.12	(0.84-1.49)
		Dose 1	24	5.95	10	2.75	**2.16**	**(1.05-4.73)**	84	4.98	58	3.85	1.30	(0.93-1.82)
		Dose 1, no prior codes cohort[f] (N=102,270)	15	3.72	9	2.48	1.50	(0.66-3.59)	68	4.04	50	3.32	1.22	(0.85-1.76)
12.1.1.3	Cellulitis and abscess of arm	All Doses	6	0.83	1	0.16	5.29	(0.78-122.41)	28	0.94	12	0.48	**1.97**	**(1.02-4.02)**
		All Doses, no prior codes cohort[f] (N=105,939)	6	0.83	1	0.16	5.29	(0.78-122.41)	28	0.94	11	0.44	**2.15**	**(1.09-4.50)**
		Dose 1	3	0.74	1	0.28	2.70	(0.29-71.20)	21	1.25	4	0.27	**4.70**	**(1.72-15.99)**
		Dose 1, no prior codes cohort[f] (N=105,939)	3	0.74	1	0.28	2.70	(0.29-71.20)	21	1.25	4	0.27	**4.70**	**(1.72-15.99)**
16	Injury and poisoning	All Doses	783	109.35	671	106.37	1.03	(0.93-1.14)	3,017	102.95	2,386	96.25	**1.07**	**(1.01-1.13)**
		All Doses, no prior codes cohort[f] (N=84,746)	471	68.45	428	70.89	0.97	(0.85-1.10)	1,955	69.17	1,569	66.00	1.05	(0.98-1.12)
		Dose 1	453	112.54	445	122.68	0.92	(0.80-1.05)	1,776	106.24	1,548	103.51	1.03	(0.96-1.10)
		Dose 1, no prior codes cohort[f] (N=84,746)	262	67.34	275	78.70	0.86	(0.72-1.01)	1,147	70.90	1,005	69.67	1.02	(0.93-1.11)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and Utilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age with at least one dose of Gardasil.

[c]Only HCUP categories with at least one increased RR (lower confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false-discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males with codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) were excluded from the analysis for that HCUP category.

Summary Table 1. Incidence Rates and Increased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Combined Potential ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
16.4.1	Concussion	All Doses	29	4.03	43	6.79	0.59	(0.37-0.95)	210	7.05	143	5.68	**1.24**	**(1.00-1.54)**
		All Doses, no prior codes cohort[f] (N=104,310)	29	4.03	41	6.48	0.62	(0.38-1.00)	201	6.75	138	5.48	1.23	(0.99-1.53)
		Dose 1	12	2.97	31	8.53	0.35	(0.17-0.67)	116	6.88	105	6.96	0.99	(0.76-1.29)
		Dose 1, no prior codes cohort[f] (N=104,310)	12	2.98	31	8.53	0.35	(0.17-0.67)	108	6.41	101	6.70	0.96	(0.73-1.26)
16.7	Sprains and strains	All Doses	250	34.80	196	30.98	1.12	(0.93-1.36)	900	30.33	683	27.22	**1.11**	**(1.01-1.23)**
		All Doses, no prior codes cohort[f] (N=98,495)	154	21.58	139	22.13	0.98	(0.78-1.23)	661	22.41	527	21.16	1.06	(0.94-1.19)
		Dose 1	147	36.47	141	38.81	0.94	(0.75-1.18)	541	32.17	450	29.90	1.08	(0.95-1.22)
		Dose 1, no prior codes cohort[f] (N=98,495)	75	18.71	94	26.04	0.72	(0.53-0.97)	381	22.78	327	21.86	1.04	(0.90-1.21)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and Utilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age with at least one dose of Gardasil.

[c]Only HCUP categories with at least one increased RR (lower confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false-discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males with codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) were excluded from the analysis for that HCUP category.

3. BACKGROUND

3.1. Product Description

GARDASIL® is a quadrivalent human papillomavirus (HPV) vaccine manufactured by Merck & Co. Inc. 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.

On 21-October-2009 the Advisory Committee on Immunization Practices (ACIP) provided guidance that GARDASIL® may be given to males 9 through 26 years of age to prevent acquisition of genital warts, but the vaccine was not included in the routine immunization schedule for males.[1] More recently on 25-October-2011, the ACIP recommended routine use of GARDASIL® in males aged 11 or 12 years, and recommended vaccination among males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series; males aged 22 through 26 years may be vaccinated. This universal recommendation was published 23-December-2011 in Morbidity and Mortality Weekly Report (MMWR).[2]

3.2. Overview of Annual Interim Report Content

This 5th Annual Interim Report is part of an observational study of the safety of GARDASIL® in males conducted by PPD (Merck Protocol V501-070-01), which is a post-licensure regulatory commitment to the US FDA following the October 2009 approval for the use of GARDASIL® in males. This 5th Annual Interim Report includes patient accrual from 16-October-2009 through 31-December-2015 with follow-up through 29-February-2016 (approximately 2 months after the end of patient accrual, to allow for the occurrence of potential health outcomes in the vaccinated cohort).

This report includes the following pre-specified data tables as described in the study protocol for Annual Interim Reports:

- Executive Summary section including a summary of the safety study results;
- The number of males accrued in the general safety cohorts (comprised of regimen initiators - males with at least one dose of GARDASIL®- and regimen completers - males completing the 3 dose regimen of GARDASIL®) and the autoimmune cohort (recipients of GARDASIL® with at least 12 months of health plan membership and comparators) (Tables 1-3);
- A description of the demographic, health care use, and general characteristics of vaccine recipients (regimen initiators), put into perspective with the general male population of the same age who has not been vaccinated with GARDASIL® (Tables 4a-4b);
- The number of events for each general safety health outcome by Healthcare Cost and Utilization Project (HCUP) categories observed within the risk and self-comparison windows.[3] Due to the pre-specified data cut-off dates, the post-vaccination self-comparison periods may be truncated (regimen initiators) (Tables 5a-6b);
- Incidence rates (IRs) and 95% confidence intervals (CIs) for general safety events Day 1-60 and Day 1-14 (emergency room (ER) visit and hospitalization outcomes combined) in the risk and self-comparison periods (regimen initiators) (Tables 5a-6b);
- Relative rates (RRs) and 95% CIs for general safety events occurring in the Day 1-60 and Day 1-14 risk periods relative to the self-comparison periods (regimen initiators) (Table 5a-6b);
- Among those with up to a 12-month baseline period, IRs and RRs and corresponding CIs for each general safety outcome among those without claims for the same HCUP category prior to the first dose (regimen initiators) (Tables 7a-8b);
- The number of claims-identified cases of venous thromboembolism (VTE) (regimen initiators) (Tables 9a, 9b, 9d);

- The number of VTE cases that were adjudicated and confirmed by physician specialists (regimen initiators) (Tables 9a, 9b, 9d);
- Narratives for VTE events identified in the risk or self-comparison periods (regimen initiators) (Table 9c);
- The number of claims-identified Day 0 outcomes in the regimen initiators and a concurrent control cohort (Tables 10a-d);
- Mortality summary among GARDASIL® recipients (regimen initiators) (Table 11a);
- Death case narratives among GARDASIL® recipients (regimen initiators) (Table 11b);
- National death rates and regimen initiator death rates (Table 11c);
- A description of healthcare utilization factors during the 12-month baseline period (autoimmune cohort and matched comparators) (Table 12);
- The number of claims-identified potential new-onset autoimmune cases by HCUP categories, and International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) codes (autoimmune cohort and matched comparators) (Tables 17-19);
- Summary tables for general safety results (separately for significantly increased and decreased RRs), VTE outcomes, Day 0 events, and autoimmune conditions (Summary Tables 1-5).

In this Annual Interim Report, all supportive data tables and figures are provided in Attachment 1 and appendices are included in Attachment 2.

Study Committees

The study's Safety Review Committee (SRC) is an external scientific committee comprised of 4 experts in adolescent medicine, vaccine safety, autoimmune conditions, and pharmacoepidemiology that was established for the study prior to any data analysis. The SRC's primary responsibility is to review and evaluate the safety data emerging

from the study. Separate from the SRC, the Case Review Committees (CRCs) are 4 independent committees of clinicians with expertise relevant to the autoimmune conditions being evaluated (i.e., gastroenterology, endocrinology, neurology, and rheumatology). The CRCs' primary responsibility is to review medical records of suspected new-onset cases of autoimmune conditions and, blinded to the vaccination status, determine the case's diagnosis and onset date according to the study's pre-specified adjudication procedure.

4. 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 ER visits or hospitalizations occurring in the combined 60-day risk periods after each dose of GARDASIL®; and b) the RRs of such health outcomes as compared to rates in a post-vaccination self-comparison reference period.

The 3 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 ER visits or hospitalizations in the 60-day risk period following the first dose of GARDASIL®; and b) the RRs of such health outcomes as compared to their incidence 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, ER, and hospital setting, to background incidence within a male population of similar age distribution (who did not receive GARDASIL®). 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 Annual Interim Report:

- 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;
- Gastroenterology conditions: Crohn's disease, 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, 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 RRs of these health outcomes as compared to their incidence in a post-vaccination self-comparison period:
   - Syncope, convulsive syncope;
   - Epilepsy, convulsions;
   - Head trauma;
   - Allergic reactions.

VTE is included as a general safety outcome, and deaths among the regimen initiators are summarized.

5. METHODS

5.1. PPD Research Database

This post-licensure observational study includes patients drawn from a proprietary research database containing eligibility, pharmacy claims, and medical claims data from a large US health plan (United HealthCare (UHC)) affiliated with PPD The PPD

Research Database PPD (formerly known as the PPD) contains claims and enrollment data dating back to 1993, capturing a longitudinal record of medical services, irrespective of treatment site. For 2014, there were approximately 12.3 million individuals within the database for whom both medical and pharmacy benefit coverage were available. The patient population in the database is geographically diverse across the US and corresponds well to the US population with respect to gender, age distribution less than 65 years of age, and census region. The underlying information is updated monthly.

Within the PPD type and site of medical encounters may be distinguished using a combination of provider, procedure, and site of care codes. For hospitalizations, claims associated with the health outcomes are identified between the beginning and end dates of a hospitalization. Each hospitalization record contains information on up to 9 ICD-9 or ICD-10 diagnosis codes associated with inpatient services, with the primary diagnosis listed in the first position, and up to 6 procedures recorded with ICD-9 Clinical Modification (ICD-9-CM) and ICD-10 Clinical Modification (ICD-10-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 PPD 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.

5.2. Institutional Review Board and Privacy Board Approval

The protocol and data analysis plan (DAP) for this study were approved by the PPD At least once a year, PPD submits documentation to the PPD in order to maintain approval status for this study. At the end of the study, PPD will submit closeout documentation to the PPD A Waiver of Patient Authorization to access medical records for abstraction purposes was obtained from The Privacy Board of the PPD Confidentiality of patient records will be

maintained at all times. Study reports contain aggregate data and outcome narratives, and do not identify individual patients or physicians. At no time during the study will the sponsor receive patient identifying information.

5.3. Overview of Study Populations

For this Annual Interim Report, 3 main cohorts of GARDASIL® recipients were created.

General safety outcomes were evaluated in 2 cohorts (i.e., general safety cohorts) (Figure A):

- Regimen initiator cohort: Comprised of any male identified in the research database who received at least one dose of GARDASIL® and who was a health plan member at the time of each dose; and

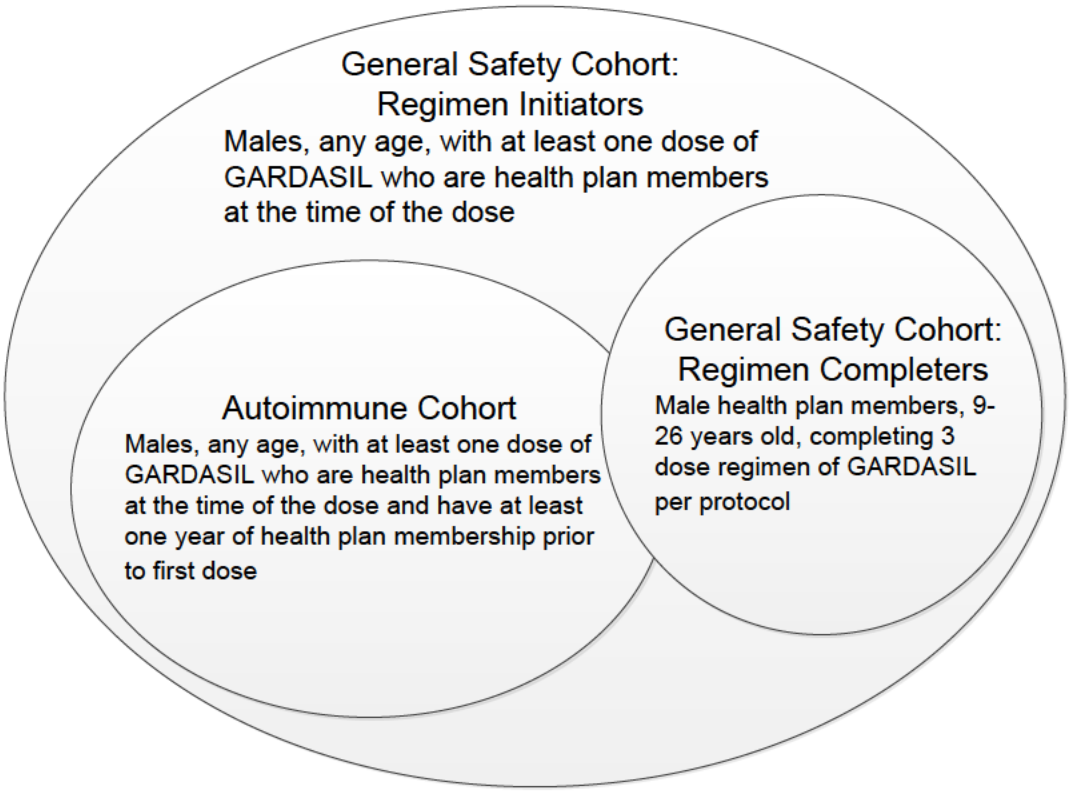
- Regimen completer cohort: Comprised of any male health plan member between the ages of 9 and 26 years at first dose of GARDASIL®, who completed the 3-dose vaccination regimen according to a pre-specified vaccine schedule (see Section 5.5).

Autoimmune conditions were monitored in the autoimmune cohort, a subset of the regimen initiator cohort comprised of males with at least 12 months of health plan membership prior to their first dose of GARDASIL®.

Accrual of study participants will continue until the earliest of:

1. Accrual of 135,000 males in the general safety regimen initiator cohort;
2. Accrual of 44,000 males in the general safety regimen completer cohort; or
3. Six years after the study start date (date of initial IRB approval; 23-June-2011).

Figure A. Study Cohorts with Gardasil Use



5.4. Regimen Initiator Cohort

The regimen initiator cohort is comprised of males in the database who received at least one GARDASIL® dose after FDA licensure (16-October-2009) and who were members of the health plan at the time of the dose (identification of subsequent GARDASIL® doses also require health plan membership). Males vaccinated with GARDASIL® were identified by the presence of insurance claims bearing the CPT code corresponding to quadrivalent GARDASIL® (CPT 90649) between 16-October-2009 and 31-December-2015 with follow-up through 29-February-2016. The 2 month period after the end of subject accrual (31-December-2015) allows for the identification of potential health outcomes even among patients accrued or vaccinated at the end of 2015. The date associated with the first claim for GARDASIL® is designated as the cohort entry date or index date and considered to be the first dose. Since the insurance claims do not specify which dose each vaccine is in a sequence, the dates of vaccination claims are used to determine the relative sequence of a dose in the vaccine series. Males in this cohort are further required to be members of the health plan affiliated with PPD at the time of GARDASIL® receipt, and have complete medical coverage and pharmacy benefits.

Males in this cohort contribute as many doses as they receive while they are health plan members. Specifically, this cohort includes:

- Any males who received at least one dose of GARDASIL®.

The following exclusions were applied to the regimen initiator cohort:

- Any females;
- Males vaccinated prior to 16-October-2009.

A second or third dose of GARDASIL® was counted if it occurred during a subsequent enrollment segment even with intervening gaps in enrollment exceeding 32 days in order to increase ascertainment of these later doses and their follow-up time.

5.5. Regimen Completer Cohort

The regimen completer cohort is a subset of the regimen initiator cohort comprised of male health plan members who received 3 doses of GARDASIL® between 16-October-2009 and 31-December-2015 with follow-up through 29-February-2016. Males in this cohort were continuously enrolled in the health plan through the receipt of all 3 doses. This cohort includes those meeting the following criteria:

- Males 9 to 26 years old at the date of first dose of GARDASIL®;
- Males with all 3 doses administered within 12 months (with a minimum of at least 28 days between Dose 1 and 2, 12 weeks between Dose 2 and Dose 3, and 24 weeks between Dose 1 and Dose 3). This schedule is consistent with the guidelines developed by the ACIP of the Centers for Disease Control and Prevention (CDC).

Specific to the regimen completer cohort, the following exclusion criteria were applied:

- Any male younger than 9 or older than 26 years of age at the date of first dose of GARDASIL®;
- 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;

- Males who had less than 24 weeks between the first and third dose.

5.6. Autoimmune Cohort

The autoimmune cohort is a subset of the regimen initiator cohort (i.e., males of any age who received at least one dose of GARDASIL® after 16-Oct-2009 and were health plan members at the time of each dose) comprised of males who had 12 months of continuous enrollment prior to their first dose (baseline period) of GARDASIL®. Specific to the autoimmune cohort, the following exclusion criterion was applied:

- Males with less than 12 months of continuous enrollment prior to their first dose of GARDASIL®.

5.7. Autoimmune Comparison Cohort

A propensity score-matched cohort of male health plan members not vaccinated with GARDASIL® was identified to calculate the background counts of autoimmune conditions (see Section 6.5.2 for Propensity Score Development). Males in this cohort could have received vaccinations other than GARDASIL®. This comparison cohort was identified from males enrolled in the health plan concurrently with the GARDASIL® recipients (i.e., between 16-October-2009 and 31-December-2015 with the potential for follow-up through 29-February-2016). The autoimmune comparison cohort includes:

- Any males with a physician office/outpatient visit, as defined by the presence of corresponding CPT codes; and
- A 12-month baseline period; and
- Complete medical coverage and pharmacy benefits to enhance comparability in access to medical care between the GARDASIL® recipients and the comparators.

The following exclusions were applied to the autoimmune comparison cohort:

- Any males vaccinated with GARDASIL® during the baseline period; and
- Males with any codes for a given autoimmune condition in the baseline period up to and including the day of cohort entry were excluded from the analysis for that condition.

The cohort entry date for the comparison group was the date of a physician office visit. The distribution of dates of cohort entry for the males not vaccinated with GARDASIL® in the autoimmune comparison was similar to the distribution of dates of office visits

corresponding to the first GARDASIL® date of vaccination for the vaccinated males in the autoimmune cohort. If a comparator receives a GARDASIL® vaccination after the cohort entry date, the follow-up time for that male is censored as of the date of the GARDASIL® dose.

5.8. Day 0 Comparison Cohort

Three comparison cohorts were identified as part of the general safety Day 0 analysis:

- Post-vaccination self-comparison period
- Concurrent control cohort #1: concurrent controls matched on age and calendar time on the day of the physician office visit (index date)
- Concurrent control cohort #2: concurrent controls matched on age and calendar time on the day of the physician office visit (index date) associated with administration of a vaccine other than GARDASIL® (Td/Tdap, meningococcal, or influenza (injectable)).

Of these 3 comparison groups, the concurrent control cohort #2 is included in the primary report table set as it appears to be the most suitable comparison group for Day 0 events. Per SRC recommendation during the review of the results of the 4th Annual Interim Report, comparisons to the other 2 groups are included in the Appendices (Attachment 2, Appendix I) for completeness, because they are considered of less relevant value and provide widely discrepant results. The results suggest that concurrent control cohort #1 may be biased because the reason for a young healthy male to visit a doctor when not receiving a vaccine will typically be either a routine physical exam or a health reason, such as a trauma or allergic reaction, while the office visit among GARDASIL® recipients will more often be for routine physical exam. Conversely, the self-comparison period not being anchored on any healthcare contact may be biased because of the likely absence of health outcomes during such a time period in young males who typically have infrequent healthcare contacts.

Concurrent Control Cohort with Outpatient Visit for Other Vaccine Administration

All males not vaccinated with GARDASIL®, but who received Td/Tdap, meningococcal, or an influenza (injectable) vaccine during the study period were eligible for inclusion in the concurrent control cohort #2 (see Appendix A for vaccine CPT codes and descriptions). Additional requirements included complete medical coverage and pharmacy benefits, as well as a physician office/outpatient visit during which at least one

of the above-mentioned vaccinations were administered (as defined by the presence of corresponding CPT codes). GARDASIL® doses were matched to comparators selected at random from the eligible males who had a physician office visit for a vaccine other than GARDASIL®, who were approximately the same age (within 1.5 years), and whose office visit occurred within 1.5 months of the GARDASIL® vaccination date. The date of the vaccine visit of the control served as Day 0 for the control (index date). GARDASIL® doses that could not be matched according to these criteria were excluded.

5.9. Outcome Definitions

5.9.1. General Safety

General safety health outcomes were identified by claims corresponding to an ER visit or hospitalization (defined by facility and procedure codes described in the DAP) and all of the associated ICD-9 and ICD-10 diagnosis codes using a well-accepted hierarchical classification developed by the Agency for Healthcare Research and Quality (AHRQ) as the Healthcare Cost Utilization Project (referred to as "HCUP" categories) (Appendix B). The HCUP coding classification has a hierarchical structure, splitting broad categories into more specific sub-categories to provide more detail about particular high-level categories. Four levels exist in the multi-level HCUP category system, such that the specificity of categories increases with the higher levels: level one categories are the most broad, second-level categories are more specific than first-level categories, third-level categories are more specific than second-level categories, and fourth-level categories are more specific than third-level categories. Health outcomes represented in a HCUP level 4 category are also represented in the corresponding levels 3, 2, and 1. General safety events were counted according to all level 1 and 2 HCUP categories, and pre-specified level 3 and 4 categories.

On 01-October-2015, ICD-10 was officially implemented in the US healthcare system. A similar mapping of ICD-10 codes into HCUP categories has been conducted by AHRQ and will be used in this study for data collected beyond 01-October-2015. Since tables reporting general safety analyses are based on the HCUP categories rather than the individual ICD-9 (or ICD-10) codes, and both ICD-9 and ICD-10 have been mapped to the same HCUP categories, integration of the 2 coding systems used within this study is possible. However, the ICD-10 mapping provides only the first 2 levels of the HCUP

hierarchy, levels 1 and 2 categories (mapping ICD-10 to levels 3 and 4 categories was not conducted by the AHRQ, see: https://www.hcup-us.ahrq.gov/toolssoftware/ccs10/ccs10.jsp). Therefore, the original level 1 and 2 HCUP categories selected for this study will remain the same. However, as approved by the SRC in March 2016, most of the level 3 and level 4 categories originally selected for this study will no longer be presented in analyses performed in 2016 onward, except for 3 categories that have shown a significantly higher incidence in the risk period in prior interim study reports: "otitis media and related conditions" (HCUP 6.8.1 of the ICD-9 version); "cellulitis and abscess of the arm" (HCUP 12.1.1.3); and "concussion" (HCUP 16.4.1). For each of these 3 level 3 or 4 HCUP categories, custom mappings of ICD-10 codes will be created to reproduce the ICD-9 codes included in the original ICD-9 HCUP category (See Appendix L for code lists).

For ICD-9, HCUP category 18 (residual codes, unclassified, all E codes) included a mix of ICD-9 diagnosis codes, status codes and injury codes (such as external causes of injury and poisoning including drowning, motor vehicle traffic accidents, and firearms). For increased clarity, 3 sub-categories were created for this study and used in previous reports: ICD-9 diagnosis codes for conditions such as organic sleep disorders, hallucinations, edema, nonspecific findings on examination of blood (referred to as HCUP 18.1), health status codes (referred to as HCUP 18.2), and external causes of injury codes (referred to as HCUP 18.3). However, due to the large number of heterogeneous codes that HCUP category 18 includes, it was not mapped to ICD-10. Indeed, with the transition to ICD-10, category 18 now has >7,500 codes, which are not easily parsed into the 3 initial subcategories (diagnosis codes, health status codes, and injury codes). As a result, we did not continue the division of HCUP 18 into the 3 sub-categories for ICD-10. The SRC suggested that future study reports should continue to present HCUP 18 and the 3 subcategories (HCUP 18.1, 18.2, and 18.3), but that these categories will not accrue person-time or counts of events beyond 01-October-2015 (date of ICD-10 transition).

A hospitalization may not have included an overnight stay if a patient was admitted and discharged from a hospital within the same day. For hospitalizations, claims associated with the health outcomes by HCUP category were identified between the beginning and end dates of a hospitalization. If an outcome occurred during a hospitalization that extended past the specified risk period (or comparison period) then the outcome was

counted if it occurred before the end of the risk or comparison period. For ER visits that led to hospitalizations (on the same day), the general safety diagnosis (by HCUP categories) was counted as a hospital claims-based event. If a male received multiple claims for the same outcome from the ER on different days, the first unique outcome was counted as a potential event. Similarly, if a male received multiple claims for the same outcome from an inpatient stay, the first event during the inpatient stay was counted. Males could have more than one outcome (different HCUP category codes) during a hospitalization, but only the first outcome within the same HCUP category was counted.

5.9.2. Venous Thromboembolism

Potential VTE outcomes were identified among the general safety cohorts using ICD-9 and ICD-10 codes associated with an outpatient visit, ER visit, or hospitalization (see Appendix C) during risk periods and post-vaccination self-comparison periods. If there were multiple claims for VTE on the same date then the outcome was assigned to a single place of service using the following hierarchy: hospitalization, ER visit, and outpatient physician visit. A diagnosis of VTE could occur in the post-vaccination risk or self-comparison period. The first VTE outcome claim within a period was considered and counted as a potential event, and sequences of claims occurring within 7 days of one another (regardless of site of care) were assumed to represent continuing care for a single event as an approach to balance sensitivity and specificity for identification of new VTE events. VTE outcome claims occurring more than 7 days apart were considered separate potential events. VTE outcomes were chart-reviewed and adjudicated by 2 clinicians.

5.9.3. Day 0

Selected events of interest occurring on the day of vaccination (Day 0) include:

- Allergic events (identified by ICD-9 diagnosis codes);
- Syncope (HCUP 17.1.1);
- Epilepsy (HCUP 6.4.1), convulsions (HCUP 6.4.2);
- Head trauma (HCUP 16.4 and 16.2.2).

Appendix D includes the HCUP categories and associated ICD-9 and ICD-10 codes for Day 0 events. Day 0 outcomes were identified by ICD-9 and ICD-10 diagnosis codes associated with an outpatient visit, ER visit, or hospitalization.

5.9.4. Autoimmune Conditions

Potential new-onset autoimmune conditions were identified among the autoimmune cohort and matched comparison group using ICD-9 and ICD-10 codes associated with an outpatient visit, ER visit, or hospitalization (see Appendix E-G for the specific codes). Autoimmune conditions will be chart-reviewed and adjudicated by members of the 4 CRCs. These conditions include:

- 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
- Gastroenterology conditions:
  - Crohn's disease
  - 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
  - Uveitis

5.9.5. Death

All subjects accrued are monitored for death beginning with the date of each subject's first dose of GARDASIL® through 60 days after their last dose. Along with the claims

data, additional information on the date of death was obtained for this report from linkage with the Social Security Administration Death Master File (SSA DMF)[7], a compilation of mortality information derived from the US SSA payment records. The SSA's DMF is a publicly available database containing more than 60 million death notices for individuals enrolled in the US Social Security program since 1936. The DMF is extracted on a quarterly basis from the Numident, SSA's master file containing identifying information about each individual to whom SSA has assigned a Social Security number. Introduced in 1988, the DMF supersedes earlier files used internally by Social Security personnel and contains information on deaths reported to SSA for beneficiaries and non-beneficiaries. Relatives of deceased individuals, funeral directors, financial institutions, and postal authorities are the primary sources of death information recorded in the DMF. Additional deaths are identified from computer files provided to SSA from a variety of government agencies.

Potential deaths were identified in the claims data and the SSA DMF using the following algorithm:

- An ER visit/inpatient admission with a discharge status of death (Patient Status Codes 20, 40, 41, 42); or
- An ICD-9 diagnosis code of sudden death (ICD-9 798.xx or ICD-10 R99); or
- An ICD-9 diagnosis code of cardiac arrest (ICD-9 427.5 or ICD-10 I46.2 or I46.8 or I46.9); or
- Identification of death using the SSA DMF (using a combination of the patient's Social Security number, date of birth, first and last name, middle initial, or first name (1st initial); and
    - The death occurred within 60 days following health plan disenrollment; and
    - No healthcare claims were received for the patient more than 30 days following the date of death identified by any of the above criteria.

If a death was identified in both the PPD and the SSA DMF, the date of death from the SSA DMF was selected. Deaths were identified until 60 days after the subject's last dose, and up to 60 days following health plan disenrollment. Potential deaths were chart-reviewed and narratives were written by a clinician who is a member of the CRCs.

As requested by the SRC, a specific National Death Index (NDI) search was recently conducted to determine facts, date and cause of death for a regimen initiator who had a claim for death in 2014 and a claim for CPT 90649 (GARDASIL®) on the same day. This NDI search was broadened to all eligible regimen initiators who were accrued through 31-December-2014 and who were no longer enrolled in the health plan during the time period from 31-December-2014 through 29-February-2016 (n=34,166). A final NDI search will be conducted at the end of the study and summarized in the Final Report.

5.10. Overview of Risk Periods and Comparison Periods

The risk period is a time period immediately following vaccination during which those vaccinated with GARDASIL® are followed, and claims-based diagnosis codes occurring after the vaccination are tabulated to count the occurrence of health outcomes. The self-comparison period is a time period more remotely following vaccination during which outcomes are tabulated for comparison to those observed in the risk period. In-between periods are neither risk periods nor comparison periods. General safety outcomes were counted by HCUP category. A male may have the same general safety outcome in the risk and comparison periods. Each subject can contribute only once to each specific HCUP category within a given period (i.e., risk or comparison). For the all dose analysis where risk (or comparison) periods after each dose are combined, if an outcome occurs in the first or second risk (or comparison) period, subsequent risk (or comparison) periods are censored for that same outcome entirely.

Males vaccinated with GARDASIL® but who do not have a self-comparison period are included in the analysis. For the regimen initiator group, the length of the comparison period is dependent upon the number of doses of GARDASIL® received, irrespective of the total length of the risk period. For example, if a male received a second dose of GARDASIL® 30 days following the first dose, the risk period corresponding to Dose 1 is censored at 30 days, but the corresponding comparison period is still 60 days. The risk and comparison periods for general safety outcomes were truncated at the date of the first occurrence of the diagnosis during the period of interest, or at the censor date if there was no diagnosis during the period. Males with up to a 32-day membership gap were considered to have continuous enrollment. This permits short periods (up to 32 days) of disenrollment that might arise for administrative reasons to be considered as continuous enrollment and not lead to patient censoring. The end of follow-up

(censoring) for risk periods and comparison periods are determined independently of one another. The censor date for both the risk and comparison periods is the earliest of:

- Death;
- Disenrollment from the health plan;
- Calendar date before receipt of subsequent dose;
- End of risk period or comparison period.

Due to the pre-specified dates for data cut-off in the conduct of this study, the duration of risk or self-comparison periods may be truncated before it reaches one of these censoring dates. However, a later report will fill in this truncated follow-up and include all of the eligible risk or self-comparison time. Furthermore, it is possible for events to shift between the self-comparison and risk period in subsequent reports due to data settling.

5.10.1. General Safety Cohort Risk Periods

Among the general safety cohorts, risk periods were defined starting in the period immediately following the receipt of each GARDASIL® dose:

- Day 1 (day following vaccination) - Day 14;
- Day 1 - Day 60.

Among the general safety cohort, the count of health outcomes by HCUP category was calculated as the number of first occurrences of the health outcome across the combined risk periods. General safety outcomes in the combined risk period were calculated by summing the outcomes in the individual risk periods occurring immediately after each dose as follows:

General Safety Cohort Combined Day 1-60 Risk Period:
(Day 1 through Day 60 after Dose 1) + (Day 1 through Day 60 after Dose 2) + (Day 1 through Day 60 after Dose 3)

General Safety Cohort Combined Day 1-14 Risk Period:
(Day 1 through Day 14 after Dose 1) + (Day 1 through Day 14 after Dose 2) + (Day 1 through Day 14 after Dose 3)

General Safety Cohort Combined Day 0 Risk Period:
(Day 0 after Dose 1) + (Day 0 after Dose 2) + (Day 0 after Dose 3)

In addition, general safety outcomes following Dose 1 were counted in a sub-analysis for the general safety cohort as follows:

General Safety Cohort Dose 1 Day 1-60 Risk Period:
Day 1 through Day 60 after Dose 1

General Safety Cohort Dose 1 Day 1-14 Risk Period:
Day 1 through Day 14 after Dose 1

General Safety Cohort Dose 1 Day 0 Risk Period:
Day 0 after Dose 1

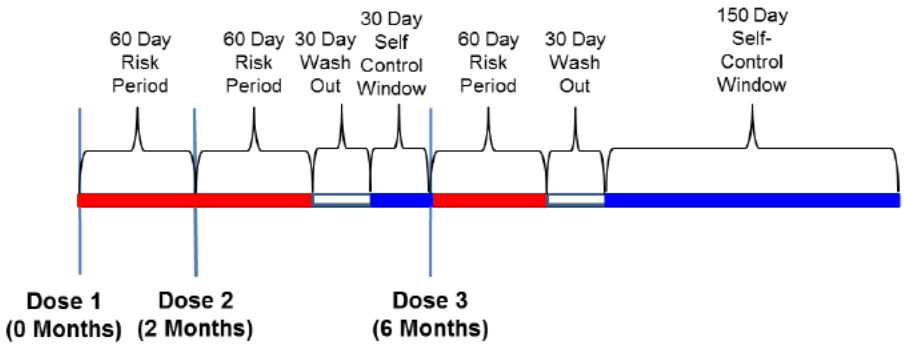
5.10.2. General Safety Cohort Self-Comparison Period

For the analysis of general safety outcomes among the general safety cohort, a post-vaccination self-comparison period was used as the comparison group. The self-comparison period started 91 days after the last dose of GARDASIL®, which allows for the risk period (e.g., 0, 1-14, or 60 days after the vaccination) and a washout period of 30 days prior to the start of the comparison period. The length of the comparison period time depended on the number of doses of GARDASIL® received, and not the total length of the risk period, so that the self-comparison period was fixed.

5.10.3. Day 1-60 Self-Comparison Period

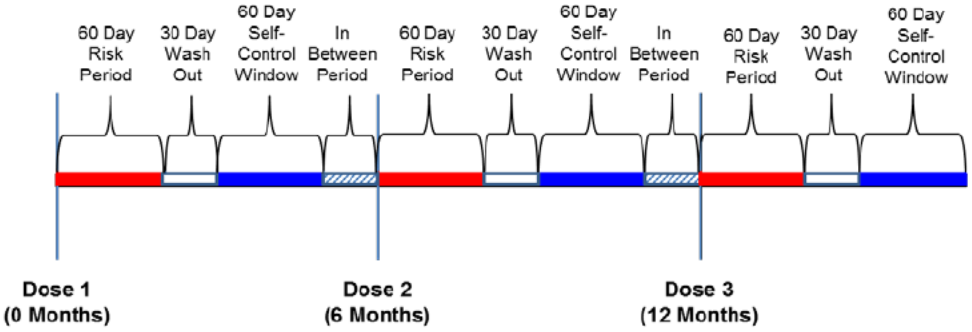
For the Day 1-60 analysis of general safety outcomes among the general safety cohort, a post-vaccination self-comparison period up to 180 days in length was used. Figure B shows a male following the recommended dosing schedule with the post-vaccination self-comparison period starting 91 days after each dose. Figure C depicts a male receiving doses at 0, 6, and 12 months rather than following the recommended dosing schedule. The duration of the comparison period was dependent on the total number of doses received. Among subjects with only one dose of GARDASIL®, the comparison period was 60 days, and among those with 2 doses, the comparison period was 120 days. Likewise, those who received 3 doses had a comparison period of up to 180 days in duration.

Figure B. Day 1-60 Risk and Comparison Periods for Males Following the Dosing Schedule[1,2,3,4]



[1]Figure includes possible scenarios where recipients received 1, 2, and 3 doses.
[2]Figure depicts general safety cohorts.
[3]Exceptions could occur.
[4]The washout periods represent time during which outcomes are not identified.

Figure C. Example of Day 1-60[1,2,3,4] Risk and Comparison Periods for Males not Following the Dosing Schedule

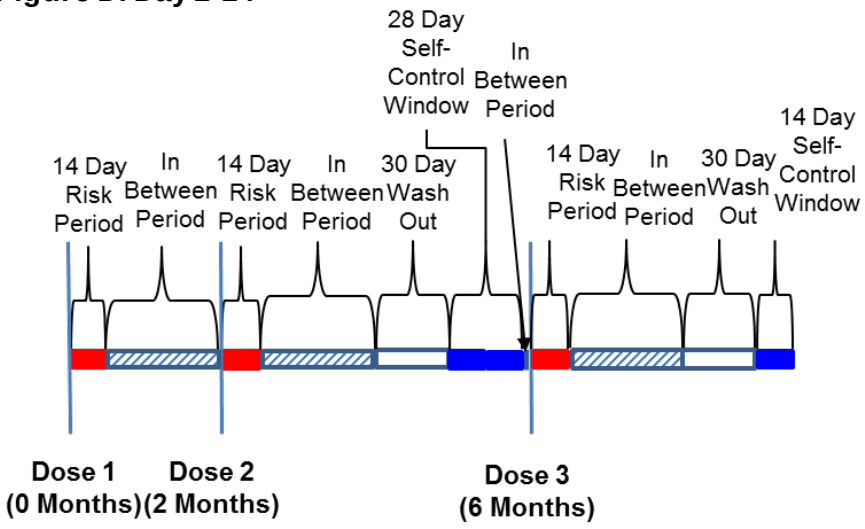


[1]Figure includes possible scenarios where recipients received 1, 2, and 3 doses.
[2]Figure depicts general safety cohorts.
[3]Exceptions could occur.
[4]The dashed lines and washout periods represent time during which outcomes are not identified.

5.10.4. Day 1-14 Self-Comparison Period

For the Day 1-14 analysis of general safety outcomes, a post-vaccination self-comparison period up to 42 days in length was used (Figure D), the maximum duration of which was dependent on the total number of doses received. Figure D shows a male following the recommended dosing schedule with the post-vaccination self-comparison period starting 91 days after each dose. Among subjects with only one dose of GARDASIL®, the comparison period was 14 days long, while among those with 2 doses and 3 doses, the comparison period was 28 days long and 42 days long, respectively.

Figure D. Day 1-14[1,2,3,4]



[1]Figure includes possible scenarios where recipients received 1, 2, and 3 doses.
[2]Figure depicts general safety cohorts.
[3]Exceptions could occur.
[4]The dashed lines and washout periods represent time during which outcomes are not identified.

5.10.5. VTE Risk and Self-Comparison Periods

Similar to general safety outcomes, VTE was evaluated among the general safety cohort during risk periods defined starting in the period immediately following the receipt of the GARDASIL® dose:

- Day 1 (day following vaccination) -60; and
- Day 1-14.

The Day 1-60 analysis of VTE outcomes among the general safety cohort included a post-vaccination self-comparison period up to 180 days in length. The duration of the comparison period was dependent upon the total number of doses.

For the Day 1-14 analysis of VTE outcomes among the general safety cohort, a post-vaccination self-comparison period up to 42 days in length was used. The duration of the comparison period was dependent upon the total number of doses.

5.10.6. Day 0 Risk Period and Concurrent Control Period

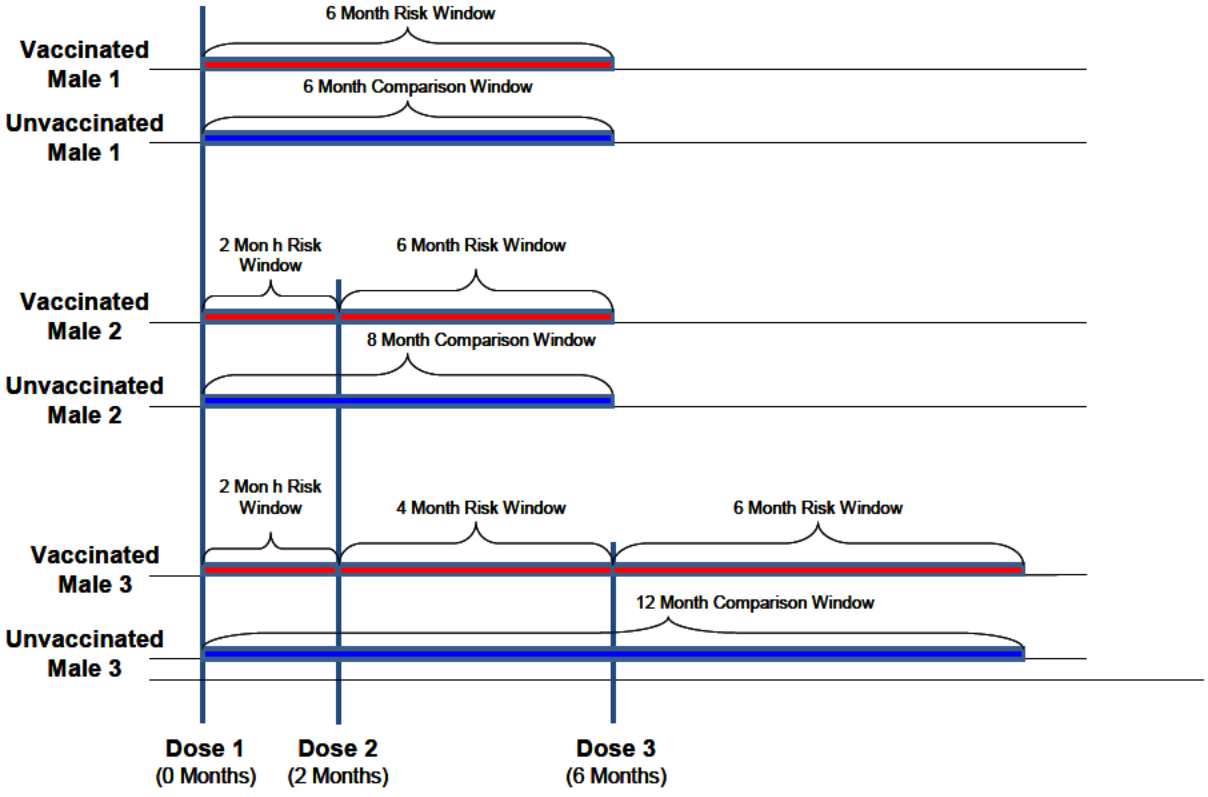
The risk period for selected events occurred on the day of vaccination (Day 0). General safety pre-specified Day 0 events were evaluated among concurrent control cohort #2 who had not received Gardasil at the time of cohort entry and who were matched on age within 1.5 years and calendar time (within 1.5 months of the vaccination date), on the

day of a physician office visit (index date) associated with another vaccine administration (Td/Tdap, meningococcal, or influenza (injectable)).

5.10.7. Autoimmune Population - Risk Period

Potential new-onset autoimmune condition outcomes that occur within 6 months after receipt of any dose of GARDASIL® were identified. The risk period for the autoimmune population began the day after a dose of GARDASIL® and continued until 183 days (6 months) after a vaccine recipient's final dose (Figure E). If more than one dose was administered to an individual during the accrual period, each risk period was evaluated for diagnosis codes of the specified autoimmune conditions. If there was less than 6 months between the doses, the risk period associated with the earlier dose was truncated at the subsequent dose. The total length of the risk period was a maximum of 18 months. If there was more than 6 months between doses then the risk period associated with the earlier dose was censored at 6 months.

Figure E. Autoimmune Population - Risk and Comparison Periods[1]



[1]Figure includes possible scenarios where recipients receive 1, 2, and 3 doses.

5.10.8. Autoimmune Population - Comparison Period

A propensity score-matched cohort of males not vaccinated with GARDASIL® was identified as a comparison group for the autoimmune cohort. Figure E represents a potential illustration of the follow-up for the GARDASIL® and comparison cohorts. To account for variations in vaccination administration schedules, the comparison cohort was followed for up to 18 months (corresponding to the potential follow-up among the GARDASIL® recipients - 3 doses with 6 non-overlapping months of follow-up each). Observed patterns of GARDASIL® administration may suggest an alternate number of months for the end of comparison cohort follow-up for future reports. If a male in the autoimmune comparison cohort received a dose of GARDASIL® then the comparison period was censored at the date of vaccination.

5.11. Medical Chart Abstraction and Adjudication

5.11.1. Autoimmune Outcomes

Although a 6-month risk window will be utilized in the risk calculation for autoimmune outcomes, all potential autoimmune events occurring (during health plan enrolled period) up to one year following the receipt of the third dose of GARDASIL® will be initially identified from the underlying database to help ensure capture of all outcomes (including those initially identified outside of the 6-month risk windows). Likewise, autoimmune conditions among the general population cohort are identified using the same algorithm and diagnosis codes as for the autoimmune population cohort within the corresponding follow-up period. Medical records are then obtained for review and adjudication of potential new-onset autoimmune outcomes. Medical records are being reviewed by members of the CRCs to determine the outcome diagnosis and whether the outcome was new onset, and if so, to determine the date of symptom onset and the date of disease diagnosis in order to ascertain the temporal relationship between the vaccination and disease onset. The details of the review and adjudication procedures of potential autoimmune cases are provided in the CRC standard operating procedure (SOP).

Claims Profile Review

In the first stage of the medical abstraction process, the electronic claims record for each potential case is examined (claims-profile review). For patients with potential outcomes, chronologic listings of their electronic health claims including medical claims, and

pharmacy claims are examined by a clinical consultant (a nurse with experience reviewing claims profiles) in order to determine the medical site of care most likely to yield medical records with the necessary information to confirm case status. Additional details of the claims-profile review and medical chart abstraction processes are provided in the CRC SOP.

Abstraction of Medical Chart Data for Potential Autoimmune Condition Cases

Medical records marked for abstraction during the claims-profile review are sought to confirm or refute autoimmune condition outcome events identified electronically.

Adjudication

This report does not include adjudication results for autoimmune outcomes. After the 3rd Annual Report (December 2014), the SRC made several recommendations about the adjudication process that have been implemented and the CRC SOP was updated accordingly (see details below). The review and adjudication of a sample of autoimmune outcome cases using the new SOP is being performed by the CRCs for evaluation by the SRC prior to initiating the review of all potential cases in the study. Once the reviews are completed, the chart review results will be included in future reports.

The structure of the CRCs was revised to expand both the number of specialties represented and the number of specialists reviewing cases. With the addition of a gastroenterology CRC, 4 separate CRCs were designed, one for each of the specialties covering the autoimmune conditions to be reviewed in the study: rheumatology, gastroenterology, endocrinology and neurology. Each specialty CRC is now composed of 3 or more physician specialists of that specialty. In addition, the new and existing CRC members have reviewed and revised the diagnostic criteria within the CRC SOP to align with the most current published guidelines. As part of the update of the CRC SOP, the number of charts sought for each potential new-onset case was also increased to optimize the information available to CRC reviewers, and additional blinding of all vaccination information within the medical records was performed. The CRC SOP was updated to incorporate all the changes, and training of the CRC reviewers to the new procedures was conducted.

The updated CRC SOP is currently being evaluated through the review and adjudication of a sample of autoimmune outcomes (n=10 cases from each autoimmune condition

group to be reviewed by the appropriate CRC subcommittee) and the writing of the narratives. The SRC will review the narratives from this sample of cases to evaluate the new CRC SOP. Once the CRC SOP evaluation is completed successfully, the CRCs will review all potential new-onset autoimmune cases in the study. When reviews are completed, the results will be presented in future reports.

5.11.2. VTE Outcomes

VTE was included as a general safety outcome of special interest because of the suggestion of a potential increased risk in females vaccinated with GARDASIL® in previous publications[8]. In this context, it was decided to consider VTE as a general safety outcome of special interest in the male safety study. A recent assessment of VTE in females after receipt of GARDASIL® was conducted by the FDA's Mini-Sentinel program and found no evidence of an increased risk of VTE among females 9-26 years of age[9]. For the current study, additional details of the claims-profile review and medical chart abstraction processes are provided in the Medical Record Review (MRR) SOP. Medical records were ascertained to confirm or refute the VTE outcome for outcomes identified during the follow-up time for the prior annual report (16-October-2009 to 28-February-2015).

Claims Profile Review

In the first stage, the electronic claims for each male with a potential VTE outcome in the risk or comparison period was examined (claims-profile review). If a male had more than one claim for VTE within a risk period, the first claim for VTE was selected and a profile created for that outcome. If there were claims for VTE during the risk and comparison periods then a separate claims-profile was generated for each potential outcome. During the claims profile review, a clinical consultant conducted a detailed review of the listing of claims in order to determine the medical site of care most likely to yield medical records with the necessary information to confirm case status.

Abstraction of Medical Chart Data for Potential VTE Cases

Medical records marked for abstraction during the claim-profile review were sought for review by physician specialists to confirm or refute all potential VTE outcomes identified electronically in both the risk and comparison periods.

Adjudication

Two physicians reviewed the medical records of potential VTE cases redacted for personal identifying information and vaccine administered. Additional details of the review and consensus process are provided in the MRR SOP. After completion of the review, narratives were prepared by one of the physicians summarizing relevant information from the subject's medical chart. A vascular specialist reviewed the narratives and edited them as needed.

5.11.3. Day 0 Outcomes

As a reminder, included in the 4th Annual Interim Report (December 2015), a sample of medical records for Day 0 - Dose 1 outcomes was sought to determine the nature and timing of the potential events relative to vaccination. Dose 1 outcomes were selected, since these males may not have received a subsequent dose if an outcome occurred. A sample of 10 medical records for Day 0 - Dose 1 syncope and head trauma outcomes among each of the regimen initiators and concurrent controls with another vaccine (Td/Tdap, meningococcal, or influenza) was sought. In addition, for only the regimen initiators, medical records for Day 0 - Dose 1 allergic reaction outcomes identified by ICD-9 code 995.0 (n=2) (other anaphylactic shock not elsewhere classified, includes adverse effect of medicinal substance), and a sample of 10 medical records for Day 0 - Dose 1 allergic reaction outcomes identified by ICD-9 code 995.3 (allergy, unspecified not elsewhere classified) were sought.

Case review processes were followed as outlined in the MRR SOP. One of the CRC clinician specialists prepared a narrative for each Day 0 outcome summarizing relevant information from the subject's medical history and the nature and timing of the event relative to vaccination.

5.11.4. Death

Details of the review of potential deaths among regimen initiators are provided in the MRR SOP. Medical records were ascertained to confirm electronically identified death outcomes. For each potential death where a medical chart was abstracted, a short narrative was prepared by a physician summarizing relevant information from the subject's medical history and the cause and timing of death as available. At the SRC's request, while waiting for the medical chart information, a preliminary narrative was also prepared by a physician, summarizing information from the subject's medical claims

history. The medical claims history is derived from the claims database and as such, readily provides some information regarding the subject's health care associated with their claims. Even though the claims history is not the subject's medical chart, it provides preliminary information on the case that is particularly useful for claims-based potential deaths identified in the current round of analysis for which medical charts are not available yet.

6. DATA ANALYSIS METHODS

6.1. Cohort Accrual

The counts of regimen initiators and the autoimmune cohort are stratified by age (9-26 years, < 9 years, > 26 years) at first dose of GARDASIL® and by the dose number (1, 2 or 3). Age among the vaccinated cohort is defined as the age at first dose. The count of males with Dose 1 includes those with at least one dose of GARDASIL® during the data collection interval, while the count of males with Dose 2 includes those with at least 2 doses of GARDASIL®, so the counts are not mutually exclusive. Males in the regimen completer cohort received 3 doses of GARDASIL®; tabulation of this population is stratified by age at first dose. To provide context, an age-stratified tabulation of the number of males in the underlying PPD population is also provided, with age defined as of 31-December-2015, the end of the accrual period.

6.2. Regimen Initiator Cohort

6.2.1. Baseline Characteristics

In order to provide background characteristics of the underlying PPD population, a subset of the regimen initiator cohort with at least 6 months of continuous health plan enrollment prior to vaccination was age at vaccination- and geographic region- matched (2:1) to male subjects enrolled in the health plan who have not received GARDASIL® (general population). The baseline period included 6-months prior to and including the date of vaccination among the GARDASIL® recipients and the date of physician office visit among the matched comparators. The comparison group was required to have complete medical coverage and pharmacy benefits, a health care encounter (i.e., outpatient visit or ER visit) which was considered the day of cohort entry, as well as 6-months of continuous enrollment prior to cohort entry (baseline period). Healthcare encounters were defined by the presence of CPT codes that are specific for billing associated with office visits that involve physician evaluation and management, as well

as specific facility site codes that correspond to healthcare settings of interest (such as ER visits). The dates of cohort entry for the comparison group were matched to within 6 months of the office visit dates for the first GARDASIL® vaccination for the regimen initiator group with 6 months prior continuous enrollment. Demographics and baseline attributes among the matched regimen initiators were compared to those of the matched unvaccinated PPD population during the 6-month baseline period including the date of cohort entry. Pharmacy (Hierarchical Ingredient Code List (HICL), American Hospital Formulary Service (AHFS), National Drug Code (NDC), or First Databank Specific Therapeutic Class (TherSpec) codes), procedure (ICD-9, ICD-10, CPT, or HCPCS codes), and disease codes (ICD-9, ICD-10) were used to define potential confounders. Immune-related medical conditions evaluated were similar to those identified as being most common in this age group in a female safety study of HPV vaccine[10] (definitions are provided in Appendix H). The characteristics include:

- Demographics (as identified on date of cohort entry)
  - Age category in years [<9, 9-10, 11-12, 13-14, 15-17, 18-20, 21-23, 24-26, >26]
  - Geographic region [Northeast, Midwest, South, West]
  - Duration of preceding continuous health plan membership [mean, SD]
- Measures of health care service utilization during the baseline period
  - Number of drug classes dispensed [mean, SD]
  - Number of unique medications dispensed [mean, SD]
  - Number of all drugs dispensings (including unique and refill dispensings) [mean, SD]
  - Number of hospitalizations [mean, SD]
  - Number of inpatient hospital days [mean, SD]
  - Number of hospitalization days (identified between the beginning and end dates of a hospitalization) [mean, SD]
  - Number of outpatient visits [mean, SD]
  - Number of preventive medicine outpatient visits [mean, SD]
  - Number of outpatient primary care or pediatrician physician visits [mean, SD]
  - Number of outpatient specialist visits [mean, SD]
  - Number of ER visits [mean, SD]

  - Number of 3-digit ICD-9/ICD-10 diagnostic codes (including inpatient and outpatient) [mean, SD]
  - Number of procedures [mean, SD]
  - Total healthcare utilization costs ($US) [mean, SD]
- Immune-related medical conditions
  - Rheumatologic conditions
  - Asthma
  - Allergies (including hay fever, eczema, contact dermatitis, urticaria, food allergies, and unspecified allergy)
  - Number of infections (including urinary tract, respiratory tract, intestinal, and skin) [mean, SD]
  - Number of antibiotic dispensings [mean, SD]
- The 25 most frequent diagnoses, procedures, procedure categories, and drug dispensings (Tables 22-25)

Baseline frequencies were calculated for these characteristics. The means and standard deviations for continuous variables are presented; counts and proportions are presented for categorical variables.

This matched comparison group was designed specifically to provide an assessment of the similarities or differences between GARDASIL® recipients and the general population on baseline characteristics. Comparisons conducted for the general safety analyses do not use this matched comparison group, but instead are conducted using self-comparison post-vaccination periods.

6.2.2. Incidence Rates

The incidence of a health outcome (by HCUP category) was calculated as the number of first occurrences of the health outcome across the combined risk periods divided by the sum of the person-time across the risk periods per 1,000 person-years. Similar calculations were conducted for each of the self-comparison periods. For analyses in which subjects may have had more than one dose, each subject could only contribute once for each specific health outcome throughout the combined risk periods. Incidence rates and 95% CIs were calculated using the mid-probability method.[11] When zero events occurred in the risk or comparison period, the lower bound of the 95% CI was set to zero and the upper bound of the CI was calculated using an asymptotic method.

6.2.3. Relative Rate (as Rate Ratio)

Relative rates were calculated as the ratio of the IRs (events divided by person-time) of the health outcome in the risk and comparison periods and 95% CIs were estimated using a mid-probability exact method. A crude (no adjustment for covariates) analysis was conducted. When there were zero events in the risk period and at least one event in the comparison period, the lower bound of the 95% CI was set to zero, and the upper bound was calculated. Rate ratios were not calculated when there were zero events in the comparison period.

6.2.4. Pre-existing Conditions

To provide interpretation context for study results corresponding to the primary general safety objective and to facilitate assessment of the extent that pre-existing conditions influence the results, the general safety analyses were repeated after excluding from the analysis of a given HCUP category those with codes for the same HCUP category prior to Dose 1. Specifically for each HCUP category analysis, males with codes for the same HCUP category up to 12 months prior to and including the date of first dose of GARDASIL® in any healthcare setting (outpatient visit, ER, or hospitalization) were excluded from the analysis for that same HCUP category for the all doses combined Day 1-60 and Day 1-14 analysis, and Dose 1 Days 1-60 and Days 1-14 analyses. For example, a male with a code for HCUP category 1.3 in the follow-up period and a code for HCUP category 1.3 in the 12 months prior to receiving his first dose of GARDASIL® was excluded from analyses for HCUP category 1.3.

6.2.5. Multiplicity

To provide perspective on the possible contribution of chance that might arise from the numerous comparisons made in this study, general safety results for Days 1-60 and Days 1-14 (including the general safety analyses excluding pre-existing conditions) are presented in report tables with an additional analysis that serves as an adjustment for multiple comparisons. This adjustment was made using the double false discovery rate (DFDR) method.[12] The DFDR method acknowledges the multiple comparisons that are made under assumptions related to groupings of similar conditions. In report tables, bolded RRs and CIs indicate the interval excludes 1.00, while bolded and highlighted RRs and CIs indicate the DFDR adjusted *p*-value remained significant ($p < 0.05$). For the DFDR adjustment, the type I error rate (α) was set at 0.10. All HCUP categories were

adjusted for multiple comparisons. Groupings for application of the DFDR were limited to HCUP levels 1 and 2.

6.3. VTE Outcomes

6.3.1. Claims-Identified VTE Outcomes

Among the regimen initiators, cumulative counts of VTEs that occurred during the risk and self-comparison periods are presented for the Day 1-60 and Day 1-14 after all doses combined analysis by site of care (outpatient visits, ER visits, and hospitalizations).

To aid in the interpretation of counts of VTE outcomes, the sum of the risk and comparison period days was calculated for the Day 1-60 and Day 1-14 after all doses combined analysis. The sum of risk period days was calculated as the sum of time between the start of the risk period and the end of the risk period among males with at least one risk day. The sum of self-comparison period days was calculated similarly as the sum of the time between the start of the self-comparison period and the end of the self-comparison period among males with at least one self-comparison period day.

6.3.2. Medical Chart Confirmed VTE Outcomes

Medical chart confirmed VTE outcomes are presented for potential VTE outcomes identified during the prior annual report study period, as well as the number of potential VTE cases for profile review, the number of charts requested, the number of charts received, the number of cases reviewed by the clinicians, and VTE narratives.

6.4. Counts of Day 0 Events

Counts of the pre-specified Day 0 events of interest that occurred among the matched control cohort #2 are presented by site of care (outpatient visit, ER visit, or hospitalization, and all healthcare settings combined) for all doses combined and Dose 1. Counts of Day 0 events that occurred among the 2 alternate comparison groups (the self-comparison period and concurrent control cohort #1) are presented in Appendix I.

6.5. Autoimmune Cohort and Outcomes

6.5.1. Empirical Covariates

Predictors of vaccination were identified on an empiric basis by examining the most frequently occurring diagnoses, drugs dispensed, and procedures performed among GARDASIL® recipients (autoimmune cohort) and the comparator cohort to be used in the

propensity score matching process. The 100 most frequently occurring diagnoses in the 12-month baseline period preceding and including the date of cohort entry (date of first dose among those vaccinated) were tabulated, as well as the 100 most frequently dispensed drugs, and the 100 most frequent procedures (see Tables 13-16) among 53,998 males in the autoimmune cohort and 988,810 potential comparators. These characteristics were available for inclusion in the prediction model for discriminating GARDASIL® recipients from the comparator cohort, as well as the covariates described in Section 6.2.1.

6.5.2. Propensity Score Development

A propensity score-matched cohort of males not vaccinated with GARDASIL® was identified to calculate background counts of autoimmune conditions. The cohort entry date for the comparison group was a physician office visit, and these visit dates were chosen to match the distribution of dates of office visits corresponding to the first GARDASIL® vaccination for the vaccinated males. Using information derived from the baseline characterization of the study cohorts (both specified and empiric covariates), propensity scores for GARDASIL® initiation relative to an unvaccinated comparator cohort were developed. The propensity score is each person's predicted probability of GARDASIL® initiation, given membership in the study population and his baseline characteristics. For the primary comparison of recipients of GARDASIL® and the unvaccinated comparator cohort, the propensity score model included variables generated using the claims data from the 12-month baseline period. Since the prescribing of drugs and health care delivery patterns may change over time, separate propensity score models within yearly blocks were created. For this 5th Annual Report, a yearly block for 2015 was created and combined with the previous blocks (2009 and 2010 combined, 2011, 2012, 2013, and 2014). Thus, within the 2015 one-year period, new initiators and comparators were assigned a propensity score derived from a regression model that incorporated predictors of GARDASIL® vaccination.

The propensity score was estimated using an unconditional logistic regression model incorporating the predictors of GARDASIL® initiation. Included in the model were the empirical variables in Section 6.2.1 and the following baseline variables were forced in:

- Age (categories)
- Region

- Duration of preceding continuous health plan membership
- Number of drug dispensings (defined by HICL codes)
- Number of inpatient hospitalizations
- Number of hospital days
- Number of outpatient physician visits
- Number of outpatient specialist visits
- Number of outpatient primary care/pediatric physician visits
- Number of outpatient preventive medicine visits
- Number of ER visits
- Number of procedures
- Number of 3-digit ICD-9 and ICD-10 diagnostic codes
- Total healthcare utilization costs
- Total drug dispensing costs
- Rheumatologic conditions
- Asthma
- Allergies (including hay fever, eczema, contact dermatitis, urticaria, food allergies, and unspecified allergy)
- Number of infections (including urinary tract, respiratory tract, intestinal, and skin)
- Number of antibiotic dispensings

A stepwise selection of the remaining pre-specified and empirical variables was then used to increase model discrimination and to reduce the number of variables included in the model. The stepwise criteria consisted of a *p*-value of 0.2 for model entry and 0.3 for retaining variables. Where consistent with the variable type, binary variables or counts of unique claims were used for inclusion into the propensity score model. Categorical variables with more than 2 categories were represented by indicator variables.

The propensity score model comparing the probability of GARDASIL® initiation to being a member of the cohort not vaccinated with GARDASIL® based on the baseline variables, empirical variables, and healthcare utilization variables indicated a high level of discrimination between GARDASIL® initiation and membership in the nonvaccinated cohort in each prior yearly block (2013 c-statistic = 0.957). The c-statistic can range from 0.5 to 1.0 (with higher values indicating greater model discrimination between the groups). This high level of discrimination prompted a re-examination of the codes

selected for the propensity score and subsequent exclusion of codes associated with vaccination for administrative reasons or coding conventions (e.g., procedure codes or diagnostic codes indicating a need for vaccination) for 2014. These codes were identified as having a strong association (RR > 3.0) with vaccination and no plausible direct or indirect causal effect on any study outcome; therefore including them in the propensity-score model may lead to greater model discrimination (as indicated by a high c-statistic) that reduces available matches without improving confounder control. The 2014 propensity score model c-statistic was 0.917, reflecting reduced discrimination (and greater availability of matches) by the exclusion of administrative variables, and a similar 2015 propensity score model c- statistic of 0.909.

The nonvaccinated comparison cohort is comprised of those selected at random from potential comparators whose propensity score was sufficiently close to each GARDASIL® initiator (matched in a 1:1 ratio) using a greedy match algorithm.[13] The 4 blocks of matched recipients of GARDASIL® and non-vaccinated males were combined to create a pooled matched cohort.

6.5.3. Claims-Identified Autoimmune Outcomes

The cumulative number of electronically identified potential new-onset autoimmune cases by diagnosis codes and HCUP category is presented for the autoimmune cohort, the matched subset of the autoimmune cohort, and matched unvaccinated comparison cohort. To aid in the interpretation of counts of autoimmune outcomes, the sum of risk period years was calculated as the sum of time between the start of each risk period (if males had more than one dose) and the end of the risk period, death, disenrollment, or end of study period divided by 365.25 days, among vaccinated males with at least one risk day. The sum of risk period years among the comparison cohort included up to 18 months or until death, disenrollment, or end of the study period divided by 365.25 days.

6.6. Death

A tabulation of deaths identified in the claims or the SSA DMF is presented along with the number of days between the claims-based date of death and GARDASIL® dose, age at death, year of death, and death narratives based on claims-profile review and/or medical record review as well as narratives summarizing the facts related to each potential death. The observed number of deaths and the age-standardized expected mortality rates from the National Vital Statistics Report are presented for context.[14] The

racial distribution of the PPD was used to determine the expected number of deaths among initiators using age, sex, and race-specific national death rates. Among 106,110 GARDASIL® initiators, person-years of follow-up between first dose and date after last dose were tabulated by age group.

SAS version 9.4 (SAS Institute) was used for all analyses.

7. PRIVACY AND CONFIDENTIALITY

Confidentiality of patient records was maintained at all times. All analyses were performed in accordance with applicable laws and regulations. This Annual Interim Report contains aggregate results and outcome narratives and does not identify individual patients or physicians. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule [45 CRF 164.512(i)(2)] permits protected health information (PHI) to be used or disclosed for research, without patient authorization if certain criteria are met. At no time during the study did Merck, CRCs, or the SRC receive patient identifying information.

8. QUALITY ASSURANCE

The study was carried out according to PPD internal SOPs that are consistent with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (http://www.pharmacoepi.org). In particular, the SOPs in place at PPD specify that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

9. RESULTS

Summary Tables 1-6 are provided in the Results Section of the report for general safety Days 1-60 and Days 1-14 (Section 9.3 and 9.4), VTE (Section 9.5), Day 0 (Section 9.6), death (Section 9.7), and autoimmune outcomes (Section 9.8). Complete data tables (Tables 1-25) are provided in Attachment 1.

9.1. Accrual

A total of 106,110 males who received at least one dose of GARDASIL® (the regimen initiator cohort), 55,371 males who received at least 2 doses of GARDASIL®, and 28,411 males who received 3 doses of GARDASIL® (19,610 of whom met the criteria for the

regimen completer cohort) were identified between 16-October-2009 and 31-December-2015 (Table 1). A total of 189,892 doses of GARDASIL® were administered to the regimen initiator cohort of 106,110 males. Eighty-nine percent (89%) of the regimen initiator cohort was in the range of 11 to 18 years.

Table 2 presents the cumulative count of regimen initiators by dose and calendar quarter, as well as the cumulative count of regimen completers by calendar quarter. Note that the presentation of counts in this table differs slightly from that of the remaining tables; the provided counts are cumulative totals from start of the study accrual (16-October-2009) rather than totals accrued per quarter. Counts are displayed for the quarter in which each dose was received, e.g., males that received 3 doses in 3 different quarters would contribute counts to multiple quarters.

Table 3 includes the cumulative count of males in the autoimmune cohort by age at first dose of GARDASIL® and dose number (1, 2, or 3 doses). PPD identified 61,389 males in the autoimmune cohort who received at least one dose of GARDASIL®, 36,619 males who received at least 2 doses of GARDASIL®, and 20,665 males who received at least 3 doses of GARDASIL® between 16-October-2009 and 31-December-2015. There appears to be a somewhat higher completion of the 3-dose regimen among the autoimmune cohort (34%) than among the general safety cohort (27%), which is likely due to the requirement of a one-year baseline period among the autoimmune cohort since this will tend to select a more stable population enriched with members who have demonstrated longer residence in the health plan. The age at first dose is similar to that in the regimen initiator cohort (greatest numbers in the age range from 11 to 18 years).

Figure 1 (in Attachment 1) includes the cumulative study accrual of regimen initiators and completers by calendar quarter (similar to the data presented in Table 2). The y-axis represents the number of vaccine recipients from zero through 135,000 and the x-axis represents the calendar quarter from October 2009 through June 2017 (6 years following the study start date of June 2011). With the cumulative accrual total of 106,110 Gardasil initiators through December 2015, an additional 28,890 initiators would be needed to bring total accrual to the target number of 135,000. If the most recent quarterly accrual were to continue, these 28,890 additional males would be accrued over approximately 12 additional quarters (28,890/2,449 = 11.80), or approximately 3 years. Under this projection, the accrual target would be reached at the end of the fourth quarter of 2018

(December 2018). Projection estimates for reaching the study accrual end point of 44,000 regimen completers would occur at the end of the fourth quarter of 2024. However, these projections do not take into account the increasing use of GARDASIL®9, a 9-valent HPV vaccine licensed to Merck by the US FDA at the end of 2014, and may therefore overestimate the rate of future accrual. As a result, this study will most likely not meet either of its numerical stopping points (135,000 regimen initiators or 44,000 regimen completers) by the 6-year stopping point (June 2017). However, it should be noted that the study has already accrued more GARDASIL® doses (189,892) than assumed in the protocol power calculation (132,000).

To further explore timing patterns of second and third doses of Gardasil, at the SRC's request, a Kaplan-Meier (KM) curve of the cumulative dose completion for all regimen initiators was constructed (Figure 2 in Attachment 1, n=106,110). The KM curve includes the time from first dose of GARDASIL® through maximum available follow-up on the x-axis and cumulative incidence on the y-axis. The graph includes 2 separate lines: the solid line represents the cumulative incidence of a second dose and the dashed line represents the cumulative incidence of a third dose. Between 2012 and 2014, 52% of males who received a first dose of GARDASIL® completed the 3-dose series within 3 years; 45% within 2 years; and 30% within 12 months. During that same time period, 74% of males who received a first dose received a second dose within 3 years; 72% within 2 years; and 56% within 12 months. In all ages, an increase in cumulative receipt of Dose 2 (19%) and Dose 3 (5%) occurred at expected times following initiation of the regimen (i.e., 2 and 6 months) with gradual catch-up afterward, including an inflection at 12 and 24 months, most likely corresponding to annual physician office visits when there is an opportunity for providers to recommend initiation of the vaccine and completion of the vaccine series in males.

9.2. Baseline Characteristics

To provide context on the underlying male PPD population, the age distribution of the underlying male PPD population (prior to matching) is presented and compared with the age distribution of the GARDASIL® vaccinated population (Table 4A). Age was calculated at first dose for initiators, and on 31-December-2014 for the comparator population. A greater proportion of males in the GARDASIL® vaccinated cohort were between the ages 11 and 20 as compared to the underlying male PPD population, 93% versus 12%, respectively.

The demographic characteristics, health care utilization factors, and immune-related conditions of a subset of regimen initiators with 6 months of continuous enrollment prior to vaccination (n=57,553) and an age- and region-matched (1:2) male population not vaccinated with GARDASIL® (n=115,106) are presented in Table 4B. It should be noted that the purpose of Table 4B is to descriptively compare GARDASIL® regimen initiators to males not vaccinated with GARDASIL®; the comparison group shown in this table is not used in any other analyses.

9.3. General Safety

Summary Table 1 includes HCUP categories with at least one significantly increased RR (denoted by bolding and/or shading), while Summary Table 2 includes HCUP categories with at least one significantly decreased RR for the combined ER/hospitalization analyses; all related comparisons are shown for each HCUP category for context of review.

The general safety results for this 5th Annual Interim Report were compared to those of the 4th Annual Interim Report, and the majority of HCUP categories that had either increased or decreased RRs were observed in both reports. In the current report, there were 8 HCUP categories with at least one significantly elevated RR in either risk interval (Days 1-60 or Days 1-14) or dose level (all doses combined or Dose 1 only); whereas in last year's report, there were 8 HCUP categories with at least one significantly elevated RR, with overlap in 6 of the 8 HCUP categories with this year's report. In the current report, 26 HCUP categories were identified with at least one significantly decreased RR; whereas in the 4th Annual Interim Report, there were 32 HCUP categories with decreased RRs, 18 of which were also decreased in this year's report. HCUP categories with significant increases or decreases were discussed and explored already by the SRC when reviewing previous annual reports; they did not trigger concern or further exploration.

9.3.1. ER/Hospitalizations Combined – All Doses Combined

Days 1-60

Combined ER/hospitalization analyses for Days 1-60 all doses combined revealed that 7 HCUP categories had elevated RRs, and 2 categories had significantly decreased RRs (Table 5A). Of the 7 HCUP categories with elevated RRs, 4 HCUP categories were not embedded in an already represented HCUP category: one HCUP category was level 1

('injury and poisoning' (HCUP category 16)); 2 HCUP categories were level 2 ('coma; stupor; and brain damage' (HUCP 6.6) and 'ear conditions' (HCUP 6.8); and one HCUP category was level 4 ('cellulitis and abscess of arm' (HCUP 12.1.1.3). Because the HCUP classification is hierarchical, health outcomes included in an HCUP level 4 category are also included in the corresponding levels 3, 2 and 1.

Following multiple-comparison adjustment, 4 HCUP categories remained significantly elevated in the Days 1-60 window for all doses combined analysis; 'ear conditions' (HCUP 6.8) (RR 1.32; 95% CI 1.05-1.67); 'otitis media and related conditions' (HCUP 6.8.1) (RR 1.55; 95% CI 1.03-2.35); 'cellulitis and abscess of arm' (HCUP 12.1.1.3) (RR 1.97; 95% CI 1.02-4.02); and 'concussion' (HCUP 16.4.1) (RR 1.24; 95% CI 1.00-1.54) (Table 5A). Of the 2 HCUP categories with significantly decreased RRs, none remained significantly decreased after multiple-comparison adjustment.

Days 1-14

In the ER/hospitalization analyses for Days 1-14 all doses combined, zero HCUP categories had significantly elevated RRs (Table 5B). Eight HCUP categories had a significantly decreased RR but did not remain significant after multiple-comparison adjustment: 'personality disorders' (HCUP 5.9); 'alcohol-related disorders' (HCUP 5.11); 'respiratory infections' (HCUP 8.1); 'pleurisy; pneumothorax; pulmonary collapse' (HCUP 8.5); 'disorders of teeth and jaw' (HCUP 9.2); 'other skin disorders' (HCUP 12.4); 'concussion' (HCUP 16.4.1); and 'factors influencing health care' (HCUP 17.2).

9.3.2. ER/Hospitalizations Combined – Dose 1

Days 1-60

Following Dose 1, combined ER/hospitalization analyses for Days 1-60 revealed that one HCUP categories had elevated RRs; 'cellulitis and abscess of arm' (HCUP 12.1.1.3); it remained significant after multiple-comparison adjustment (RR 4.70; 95% CI 1.72 – 15.99) (Table 6A). Two HCUP categories had significantly decreased RRs, but did not remain significant after multiple-comparison adjustment: 'personality disorders' (HCUP 5.9); and 'burns' (HCUP 16.9).

Days 1-14

Following Dose 1, combined ER/hospitalization analyses for Days 1-14 revealed that one HCUP category had an elevated RR, 'skin and subcutaneous tissue infections'

(HCUP 12.1), while 5 HCUP categories were significantly decreased (Table 6B), including 'intracranial injury' (HCUP 16.4); 'concussion' (HCUP 16.4.1); 'other injuries and conditions due to external causes' (HCUP 16.12); 'symptoms; signs; and ill-defined conditions and factors influencing health status' (HCUP 17); and 'factors influencing health care' (HCUP 17.2); 2 remained significant after multiple-comparison adjustment; 'intracranial injury' (HCUP 16.4) (RR 0.45, 95% CI 0.24 – 0.82); and 'concussion' (HCUP 16.4.1) (RR 0.35, 95% CI 0.17 – 0.67).

9.4. General Safety Excluding Conditions with Claims for the Same HCUP Category Prior to Dose 1 (i.e., no prior code for the event)

9.4.1. ER/Hospitalizations Combined – All Doses Combined

Days 1-60

The combined ER/hospitalization analyses for Days 1-60 all doses combined were repeated excluding from the analysis of a given HCUP category those with codes for that HCUP category prior to and including the day of the first dose ("no prior code" analysis). These analyses revealed that 2 HCUP categories had significantly elevated RRs, while 11 HCUP categories had significantly decreased RRs (Table 7A). The outcomes with increased RRs include: 'coma; stupor; and brain damage' (HCUP 6.6); and 'cellulitis and abscess of arm' (HCUP 12.1.1.3); one remained significant after multiple-comparison adjustment 'cellulitis and abscess of arm' (HCUP 12.1.13) (RR 2.15, 95% CI 1.09-4.50).

The HCUP categories with a decreased RR were: 'mental illness' (HCUP 5); 'anxiety disorders' (HCUP 5.2); 'mood disorders' (HCUP 5.8); 'suicide and intentional self-inflicted injury (HCUP 5.13); 'coma; stupor; and brain damage' (HCUP 6.6); 'diseases of the digestive system' (HCUP 9); 'disorders of teeth and jaw' (HCUP 9.2); 'diseases of the musculoskeletal system and connective tissue' (HCUP 13); 'spondylosis; intervertebral disc disorders; other back problems' (HCUP 13.3); 'other connective tissue disorders' (HCUP 13.8); 'other bone disease and musculoskeletal deformities' (HCUP 13.9); and 'crushing injury or internal injury' (HCUP 16.5). Two remained significant after multiple-comparison adjustment: 'mental illness' (HCUP 5) (RR 0.74, 95% CI 0.63-0.87); and 'diseases of the musculoskeletal system and connective tissue' (HCUP 13) (RR 0.84, 95% CI 0.76-0.92) (Table 7A).

Days 1-14

The combined ER/hospitalization analyses for Days 1-14 all doses combined were repeated excluding those with codes for the same HCUP category prior to Dose 1 from the analysis of that HCUP category. These analyses revealed that no HCUP categories had elevated RRs, while 10 HCUP categories had significantly decreased RRs (Table 7B). The outcomes with decreased RRs are: 'mental illness' (HCUP 5); 'mood disorders' (HCUP 5.8); 'personality disorders' (HCUP 5.9); 'suicide and self-inflicted injury' (HCUP 5.13); respiratory infections' (HCUP 8.1); 'disorders of teeth and jaw' (HCUP 9.2); 'diseases of the musculoskeletal system and connective tissue' (HCUP 13); 'spondylosis; intervertebral disc disorders; other back problems' (HCUP 13.3); 'other connective tissue disorders' (HCUP 13.8); and 'other bone disorders and musculoskeletal deformities' (HCUP 13.9). Following multiple-comparison adjustment, 2 outcome categories remained significantly decreased: 'mental illness' (HCUP 5) (RR 0.55; 95% CI 0.40-0.74); and 'diseases of the musculoskeletal system and connective tissue' (HCUP 13) (RR 0.76, 95% CI 0.65-0.90).

9.4.2. ER/Hospitalizations Combined – Dose 1

Days 1-60

Following Dose 1, combined ER/hospitalization analyses for Days 1-60 were repeated excluding those with codes for the same HCUP category prior to Dose 1 from the analysis of that HCUP category (Table 8A). In these analyses, there was one HCUP category with a significantly elevated RR; 'cellulitis and abscess of arm' (HCUP 12.1.13), and it remained significant after multiple-comparison adjustment (RR 4.70, 95% CI 1.72 – 15.99). Eight HCUP categories had significantly decreased RRs including 'mental illness' (HCUP 5); 'mood disorders' (HCUP 5.8); 'diseases of the digestive system' (HCUP 9); 'pancreatic disorders (not diabetes)' (HCUP 9.9); 'diseases of the musculoskeletal system and connective tissue' (HCUP 13); 'spondylosis; intervertebral disc disorders; other back problems' (HCUP 13.3); 'other connective tissue disease' (HCUP 13.8); and 'other bone disease and musculoskeletal deformities' (HCUP 13.9); one remained significantly decreased after multiple-comparison adjustment: 'diseases of the musculoskeletal system and connective tissue' (HCUP 13) (RR 0.74, (95% CI 0.65-0.84).

Days 1-14

Following Dose 1, combined ER/hospitalization analyses for Days 1-14 were repeated excluding those with codes for the same HCUP category prior to Dose 1 from the analysis of that HCUP category (Table 8B). In these analyses, there were no HCUP categories with significantly elevated RRs and 11 HCUP categories had significantly decreased RRs: 'mental illness' (HCUP 5); 'mood disorders' (HCUP 5.8); 'suicide and intentional self-inflicted injury' (HCUP 5.13); 'headache; including migraine' (HCUP 6.5); 'diseases of the musculoskeletal system and connective tissue' (HCUP 13); 'other connective tissue disease' (HCUP 13.8); 'other bone disease and musculoskeletal deformities' (HCUP 13.9); 'intracranial injury' (HCUP 16.4); 'concussion' (HCUP 16.4.1); 'sprains and strains' (HCUP 16.7); 'other injuries and conditions due to external causes' (HCUP 16.12). Of the 11 HCUP categories with decreased RRs, 4 were not embedded in an already represented HCUP category. Following multiple-comparison adjustment, 3 of the RRs remained significantly decreased: 'diseases of the musculoskeletal system and connective tissue' (HCUP 13) (RR 0.53, 95% CI 0.42-0.68); 'intracranial injury' (HCUP 16.4) (RR 0.48, 95% 0.26-0.88); and 'concussion' (HCUP 16.4.1) (RR 0.35, 95% CI 0.17-0.67).

To assist in identification of potential signals, a table summarizing the HCUP categories with one or more events in the risk period and zero in the post-vaccination self-comparison periods was created (Summary Table 6). There were 17 HCUP categories that had one or more events in the risk period and zero in the post-vaccination period. For each of the 17 HCUP categories, the number of events in the risk period was 3 or less compared to zero in the post-vaccination period. Similarly, there were 17 HCUP categories that had zero events in the risk period and one or more events in the post-vaccination self-comparison period.

Summary Table 1. Incidence Rates and Increased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Combined Potential ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
6.6	Coma; stupor; and brain damage	All Doses	9	1.25	3	0.47	2.64	(0.75-12.10)	29	0.97	11	0.44	**2.23**	**(1.13-4.64)**
		All Doses, no prior codes cohort[f] (N=106,028)	9	1.25	3	0.47	2.64	(0.75-12.10)	28	0.94	11	0.44	**2.15**	**(1.09-4.50)**
		Dose 1	7	1.74	2	0.55	3.15	(0.70-22.16)	18	1.07	7	0.46	2.30	(0.98-5.91)
		Dose 1, no prior codes cohort[f] (N=106,028)	7	1.74	2	0.55	3.15	(0.70-22.16)	17	1.01	7	0.46	2.17	(0.92-5.62)
6.8	Ear conditions	All Doses	44	6.12	28	4.42	1.38	(0.86-2.25)	188	6.31	120	4.76	**1.32**	**(1.05-1.67)**
		All Doses, no prior codes cohort[f] (N=93,749)	31	4.32	22	3.48	1.24	(0.72-2.17)	141	4.74	97	3.86	1.23	(0.95-1.59)
		Dose 1	25	6.20	20	5.50	1.13	(0.62-2.05)	110	6.53	84	5.57	1.17	(0.88-1.56)
		Dose 1, no prior codes cohort[f] (N=93,749)	17	4.22	16	4.41	0.96	(0.48-1.92)	80	4.75	70	4.65	1.02	(0.74-1.41)
6.8.1	Otitis media and related conditions	All Doses	16	2.22	7	1.10	2.01	(0.84-5.24)	64	2.15	35	1.39	**1.55**	**(1.03-2.35)**
		All Doses, no prior codes cohort[f] (N=100,444)	11	1.53	6	0.95	1.61	(0.60-4.72)	50	1.68	27	1.07	1.56	(0.98-2.53)
		Dose 1	9	2.23	5	1.38	1.62	(0.54-5.34)	39	2.31	21	1.39	1.66	(0.98-2.87)
		Dose 1, no prior codes cohort[f] (N=100,444)	5	1.24	4	1.10	1.13	(0.29-4.72)	29	1.72	19	1.26	1.37	(0.77-2.48)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and Utilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age with at least one dose of Gardasil.

[c]Only HCUP categories with at least one increased RR (lower confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false-discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males with codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) were excluded from the analysis for that HCUP category.

Summary Table 1. Incidence Rates and Increased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Combined Potential ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
12.1.	Skin and subcutaneous tissue infections	All Doses	37	5.14	25	3.95	1.30	(0.79-2.19)	132	4.43	97	3.85	1.15	(0.89-1.50)
		All Doses, no prior codes cohort[f] (N=102,270)	25	3.48	23	3.63	0.96	(0.54-1.70)	110	3.69	83	3.30	1.12	(0.84-1.49)
		Dose 1	24	5.95	10	2.75	**2.16**	**(1.05-4.73)**	84	4.98	58	3.85	1.30	(0.93-1.82)
		Dose 1, no prior codes cohort[f] (N=102,270)	15	3.72	9	2.48	1.50	(0.66-3.59)	68	4.04	50	3.32	1.22	(0.85-1.76)
12.1.1.3	Cellulitis and abscess of arm	All Doses	6	0.83	1	0.16	5.29	(0.78-122.41)	28	0.94	12	0.48	**1.97**	**(1.02-4.02)**
		All Doses, no prior codes cohort[f] (N=105,939)	6	0.83	1	0.16	5.29	(0.78-122.41)	28	0.94	11	0.44	**2.15**	**(1.09-4.50)**
		Dose 1	3	0.74	1	0.28	2.70	(0.29-71.20)	21	1.25	4	0.27	**4.70**	**(1.72-15.99)**
		Dose 1, no prior codes cohort[f] (N=105,939)	3	0.74	1	0.28	2.70	(0.29-71.20)	21	1.25	4	0.27	**4.70**	**(1.72-15.99)**
16	Injury and poisoning	All Doses	783	109.35	671	106.37	1.03	(0.93-1.14)	3,017	102.95	2,386	96.25	**1.07**	**(1.01-1.13)**
		All Doses, no prior codes cohort[f] (N=84,746)	471	68.45	428	70.89	0.97	(0.85-1.10)	1,955	69.17	1,569	66.00	1.05	(0.98-1.12)
		Dose 1	453	112.54	445	122.68	0.92	(0.80-1.05)	1,776	106.24	1,548	103.51	1.03	(0.96-1.10)
		Dose 1, no prior codes cohort[f] (N=84,746)	262	67.34	275	78.70	0.86	(0.72-1.01)	1,147	70.90	1,005	69.67	1.02	(0.93-1.11)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and Utilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age with at least one dose of Gardasil.

[c]Only HCUP categories with at least one increased RR (lower confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false-discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males with codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) were excluded from the analysis for that HCUP category.

Summary Table 1. Incidence Rates and Increased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Combined Potential ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
16.4.1	Concussion	All Doses	29	4.03	43	6.79	0.59	(0.37-0.95)	210	7.05	143	5.68	**1.24**	**(1.00-1.54)**
		All Doses, no prior codes cohort[f] (N=104,310)	29	4.03	41	6.48	0.62	(0.38-1.00)	201	6.75	138	5.48	1.23	(0.99-1.53)
		Dose 1	12	2.97	31	8.53	0.35	(0.17-0.67)	116	6.88	105	6.96	0.99	(0.76-1.29)
		Dose 1, no prior codes cohort[f] (N=104,310)	12	2.98	31	8.53	0.35	(0.17-0.67)	108	6.41	101	6.70	0.96	(0.73-1.26)
16.7	Sprains and strains	All Doses	250	34.80	196	30.98	1.12	(0.93-1.36)	900	30.33	683	27.22	**1.11**	**(1.01-1.23)**
		All Doses, no prior codes cohort[f] (N=98,495)	154	21.58	139	22.13	0.98	(0.78-1.23)	661	22.41	527	21.16	1.06	(0.94-1.19)
		Dose 1	147	36.47	141	38.81	0.94	(0.75-1.18)	541	32.17	450	29.90	1.08	(0.95-1.22)
		Dose 1, no prior codes cohort[f] (N=98,495)	75	18.71	94	26.04	0.72	(0.53-0.97)	381	22.78	327	21.86	1.04	(0.90-1.21)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and Utilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age with at least one dose of Gardasil.

[c]Only HCUP categories with at least one increased RR (lower confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false-discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males with codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) were excluded from the analysis for that HCUP category.

Summary Table 2. Incidence Rates and Decreased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Potential Combined ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
4	Diseases of the blood and blood-forming organs	All Doses	13	1.81	15	2.37	0.76	(0.36-1.62)	51	1.71	64	2.54	**0.67**	**(0.46-0.97)**
		All Doses, no prior codes cohort[f] (N=105,379)	11	1.53	12	1.89	0.81	(0.35-1.86)	47	1.58	54	2.14	0.74	(0.50-1.09)
		Dose 1	9	2.23	7	1.93	1.16	(0.42-3.28)	32	1.90	34	2.25	0.84	(0.52-1.37)
		Dose 1, no prior codes cohort[f] (N=105,379)	8	1.98	4	1.10	1.80	(0.55-6.86)	30	1.78	25	1.66	1.07	(0.63-1.84)
5	Mental illness	All Doses	251	34.95	256	40.48	0.86	(0.73-1.03)	767	25.83	672	26.79	0.96	(0.87-1.07)
		All Doses, no prior codes cohort[f] (N=85,109)	67	9.46	108	17.34	**0.55**	**(0.40-0.74)**	272	9.27	309	12.50	**0.74**	**(0.63-0.87)**
		Dose 1	162	40.20	147	40.47	0.99	(0.79-1.24)	477	28.37	437	29.04	0.98	(0.86-1.11)
		Dose 1, no prior codes cohort[f] (N=85,109)	28	7.04	50	13.96	**0.50**	**(0.31-0.80)**	140	8.42	177	11.92	**0.71**	**(0.57-0.88)**
5.2	Anxiety disorders	All Doses	85	11.82	72	11.37	1.04	(0.76-1.43)	236	7.92	206	8.18	0.97	(0.80-1.17)
		All Doses, no prior codes cohort[f] (N=102,053)	45	6.27	46	7.28	0.86	(0.57-1.30)	132	4.44	147	5.85	**0.76**	**(0.60-0.96)**
		Dose 1	53	13.14	43	11.83	1.11	(0.74-1.67)	149	8.84	122	8.09	1.09	(0.86-1.39)
		Dose 1, no prior codes cohort[f] (N=102,053)	23	5.72	27	7.44	0.77	(0.44-1.34)	70	4.16	82	5.45	0.76	(0.55-1.05)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and U ilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age w ith at least one dose of Gardasil.

[c]Only HCUP categories w ith at least one decreased RR (upper confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males w i h codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) w ere excluded from the analysis for hat HCUP category.

Summary Table 2. Incidence Rates and Decreased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Potential Combined ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
5.8	Mood disorders	All Doses	159	22.13	158	24.96	0.89	(0.71-1.11)	404	13.58	367	14.60	0.93	(0.81-1.07)
		All Doses, no prior codes cohort[f] (N=102,475)	45	6.29	71	11.27	**0.56**	**(0.38-0.81)**	176	5.93	191	7.63	**0.78**	**(0.63-0.95)**
		Dose 1	106	26.29	98	26.97	0.97	(0.74-1.28)	264	15.68	244	16.20	0.97	(0.81-1.15)
		Dose 1, no prior codes cohort[f] (N=102,475)	16	3.99	34	9.40	**0.42**	**(0.23-0.76)**	84	5.01	108	7.20	**0.70**	**(0.52-0.92)**
5.9	Personality Disorders	All Doses	1	0.14	8	1.26	**0.11**	**(0.00-0.69)**	11	0.37	19	0.75	0.49	(0.22-1.02)
		All Doses, no prior codes cohort[f] (N=106,007)	0	0.00	6	0.95	**0.00**	**(0.00-0.41)**	10	0.34	17	0.67	0.50	(0.22-1.08)
		Dose 1	1	0.25	6	1.65	0.15	(0.01-1.02)	6	0.36	14	0.93	**0.38**	**(0.14-0.98)**
		Dose 1, no prior codes cohort[f] (N=106,007)	0	0.00	3	0.83	0.00	(0.00-1.04)	5	0.30	10	0.66	0.45	(0.14-1.30)
5.11	Alcohol-related disorders	All Doses	19	2.64	30	4.74	**0.56**	**(0.31-0.99)**	109	3.66	110	4.37	0.84	(0.64-1.09)
		All Doses, no prior codes cohort[f] (N=105,774)	17	2.36	27	4.26	0.55	(0.30-1.01)	102	3.42	104	4.13	0.83	(0.63-1.09)
		Dose 1	6	1.49	13	3.58	0.42	(0.15-1.08)	50	2.97	64	4.24	0.70	(0.48-1.01)
		Dose 1, no prior codes cohort[f] (N=105,774)	6	1.49	13	3.58	0.42	(0.15-1.08)	47	2.79	61	4.05	0.69	(0.47-1.01)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and U ilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age w ith at least one dose of Gardasil.

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[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males w i h codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) w ere excluded from the analysis for hat HCUP category.

Summary Table 2. Incidence Rates and Decreased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Potential Combined ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
5.13	Suicide and intentional self-inflicted injury	All Doses	26	3.62	36	5.68	0.64	(0.38-1.05)	115	3.86	120	4.76	0.81	(0.63-1.05)
		All Doses, no prior codes cohort[f] (N=105,851)	21	2.92	33	5.21	**0.56**	**(0.32-0.97)**	100	3.35	113	4.49	**0.75**	**(0.57-0.98)**
		Dose 1	15	3.72	24	6.60	0.56	(0.29-1.07)	70	4.15	73	4.84	0.86	(0.62-1.19)
		Dose 1, no prior codes cohort[f] (N=105,851)	11	2.73	22	6.05	**0.45**	**(0.21-0.92)**	59	3.50	66	4.38	0.80	(0.56-1.14)
6.5	Headache; including migraine	All Doses	74	10.29	74	11.68	0.88	(0.64-1.22)	277	9.30	228	9.06	1.03	(0.86-1.22)
		All Doses, no prior codes cohort[f] (N=101,999)	44	6.13	56	8.86	0.69	(0.46-1.03)	207	6.96	184	7.32	0.95	(0.78-1.16)
		Dose 1	44	10.91	52	14.30	0.76	(0.51-1.14)	173	10.27	157	10.42	0.99	(0.79-1.22)
		Dose 1, no prior codes cohort[f] (N=101,999)	24	5.96	41	11.30	**0.53**	**(0.31-0.87)**	122	7.25	123	8.17	0.89	(0.69-1.14)
8.1	Respiratory infections	All Doses	77	10.71	98	15.48	**0.69**	**(0.51-0.93)**	364	12.22	328	13.04	0.94	(0.81-1.09)
		All Doses, no prior codes cohort[f] (N=77,483)	39	5.47	56	8.92	**0.61**	**(0.40-0.92)**	202	6.83	181	7.26	0.94	(0.77-1.15)
		Dose 1	49	12.15	54	14.86	0.82	(0.55-1.21)	216	12.82	200	13.27	0.97	(0.80-1.17)
		Dose 1, no prior codes cohort[f] (N=77,483)	22	5.49	26	7.21	0.76	(0.43-1.35)	121	7.23	109	7.28	0.99	(0.77-1.29)

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[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

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Summary Table 2. Incidence Rates and Decreased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Potential Combined ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
8.5	Pleurisy; pneumothorax; pulmonary collapse	All Doses	8	1.11	18	2.84	**0.39**	**(0.16-0.89)**	29	0.97	36	1.43	0.68	(0.41-1.11)
		All Doses, no prior codes cohort[f] (N=106,000)	8	1.11	16	2.53	0.44	(0.18-1.02)	28	0.94	34	1.35	0.70	(0.42-1.15)
		Dose 1	7	1.74	8	2.20	0.79	(0.27-2.24)	15	0.89	24	1.59	0.56	(0.29-1.06)
		Dose 1, no prior codes cohort[f] (N=106,000)	7	1.74	7	1.93	0.90	(0.30-2.68)	14	0.83	23	1.52	0.54	(0.27-1.06)
9	Diseases of the digestive system	All Doses	128	17.81	125	19.74	0.90	(0.70-1.15)	514	17.28	461	18.35	0.94	(0.83-1.07)
		All Doses, no prior codes cohort[f] (N=98,684)	87	12.16	101	16.03	0.76	(0.57-1.01)	367	12.39	372	14.87	**0.83**	**(0.72-0.96)**
		Dose 1	73	18.10	70	19.26	0.94	(0.68-1.31)	292	17.34	289	19.18	0.90	(0.77-1.06)
		Dose 1, no prior codes cohort[f] (N=98,684)	47	11.70	54	14.92	0.78	(0.53-1.16)	201	11.98	226	15.07	**0.80**	**(0.66-0.96)**
9.2	Disorders of teeth and jaw	All Doses	6	0.83	16	2.53	**0.33**	**(0.12-0.82)**	29	0.97	48	1.90	**0.51**	**(0.32-0.81)**
		All Doses, no prior codes cohort[f] (N=105,385)	5	0.70	16	2.53	**0.28**	**(0.09-0.72)**	27	0.91	45	1.79	**0.51**	**(0.31-0.81)**
		Dose 1	4	0.99	7	1.93	0.52	(0.13-1.78)	21	1.25	22	1.46	0.85	(0.47-1.56)
		Dose 1, no prior codes cohort[f] (N=105,385)	3	0.74	7	1.93	0.39	(0.08-1.47)	19	1.13	19	1.26	0.89	(0.47-1.71)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and U ilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

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[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

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Summary Table 2. Incidence Rates and Decreased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Potential Combined ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
9.9	Pancreatic disorders (not diabetes)	All Doses	2	0.28	2	0.32	0.88	(0.09-8.46)	5	0.17	8	0.32	0.53	(0.16-1.63)
		All Doses, no prior codes cohort[f] (N=106,081)	2	0.28	1	0.16	1.76	(0.13-51.97)	3	0.10	6	0.24	0.42	(0.09-1.70)
		Dose 1	0	0.00	0	0.00	N/A	N/A	2	0.12	4	0.27	0.45	(0.06-2.52)
		Dose 1, no prior codes cohort[f] (N=106,081)	0	0.00	0	0.00	N/A	N/A	0	0.00	4	0.27	**0.00**	**(0.00-0.70)**
12.4	Other skin disorders	All Doses	21	2.92	33	5.21	**0.56**	**(0.32-0.97)**	114	3.82	81	3.21	1.19	(0.90-1.59)
		All Doses, no prior codes cohort[f] (N=90,310)	11	1.53	19	3.00	0.51	(0.23-1.07)	78	2.62	51	2.03	1.29	(0.91-1.85)
		Dose 1	14	3.47	19	5.23	0.66	(0.33-1.33)	66	3.92	53	3.51	1.11	(0.78-1.61)
		Dose 1, no prior codes cohort[f] (N=90,310)	8	1.99	13	3.58	0.55	(0.22-1.34)	43	2.55	34	2.26	1.13	(0.72-1.79)
13	Diseases of the musculoskeletal system and connective tissue	All Doses	722	100.81	610	96.68	1.04	(0.94-1.16)	1,844	62.53	1,545	62.02	1.01	(0.94-1.08)
		All Doses, no prior codes cohort[f] (N=89,065)	263	37.49	303	49.16	**0.76**	**(0.65-0.90)**	840	28.98	844	34.59	**0.84**	**(0.76-0.92)**
		Dose 1	427	106.09	403	111.10	0.95	(0.83-1.09)	1,158	69.13	1,045	69.73	0.99	(0.91-1.08)
		Dose 1, no prior codes cohort[f] (N=89,065)	106	26.85	179	50.41	**0.53**	**(0.42-0.68)**	429	26.05	520	35.39	**0.74**	**(0.65-0.84)**

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and Utilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

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[d]Incidence rates per 1,000 person-years.

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HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
13.3	Spondylosis; intervertebral disc disorders; other back problems	All Doses	377	52.53	321	50.77	1.03	(0.89-1.20)	896	30.20	805	32.13	0.94	(0.85-1.03)
		All Doses, no prior codes cohort[f] (N=102,253)	177	24.81	203	32.34	**0.77**	**(0.63-0.94)**	494	16.73	540	21.68	**0.77**	**(0.68-0.87)**
		Dose 1	223	55.35	200	55.07	1.00	(0.83-1.22)	573	34.10	512	34.05	1.00	(0.89-1.13)
		Dose 1, no prior codes cohort[f] (N=102,253)	66	16.48	117	32.43	**0.51**	**(0.37-0.69)**	249	14.89	312	20.87	**0.71**	**(0.60-0.84)**
13.8	Other connective tissue disease	All Doses	315	43.88	260	41.11	1.07	(0.91-1.26)	805	27.12	661	26.35	1.03	(0.93-1.14)
		All Doses, no prior codes cohort[f] (N=99,312)	144	20.18	176	28.03	**0.72**	**(0.58-0.90)**	465	15.74	463	18.58	**0.85**	**(0.75-0.96)**
		Dose 1	184	45.66	186	51.22	0.89	(0.73-1.09)	478	28.43	466	30.98	0.92	(0.81-1.04)
		Dose 1, no prior codes cohort[f] (N=99,312)	62	15.47	118	32.70	**0.47**	**(0.35-0.64)**	225	13.45	307	20.53	**0.65**	**(0.55-0.78)**
13.9	Other bone disease and musculoskeletal deformities	All Doses	438	61.06	355	56.17	1.09	(0.95-1.25)	1,012	34.15	839	33.50	1.02	(0.93-1.12)
		All Doses, no prior codes cohort[f] (N=101,771)	199	27.93	216	34.45	**0.81**	**(0.67-0.98)**	520	17.64	546	21.95	**0.80**	**(0.71-0.91)**
		Dose 1	263	65.29	257	70.79	0.92	(0.78-1.10)	662	39.41	595	39.60	1.00	(0.89-1.11)
		Dose 1, no prior codes cohort[f] (N=101,771)	83	20.74	134	37.19	**0.56**	**(0.42-0.73)**	274	16.40	335	22.44	**0.73**	**(0.62-0.86)**

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and U ilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age w ith at least one dose of Gardasil.

[c]Only HCUP categories w ith at least one decreased RR (upper confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males w i h codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) w ere excluded from the analysis for hat HCUP category.

Summary Table 2. Incidence Rates and Decreased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Potential Combined ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
16.4	Intracranial injury	All Doses	33	4.59	45	7.10	0.65	(0.41-1.01)	228	7.65	160	6.35	1.20	(0.98-1.48)
		All Doses, no prior codes cohort[f] (N=104,163)	32	4.45	42	6.63	0.67	(0.42-1.06)	218	7.32	151	6.00	1.22	(0.99-1.50)
		Dose 1	16	3.97	32	8.80	**0.45**	**(0.24-0.82)**	126	7.48	112	7.43	1.01	(0.78-1.30)
		Dose 1, no prior codes cohort[f] (N=104,163)	16	3.97	30	8.26	**0.48**	**(0.26-0.88)**	118	7.01	105	6.97	1.01	(0.77-1.31)
16.4.1	Concussion	All Doses	29	4.03	43	6.79	**0.59**	**(0.37-0.95)**	210	7.05	143	5.68	1.24	(1.00-1.54)
		All Doses, no prior codes cohort[f] (N=104,310)	29	4.03	41	6.48	0.62	(0.38-1.00)	201	6.75	138	5.48	1.23	(0.99-1.53)
		Dose 1	12	2.97	31	8.53	**0.35**	**(0.17-0.67)**	116	6.88	105	6.96	0.99	(0.76-1.29)
		Dose 1, no prior codes cohort[f] (N=104,310)	12	2.98	31	8.53	**0.35**	**(0.17-0.67)**	108	6.41	101	6.70	0.96	(0.73-1.26)
16.5	Crushing injury or internal injury	All Doses	7	0.97	12	1.89	0.51	(0.19-1.30)	22	0.74	31	1.23	0.60	(0.31-1.04)
		All Doses, no prior codes cohort[f] (N=105,897)	6	0.83	12	1.89	0.44	(0.15-1.16)	21	0.70	31	1.23	**0.57**	**(0.32-0.99)**
		Dose 1	1	0.25	3	0.83	0.30	(0.01-2.82)	8	0.47	7	0.46	1.02	(0.36-2.96)
		Dose 1, no prior codes cohort[f] (N=105,897)	1	0.25	3	0.83	0.30	(0.01-2.82)	8	0.47	7	0.46	1.02	(0.36-2.96)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and U ilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age w ith at least one dose of Gardasil.

[c]Only HCUP categories w ith at least one decreased RR (upper confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males w i h codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) w ere excluded from the analysis for hat HCUP category.

Summary Table 2. Incidence Rates and Decreased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Potential Combined ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
16.7	Sprains and strains	All Doses	250	34.80	196	30.98	1.12	(0.93-1.36)	900	30.33	683	27.22	1.11	(1.01-1.23)
		All Doses, no prior codes cohort[f] (N=98,495)	154	21.58	139	22.13	0.98	(0.78-1.23)	661	22.41	527	21.16	1.06	(0.94-1.19)
		Dose 1	147	36.47	141	38.81	0.94	(0.75-1.18)	541	32.17	450	29.90	1.08	(0.95-1.22)
		Dose 1, no prior codes cohort[f] (N=98,495)	75	18.71	94	26.04	**0.72**	**(0.53-0.97)**	381	22.78	327	21.86	1.04	(0.90-1.21)
16.9	Burns	All Doses	0	0.00	3	0.47	0.00	(0.00-1.02)	9	0.30	11	0.44	0.69	(0.28-1.69)
		All Doses, no prior codes cohort[f] (N=105,923)	0	0.00	3	0.47	0.00	(0.00-1.02)	9	0.30	10	0.40	0.76	(0.30-1.91)
		Dose 1	0	0.00	2	0.55	0.00	(0.00-1.95)	4	0.24	11	0.73	**0.33**	**(0.09-0.99)**
		Dose 1, no prior codes cohort[f] (N=105,923)	0	0.00	2	0.55	0.00	(0.00-1.95)	4	0.24	10	0.66	0.36	(0.10-1.11)
16.12	Other injuries and conditions due to external causes	All Doses	122	16.97	122	19.27	0.88	(0.68-1.13)	523	17.58	437	17.39	1.01	(0.89-1.15)
		All Doses, no prior codes cohort[f] (N=101,266)	108	15.06	110	17.42	0.86	(0.66-1.13)	470	15.84	401	16.00	0.99	(0.87-1.13)
		Dose 1	67	16.61	86	23.66	**0.70**	**(0.51-0.97)**	302	17.94	297	19.72	0.91	(0.78-1.07)
		Dose 1, no prior codes cohort[f] (N=101,266)	60	14.91	79	21.79	**0.68**	**(0.49-0.96)**	275	16.37	274	18.23	0.90	(0.76-1.06)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and Utilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age with at least one dose of Gardasil.

[c]Only HCUP categories with at least one decreased RR (upper confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males with codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) were excluded from the analysis for that HCUP category.

Summary Table 2. Incidence Rates and Decreased Relative Rates among Regimen Initiators (N=106,110)[a,b] in a Risk Period Compared to a Post-Vaccination Self-Comparison Period for Potential Combined ER/Hospital General Safety Outcomes by Analysis Category[c]

HCUP Category	Description	Analysis Category	Days 1-14						Day 1-60					
			Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period		Risk Period		Self-Comparison Period		Risk vs. Self-Comparison Period	
			Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]	Events N	IR[d]	Events N	IR[d]	RR	95% CI[e]
17	Symptoms; signs; and ill-defined conditions and factors influencing health status	All Doses	234	32.57	246	38.88	0.84	(0.70-1.00)	1,007	33.94	899	35.88	0.95	(0.86-1.04)
		All Doses, no prior codes cohort[f] (N=13,912)	35	5.09	30	4.98	1.02	(0.63-1.68)	121	4.25	112	4.69	0.91	(0.70-1.17)
		Dose 1	137	33.99	156	42.94	**0.79**	**(0.63-1.00)**	587	34.92	567	37.70	0.93	(0.83-1.04)
		Dose 1, no prior codes cohort[f] (N=13,912)	25	6.45	20	5.75	1.12	(0.62-2.05)	86	5.32	75	5.20	1.02	(0.75-1.40)
17.2	Factors influencing health care	All Doses	42	5.84	61	9.63	**0.61**	**(0.41-0.90)**	201	6.74	183	7.27	0.93	(0.76-1.13)
		All Doses, no prior codes cohort[f] (N=15,748)	6	0.84	10	1.59	0.53	(0.18-1.46)	32	1.08	28	1.12	0.96	(0.58-1.61)
		Dose 1	27	6.69	40	11.00	**0.61**	**(0.37-0.99)**	110	6.53	117	7.76	0.84	(0.65-1.09)
		Dose 1, no prior codes cohort[f] (N=15,748)	4	1.00	7	1.94	0.51	(0.13-1.78)	22	1.32	18	1.20	1.09	(0.58-2.07)

Abbreviations: ER, emergency room; HCUP, Healthcare Cost and Utilization Project; IR, incidence rate; RR, relative rate; CI, confidence interval.

[a]Patient accrual 16-October-2009 through 31-December-2015

[b]Regimen Initiators include males any age with at least one dose of Gardasil.

[c]Only HCUP categories with at least one decreased RR (upper confidence limit >1.0) are presented. Results for all HCUP categories are located in Table Sets 5a-8b in Attachment 1.

[d]Incidence rates per 1,000 person-years.

[e]Bolded relative rate and confidence interval indicates the interval excludes 1.00. Bolded and highlighted relative rate and confidence interval indicates the double false discovery rate adjusted p-value remains significant. Multiplicity adjustment limited to HCUP levels 1 and 2.

[f]Males with codes for the same HCUP category up to 12 months prior to and including the day of first vaccination in any healthcare setting (ER, hospitalization or physician office/outpatient) were excluded from the analysis for that HCUP category.

9.5. VTE

Through 31-December-2015, a total of 31 potential VTE cases in any risk period and 16 potential cases in any self-comparison period were identified, representing 21 and 10 unique males, respectively (Summary Table 3).

Medical record review was conducted on the potential cases identified through 31-December-2014. A total of 21 potential VTE outcomes representing 20 unique males were identified in any risk or self-comparison period. The chart review process for these 21 cases is shown in Summary Table 3, and a line listing for these 21 cases is shown in Table 9D. Medical records were requested for all 21 potential cases and were obtained for 17 of them. Narratives are provided in Table 9C for these 17 potential VTE outcomes. Of these 17 potential cases, 11 VTE diagnoses were confirmed: 5 in the Day 1-60 risk period (1 of these outcomes occurred in the Day 1-14 risk period); 2 in the Day 1-60 self-comparison period; 2 in follow-up time that was neither a risk nor self-comparison period; and 2 that occurred prior to the first dose.

Charts have not yet been received for potential cases identified in 2015.

Days 1-60

During the Days 1-60 post-vaccination risk period for all doses combined, there were 31 potential VTE outcomes (i.e., unconfirmed VTE cases) in the regimen initiator cohort, and 16 potential VTE outcomes during the Days 1-60 post-vaccination self-comparison period (Table 9A). The sum of risk-period days was 10,896,159 among the regimen initiators, and the sum of self-comparison period days was 9,206,654.

Case Review Findings

The shaded columns within Table 9A represent the number of males with VTE outcomes that were included in the claims profile-review and medical record abstraction process. Cumulative through December 2014, 21 potential VTE outcomes were identified in the Days 1-60 all doses combined analysis (12 events occurred in the risk period, and 4 events occurred in the post-vaccination self-comparison period). Those 21 potential VTE outcomes corresponded to 20 unique males. Medical charts for these 21 potential VTE outcomes were requested and abstracted: 17 of those were received for medical record review and 4 charts could not be collected due to administrative reasons (e.g., provider refused, chart unavailable, etc.). All 17 medical records received were reviewed for

diagnosis confirmation: 11 potential VTE outcomes were confirmed in 11 unique males, 5 were determined not to be VTE outcomes, and one was marked as having insufficient information. For the 11 confirmed VTE outcomes, 5 occurred during the risk period (one occurred 42 days following the most recent dose, and the male had 2 doses prior to the outcome; one occurred 6 days following last vaccination, and the male had 3 doses prior to the outcome; one occurred 41 days after last vaccination, and the male had 1 dose prior to the outcome; one occurred 46 days after last vaccination, and the male had 3 doses prior to the outcome; one occurred 42 days after last vaccination, and the male had 2 doses prior to the outcome). Two VTE outcomes occurred during the post-vaccination self-comparison period (one occurred 122 days following the most recent dose, and the male had 2 doses prior to the VTE outcome; one occurred 143 days following last vaccination, and the male had 2 doses prior to the VTE outcome). Two confirmed VTE outcomes occurred outside of the risk or the post-vaccination self-comparison period. Two confirmed outcomes occurred prior to the first dose. An additional medical chart will be sought for the case of potential VTE outcome with insufficient information to determine diagnosis, and the information will be included in the next round of medical record abstraction. New potential VTE events (n=10) electronically identified as part of this report will be included in the next round of claims-profile review and medical record abstraction.

Narratives are provided in Table 9C for the 17 potential VTE outcomes reviewed by the physician specialists. The narratives indicate that, of the 5 non-confirmed cases, the medical records did not indicate a diagnosis of VTE for 4 of the cases and it was determined that one male had 2 potential outcomes: one confirmed as a VTE outcome and the other determined not to be a second VTE outcome (i.e., not confirmed).

Days 1-14

Potential VTE outcomes in Days 1-14 are a subset of potential VTE outcomes on Days 1-60. During the Days 1-14 post-vaccination risk period for all doses combined, 8 potential VTE outcomes were observed in the regimen initiator cohort (Table 9B) while 4 potential VTE outcomes were observed in the Days 1-14 self-comparison period. These are cumulative counts from the accrual period 16-October-2009 to 31-December-2015. Males may have had more than one potential VTE outcome. The sum of risk period days was 2,627,286, and the sum of self-comparison period days was 2,314,250.

Case Review Findings

The shaded columns within Table 9B represent the number of males with VTE outcomes that were included in the profile-review and medical record abstraction process that occurred since the last annual report. Cumulative through December 2014, 8 potential VTE outcomes were identified in the Days 1-14 all doses combined analysis. Those 8 potential VTE outcomes corresponded to 7 unique males. Medical charts for the 8 potential VTE outcomes were requested and abstracted: 6 were received for medical record review, and 2 charts were not collected due to administrative reasons. Of the 6 VTE outcomes reviewed by physician specialists, 5 were confirmed as VTE cases in 5 unique males.

Summary Table 3. Count and Case Review Summary of Venous Thromboembolism Outcomes among the Regimen Initiators[a,b] (N=106,110) in Risk Period versus Post-Vaccination Self-Control Period by Outcome Setting All Doses Combined

	Number of Potential Claims-Based Cases[a,b,c]		Number of Potential Claims-Based Cases without Charts Available	Number of Potential Claims-Based Cases Awaiting Review or Undergoing Review	Confirmed Cases[d,e] (N=11)				
					Not within Risk or Self-Comparison Periods (N=4)	Days 1-14 (N=1)		Days 1-60 (N=7)	
	Risk Period	Self-Control Period				Risk Period[f] (Person-Time =2,627,286)	Self-Comp Period[f] (Person-Time =2,314,250)	Risk Period[f] (Person-Time =2,314,250)	Self-Comp Period[f] (Person-Time =10,896,159)
Emergency Room	0	0	0	0	0	0	0	0	0
Hospital	5	2	0	0	0	1	0	4	2
Outpatient	16	8	4	0	4	0	0	1	0
Total	**21**	**10**	**4**	**0**	**4**	**1**	**0**	**5**	**2**

[a] Cumulative accrual 16-October-2009 through 31-December-2015
[b] Regimen Initiators include males any age with at least one dose of Gardasil
[c] Claims from hospital, ER, and outpatient settings. Males with claims from mulitple care settings related to a single event are counted once. The first VTE outcome was counted and any subsequent outcomes > 7 days after the previous ER visit date, hospitalization service date, or physician visit date, will be assumed to represent another event.
[d] Cases in Day 1-14 risk/comparison period are also counted in the Day 1-60 risk/comparison period.
[e] Person-time represents all eligible days of risk and comparison period times among regimen initiators.
[f] Chart review results from accrual period 16-October-2009 through 31-December-2014. Charts have not yet been received for potential cases identified in 2015.

9.6. Day 0 Events

For the Day 0 analyses, 3 comparison groups were used: a post-vaccination self-comparison period and 2 concurrent matched comparison cohorts. At the request of the SRC, the results for 2 of the comparison groups considered less relevant (the self-comparison period and the concurrent control cohort #1) were moved from the report table set to Attachment 2 (Appendix I) for reference. The Day 0 analysis using concurrent control cohort #2 (i.e., matched males vaccinated with a vaccine other than GARDASIL®) is summarized below and presented in Summary Table 4.

Day 0 Analysis Using Concurrent Controls with Other Vaccine Visit - All Doses Combined

Of 189,343 GARDASIL® doses, 80% (152,814/189,343) were matched to eligible controls with a physician office visit for another vaccine. Counts of the pre-specified Day 0 events that occurred among regimen initiators and controls matched on the day of the physician office visit associated with another vaccine administration (Td/Tdap, meningococcal, or influenza (injectable)) are presented for all doses combined (Table 10A) and for Dose 1 (Table 10B) by healthcare setting.

Among the regimen initiators there were 597 emergent events (i.e., without claims for the same HCUP category in the month prior to the vaccination date) on Day 0 all doses combined (83 syncope, 76 epilepsy/convulsions, 121 head trauma, and 316 allergic reactions); all but 7 events were associated with an outpatient visit (Table 10A). Among the matched controls with another vaccine, there were 633 emergent events on Day 0 (101 syncope, 122 epilepsy/convulsions, 152 head trauma, and 252 allergic reactions); all but 23 were associated with an outpatient setting. A further breakdown of the allergic reaction outcomes by ICD-9/ICD-10 diagnosis code is presented in Table 10C. To further investigate the imbalance of Day 0 counts (67 events among the regimen initiators and 5 among the matched comparators with another vaccine) identified by ICD-9 code 995.20 (other and unspecified adverse effect of drug, medicinal and biological substance, includes allergic reaction), the concordance between ICD-9 code 995.20 and ICD-9 code 995.3 (allergy, unspecified not elsewhere classified) was evaluated separately among the regimen initiators and concurrent controls with other vaccine visit. There were no cases with both Day 0 ICD-9 code 995.20 and ICD-9 code 995.3 among the regimen initiators or the matched comparison cohort. As a follow-up step, the SRC suggested generating claims-profiles for the males (n=67 initiators and n=5 comparators) with Day 0 events identified by ICD-9 code 995.20 to evaluate the treatment patterns following the Day 0 event. Based on the profile review, the events identified with ICD-9 code 995.20 all appeared to be limited to Day 0 and had no follow-up with medications (steroids or epinephrine), or services (ED/ER or hospitalization) that might be expected with anaphylaxis. Given these results, the SRC does not have any additional concerns and does not believe events identified with ICD-9 code 995.20 correspond to serious allergic reactions. However, the SRC noted that other allergic reaction codes may represent serious reactions such as ICD-9 code 519.11 (acute

bronchospasm), ICD-9 995.0 (other anaphylactic shock not elsewhere classified, includes adverse effect of medicinal substance), and ICD-9 code 995.1 (angioneurotonic edema, Quincke's edema). The SRC suggested generating claims-profiles for regimen initiators and comparators with Day 0 events identified by these codes to evaluate potential seriousness. The findings of this claims-profile review will be presented in future reports.

Day 0 Analysis Using Concurrent Controls with Other Vaccine Visit - Dose 1

Of the 106,110 first doses of GARDASIL®, 96% (102,858/106,110) were matched to eligible controls with a physician office visit for another vaccine. Among the regimen initiators, there were 460 emergent events on Day 0 for Dose 1 (77 syncope, 57 epilepsy/convulsions, 105 head trauma, and 221 allergic reactions), with all but 6 events associated with an outpatient visit. There were 332 Day 0 events among the matched controls with another vaccine (56 syncope, 67 epilepsy/convulsions, 98 head trauma, and 107 allergic reactions); all but 17 events were associated with an outpatient visit (Table 10B). A further breakdown of the allergic reaction outcomes by ICD-9 diagnosis codes is presented in Table 10D.

Summary Table 4. Count of Potential Outpatient, Emergency Room Visit, and Hospitalization Day 0 Outcomes among Regimen Initiators and Controls

Acute Events[a]	Analysis	Day 0 Counts	
		Regimen Initiator Matched Cohort 2: Risk Period[c]	Concurrent Control Matched Cohort with Other Vaccine Visit[d]
		All Doses: N= 94,591 Males (152,814 doses)	All Doses: N= 129,408 Males (152,814 visits)
		Dose 1: N= 102,858 Males (102,858 doses)	Dose 1: N= 91,447 Males (102,858visits)
Syncope	All Doses	97	111
	Dose 1	87	61
Epilepsy, Convulsions	All Doses	96	160
	Dose 1	76	89
Head Trauma	All Doses	185	232
	Dose 1	145	142
Allergic Reactions	All Doses	334	277
	Dose 1	233	117
Total Events	**All Doses**	712	780
	Dose 1	541	409

[a]Cumulative accrual 16-October-2009 through 31-December-2015

[b]Concurrent controls with no Gardasil doses, but with health care visit were matched (1:1) to Regimen Initiators by age, calendar year, and calendar quarter. 100% doses were matched to controls.

[c]Doses limited to first continuous enrollment period.

[c]Concurrent Controls with no Gardasil doses, but with visit for Td/Tdap, Meningococcal, or Influenza vaccine were matched (1:1) to Regimen Initiators by age, calendar year, and calendar quarter. 80% doses were matched to controls.

Medical Record Review of a Sample of Potential Events on Day 0 for Dose 1

As a reminder, included in the 4th Annual Interim Report (December 2015), a sample of medical records of Day 0 outcomes occurring at Dose 1 were sought to determine the nature and timing of the potential events relative to vaccination. Records were sought for syncope (n=10 regimen initiators, n=10 comparators), head trauma (n=10 regimen initiators, n=10 comparators), allergic reactions ICD-9 995.3 (allergy unspecified, not elsewhere classified) (n=10 regimen initiators), and allergic reactions ICD-9 code 995.0 (other anaphylactic shock not elsewhere classified, includes adverse effect of medicinal substance) (n=2 regimen initiators). These records were sought at random from the available patients with Day 0 events, except for ICD-9 code 995.0 where there were only two cases. Narratives for these potential Day 0 events were prepared by one of the CRC physicians. The results of Day 0 case review and narratives were presented in the 4th Annual Interim Report, and are provided as reference in Attachment 2 Appendix J. Of the 52 medical charts requested for this sample of Day 0 events, 41 (79%) were received and reviewed for syncope (9 initiators and 7 comparators), head trauma (7 initiators and 9 comparators), allergy unspecified (ICD-995.3) (8 initiators), and other anaphylactic shock (ICD-9 995.0) (1 initiator). A summary of the interpretation of the Day 0 events in relation to the vaccine based on the narratives is provided in Attachment 2 Appendix K. For 28 of the 41 Day 0 events (68%), the medical record indicated that the event occurred prior to vaccination, 7 medical charts did not mention the occurrence of Day 0 event on the day of vaccination (most of these indicated the patient had a history of the event, see details below), and 2 medical charts did not mention receipt of the vaccine on Day 0 (one of them represented a chart from a different site of service, see details below). There were 4 events that occurred on Day 0 following vaccination for which both the vaccination and the event was documented: 2 syncope events among the GARDASIL® recipients, and 2 syncope events among the comparators. PPD

There were 7 medical charts that had no mention of the event. In most cases these patients did have evidence in the medical record of a history of the event (such as prior allergic reaction). For the 2 patients where the medical record does not mention a vaccination on Day 0, the first case is a comparator, and the medical record obtained PPD for head trauma that occurred on the same day PPD . The medical record associated with the physician office visit where the vaccine was administered was sought, but not obtained; however, the head trauma appears unrelated to the vaccine, even if it had been received earlier the same day; the second case is a GARDASIL® recipient, for whom a medical chart from the same day as the vaccine administration did not document the vaccination and indicated the patient had a PPD near-syncope.

Concomitant Vaccinations

Because GARDASIL® recipients and comparators can receive other vaccines on Day 0, the SRC requested an assessment of concomitant vaccine use on Day 0 for the 2 cohorts in order to inform future analyses. Vaccines were limited to those defined in the current study: GARDASIL®, Td/Tdap, meningococcal, and influenza. Among the regimen initiators, 70% received GARDASIL® alone on Day 0, and the remaining 30% received any combination of GARDASIL® and/or Td/Tdap and/or meningococcal and/ or influenza vaccines. Among the matched comparators, 22% received meningococcal alone, 17% received Td/Tdap alone, and 39% received influenza alone, while the remaining 22% received any combination of Td/Tdap and/or meningococcal and/ or influenza vaccines.

9.7. Death

Nine potential deaths were identified among recipients of GARDASIL® in the PPD and the SSA DMF data sources between receipt of the first dose and 60 days after receipt of the last dose (Table 11A). Of those, 7 were identified as part of previous annual reports and information was provided already on these 7 cases PPD and 2 were identified since the last report PPD All 7 of these males were 14 to 18 years old at the time of the death claims. The timing of these claims related to death ranged between 0 to 56 days after a dose of GARDASIL®. The narratives summarizing all of the information available on the deaths as of today is provided in Table 11B.

Medical records were requested for the 2 deaths identified as part of the 2015 annual report PPD and reviewed by a physician. For ID PPD there was no mention of death in the medical record. For IDs PPD the cause of death was PPD An NDI search will be performed at the end of the study.

As requested by the SRC during the review of last year's report, an out of sequence NDI search was conducted for ID PPD for which the claim for death occurred on the day of vaccination in PPD Previously, PPD separately reviewed the claims-profile history including the patient's entire enrollment period. The claims profile indicated a physician office visit (family/general practice) followed by laboratory claims on the same day. The patient had procedure claims for GARDASIL® administration associated with the physician office visit, while diagnostic codes for sudden death (ICD-9 798.2) appeared on the laboratory claim. There were no claims after the date of the claims-based death event. The profile also reports PPD No services typically associated with mortality (such as ambulance services or ER visit) are observed in the profile. Additionally, the death does not appear in the SSA DMF. The NDI search did not confirm death for ID PPD (NDI Class=5 (low probability of being a match), Status=0 (not a matched death), NDI Score= -23).

For the other 6 potential claims-based deaths identified up through last year's report, 5 were confirmed by the NDI search (Status=1 (matched death)), while one potential death (ID PPD was not eligible for the NDI search.

Medical records will be requested for the 2 recently identified potential deaths in this report (ID PPD in Table 11B). In the interim, as requested by the SRC, preliminary narrative information for these 2 potential deaths was summarized using the patient's medical claims history for the SRC's review. A physician reviewed the medical claims history for these 2 potential deaths and summarized the information related to the death. Summary narratives were written by PPD for each of the 7 potential deaths identified through 2014 including: 1) a summary of the facts related to the death, i.e., medical chart data, claims database enrollment, SS DMF status, and NDI data; 2) an assessment of the likelihood of death; 3) cause of death from the NDI for high probability matches; and 4) any attribution to GARDASIL® recorded in the medical records. The summary narratives are provided in Table 11B.

To provide additional context for interpretation of the potential deaths among GARDASIL® recipients through this year's report, national death rates for males 5 to 29 years of age,[11] and age-standardized mortality for the GARDASIL® initiators are presented in Table 11D. The observed claims-based and expected number of deaths in each age group among the GARDASIL® initiators is also presented. The racial distribution of people in the PPD was used to determine the expected number of deaths among initiators using age-, sex-, and race-specific national death rates. Among 106,110 GARDASIL® initiators, person-years of follow-up between first dose and a date up to 60 days after last dose were tabulated by age group. The expected number of deaths was 9, similar to the observed number of potential deaths (n=9).

A final NDI search will be conducted and summarized in the Final or a Supplemental Report.

9.8. Autoimmune Conditions

The autoimmune cohort is a subset of the regimen initiator cohort required to have 12 months of continuous enrollment prior to the first dose of GARDASIL®. During the accrual period 16-October-2009 to 31-December-2015, a total of 62,615 male GARDASIL® recipients were eligible for the autoimmune cohort, accounting for 59% (62,615 of 106,110) of the regimen initiator cohort. For the purpose of further autoimmune comparative analysis, the GARDASIL® recipients were matched to males who did not receive GARDASIL®, and also had a physician office/outpatient visit (that served as the matching index date) and 12 months of membership prior to the index date. Of the 62,615 males in the autoimmune cohort, 52,679 (84%) were propensity-score matched to an equal number of comparator males not vaccinated with GARDASIL®.

Demographic Characteristics of Pre-Matched Gardasil Recipients and Comparators for the Propensity Score Process

Prior to the propensity score matching process, an empirical characterization of GARDASIL® users involving tabulation of the 100 most frequently occurring diagnoses, procedures, and drugs dispensed in the 12-month baseline period (prior to and including the day of cohort entry (day of vaccination for initiators)) was conducted among the 62,625 males in the autoimmune cohort identified in 2015 and the 1,124,031 males not vaccinated with GARDASIL® (Tables 13-16). The cohorts represented in these tables are

before matching and are not age-adjusted. The tabulated diagnoses and procedures among the GARDASIL® recipients relative to non-recipients reflect age-related characteristics that are expected and healthcare services associated with vaccination.

Healthcare Utilization Among Matched Cohorts

To compare the GARDASIL® recipients and non- GARDASIL® comparators in the matched autoimmune analysis, healthcare utilization factors measured in the 12-month baseline period are presented side by side for the matched autoimmune cohort (n=52,679) and the matched comparators (n=52,679) (Table 12a). The mean number of physician visits, ER visits, hospitalizations, procedures, laboratory tests, total health care costs, and number of drugs dispensed are similar among the matched cohorts. The matched autoimmune cohort had a slightly higher number of mean hospitalization days as compared to the matched comparators (6.13 versus 5.32 days). The distribution of annual household income and net worth was also similar among the matched autoimmune cohort and comparators.

At the request of the SRC, characteristics measured in the 12-month baseline period are presented for the autoimmune cohort and comparators: the matched autoimmune cohort and matched comparators, and the unmatched recipients. These results are presented in Table 12B.

Health Plan Enrollment Among Matched Cohorts

At the SRC's recommendation, to explore the duration of health plan enrollment among propensity-score matched initiators (n=52,679) and matched comparators (n=52,679), a KM curve was constructed (Attachment 1, Figure 3) of the proportion of males in each cohort that remained enrolled in the health plan, measured in months from cohort entry date. The KM curve includes the time from cohort entry date through disenrollment from the health plan or censoring at the end of the study period on the x-axis, and percent remaining enrolled in the health plan on the y-axis. The graph includes 2 separate lines: the solid line represents the matched initiators (n=52,679) and the dashed line represents the matched comparison cohort (n=52,679). For the initiators, 67% remained in the health plan 12 months after the first dose; 46% remained for 24 months; and 32% remained for 36 months. Similar proportions were observed for the matched comparison cohort at 12 (64%), 24 (44%), and 36 (32%) months.

Claims-Based Autoimmune Outcomes

As of 31-December-2015, a total of 256 potential claims-based autoimmune cases were identified in the entire autoimmune cohort (n=62,615) (Table 17 and Summary Table 5). The sum of risk period person-time was 44,956 person-years. In the matched cohort analysis (n=52,679 in each cohort), 214 potential claims-based outcomes were identified in the autoimmune cohort of GARDASIL® recipients (Table 18 and Summary Table 5) and 279 in the comparison cohort (Table 19 and Summary Table 5). The sum of risk period person-time was 37,232 person-years and 50,658 person-years in the matched autoimmune cohort and comparison cohort, respectively.

Among the matched vaccinated autoimmune cohort (n=52,679), the 214 potential new-onset autoimmune diagnoses electronically identified included: 2 ITP, 8 SLE, 8 RA, 5 juvenile chronic polyarthritis, 2 psoriatic arthritis, 40 ankylosing spondylitis, 5 reactive arthritis, 19 Crohn's disease, 15 ulcerative colitis, 19 Type 1 diabetes, 27 Hashimoto's disease, 16 Graves' disease, 17 MS, one ADEM, one other demyelinating diseases of the central nervous system, one neuromyelitis optica, one GBS, 2 optic neuritis, and 24 uveitis.

Among the matched males not vaccinated with GARDASIL® (n=52,679), the 279 potential new-onset autoimmune diagnoses electronically identified included: 6 ITP, 2 autoimmune hemolytic anemia, 9 SLE, 8 RA, 8 juvenile chronic polyarthritis, 2 psoriatic arthritis, 43 ankylosing spondylitis, 5 reactive arthritis, 22 Crohn's disease, 13 ulcerative colitis, 16 Type 1 diabetes, 36 Hashimoto's disease, 29 Graves' disease, 40 MS, 3 ADEM, 2 other demyelinating diseases of the central nervous system, one Guillain-Barre Syndrome, 3 optic neuritis, and 31 uveitis.

These claims-based counts of autoimmune outcomes are not adjusted for differences in follow-up time (37,232 person-years or an average of 214 days for each of the matched GARDASIL® recipients vs 50,568 person-years or an average of 279 days for each of the matched comparators). This difference in person-time follow-up of the cohorts arises due to the anchoring of the follow-up time among the comparators to cohort entry, with the assumption of 18 months follow-up after that point, while the GARDASIL® recipient follow-up extends 6 months after each dose (up to 18 months), and not all recipients are observed to receive all 3 doses. For the Final Report, RRs will be calculated for each of

the chart-confirmed autoimmune outcomes accounting for differences in person-time among the cohorts.

Case Review Findings

Figures F-H document the autoimmune case review process completed for this report among the matched males comprising each of the GARDASIL® and comparison cohorts, as well as for potential cases in the autoimmune cohort of GARDASIL® recipients who were not able to be matched, as of 31-December-2014. Outcome adjudication has yet to be completed for the potential new-onset autoimmune outcomes that were identified. As requested by the SRC, medical record review and outcome adjudication is currently being conducted for a sample of autoimmune outcomes: 10 gastroenterology outcomes; 10 endocrinology outcomes; 11 rheumatology outcomes; and 11 neurology outcomes. Adjudication results (including narratives) were completed for the sample of 10 endocrinology outcomes, and presented to the SRC. The SRC members approved of the endocrinology narratives, and adjudication of all potential new-onset endocrinology outcomes can be initiated. After successful evaluation of the updated CRC SOP for all 4 categories of outcomes, the CRCs will review and adjudicate all potential new-onset autoimmune cases in the study. When adjudication results (including narratives) for all potential new-onset autoimmune outcome cases are available, they will be presented in future reports in Tables 17 - 21 and Summary Table 5.

Summary Table 5: Case Review Summary and Counts of Claims-Based and New-Onset Autoimmune Outcomes among All Gardasil Recipients of the Autoimmune Cohort (N=62,615), Matched Autoimmune Cohort (N=52,679), and Matched Comparison Cohort (N=52,679)

Condition	Cohort	Number of Potential Claims-Based Cases[a]	Number of Charts Not Available[b]	Number of Charts in Review Process[b]	Number Cases Not Confirmed After Chart Review[b]	Number of Confirmed Cases		
						Symptom Onset Preceded Vaccination	New Onset but Not within Risk Period	New Onset within Risk Period
Immune Thrombocytopenia	Autoimmune	3						
	Matched Autoimmune	2						
	Matched Comparison	6						
Autoimmune Hemolytic Anemia	Autoimmune	0						
	Matched Autoimmune	0						
	Matched Comparison	2						
Systemic Lupus Erythematosus	Autoimmune	10						
	Matched Autoimmune	8						
	Matched Comparison	9						
Rheumatoid Arthritis	Autoimmune	10						
	Matched Autoimmune	8						
	Matched Comparison	8						
Juvenile Chronic Polyarthritis	Autoimmune	6						
	Matched Autoimmune	5						
	Matched Comparison	8						
Psoriatic Arthritis	Autoimmune	3						
	Matched Autoimmune	2						
	Matched Comparison	2						
Ankylosing Spondylitis	Autoimmune	49						
	Matched Autoimmune	40						
	Matched Comparison	43						
Reactive Arthritis	Autoimmune	5						
	Matched Autoimmune	5						
	Matched Comparison	5						

[a]Cumulative accrual 16-October-2009 through 31-December-2015

[b]Chart review results from accrual period 16-October-2009 through 31-December-2014. Charts have not yet been reviewed for potential new-onset cases identified in 2014.

[c]Total approximate follow-up (person-years): Autoimmune Cohort (44,956), Matched Autoimmune Cohort (37,232), Matched Comparison Cohort (50,658).

Summary Table 5: Case Review Summary and Counts of Claims-Based and New-Onset Autoimmune Outcomes among All Gardasil Recipients of the Autoimmune Cohort (N=62,615), Matched Autoimmune Cohort (N=52,679), and Matched Comparison Cohort (N=52,679)

Condition	Cohort	Number of Potential Claims-Based Cases[a]	Number of Charts Not Available[b]	Number of Charts in Review Process[b]	Number Cases Not Confirmed After Chart Review[b]	Number of Confirmed Cases		
						Symptom Onset Preceded Vaccination	New Onset but Not within Risk Period	New Onset within Risk Period
Crohns Disease	Autoimmune	23						
	Matched Autoimmune	19						
	Matched Comparison	22						
Ulcerative Colitis	Autoimmune	21						
	Matched Autoimmune	15						
	Matched Comparison	13						
Insulin Dependent Diabetes Mellitus (Type 1)	Autoimmune	21						
	Matched Autoimmune	19						
	Matched Comparison	16						
Hashimotos Disease	Autoimmune	30						
	Matched Autoimmune	27						
	Matched Comparison	36						
Graves Disease	Autoimmune	18						
	Matched Autoimmune	16						
	Matched Comparison	29						
Multiple Sclerosis	Autoimmune	18						
	Matched Autoimmune	17						
	Matched Comparison	40						
Acute Disseminated Encephaplomyelitis	Autoimmune	1						
	Matched Autoimmune	1						
	Matched Comparison	3						
Other Demyelinating Diseases of CNS	Autoimmune	2						
	Matched Autoimmune	1						
	Matched Comparison	2						

[a]Cumulative accrual 16-October-2009 through 31-December-2015

[b]Chart review results from accrual period 16-October-2009 through 31-December-2014. Charts have not yet been reviewed for potential new-onset cases identified in 2014.

[c]Total approximate follow-up (person-years): Autoimmune Cohort (44,956), Matched Autoimmune Cohort (37,232), Matched Comparison Cohort (50,658).

Summary Table 5: Case Review Summary and Counts of Claims-Based and New-Onset Autoimmune Outcomes among All Gardasil Recipients of the Autoimmune Cohort (N=62,615), Matched Autoimmune Cohort (N=52,679), and Matched Comparison Cohort (N=52,679)

Condition	Cohort	Number of Potential Claims-Based Cases[a]	Number of Charts Not Available[b]	Number of Charts in Review Process[b]	Number Cases Not Confirmed After Chart Review[b]	Number of Confirmed Cases		
						Symptom Onset Preceded Vaccination	New Onset but Not within Risk Period	New Onset within Risk Period
Neuromyelitis Optica	Autoimmune	1						
	Matched Autoimmune	1						
	Matched Comparison	0						
Guillain-Barre Syndrome	Autoimmune	2						
	Matched Autoimmune	2						
	Matched Comparison	1						
Optic Neuritis	Autoimmune	2						
	Matched Autoimmune	2						
	Matched Comparison	3						
Uveitis	Autoimmune	31						
	Matched Autoimmune	24						
	Matched Comparison	31						

[a]Cumulative accrual 16-October-2009 through 31-December-2015

[b]Chart review results from accrual period 16-October-2009 through 31-December-2014. Charts have not yet been reviewed for potential new-onset cases identified in 2014.

[c]Total approximate follow-up (person-years): Autoimmune Cohort (44,956), Matched Autoimmune Cohort (37,232), Matched Comparison Cohort (50,658).

Figure F. Medical Record Abstraction Process - Matched Initiators through 31-December-2014

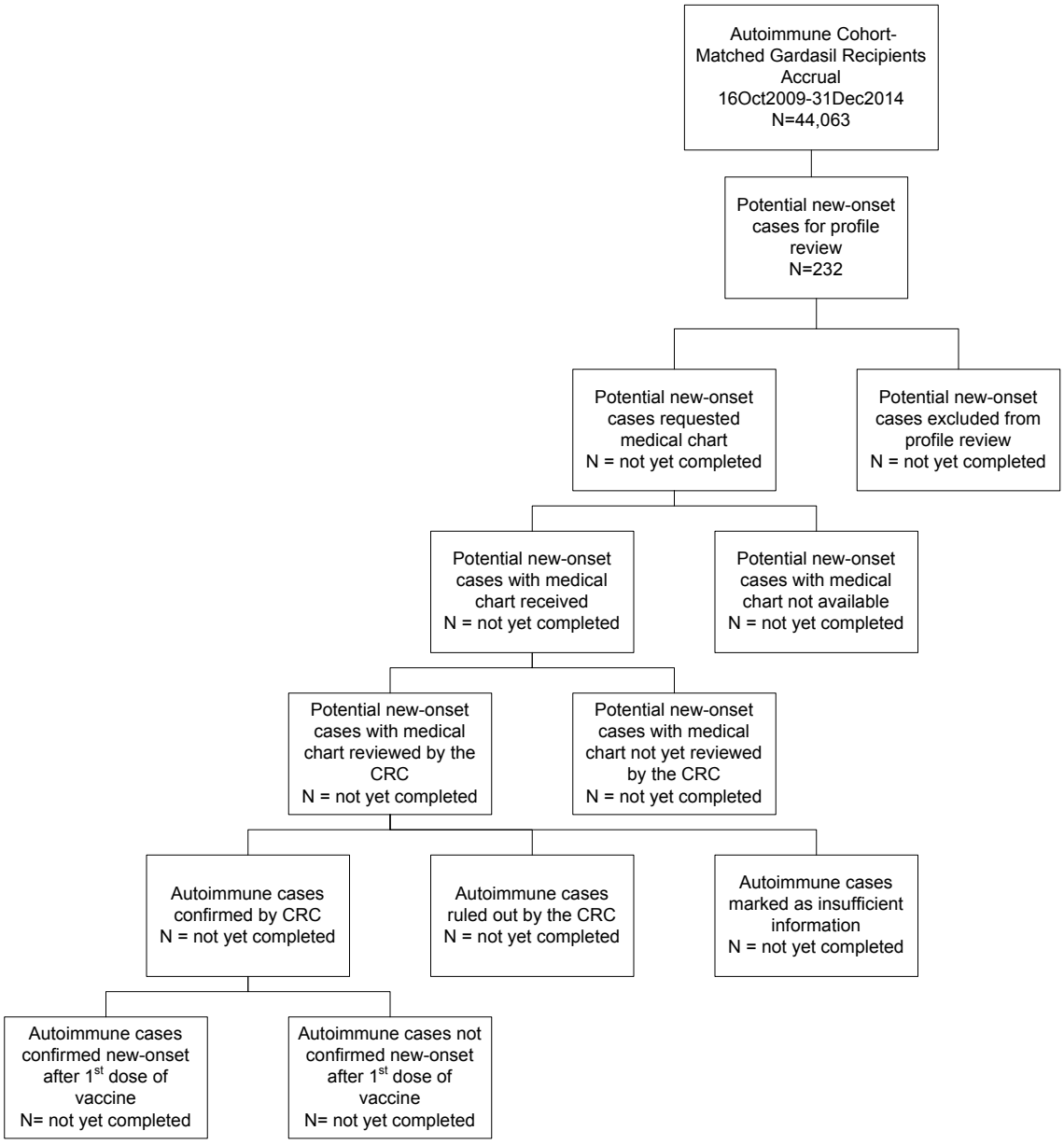


Figure G. Medical Record Abstraction Process - Comparators through 31-December-2014

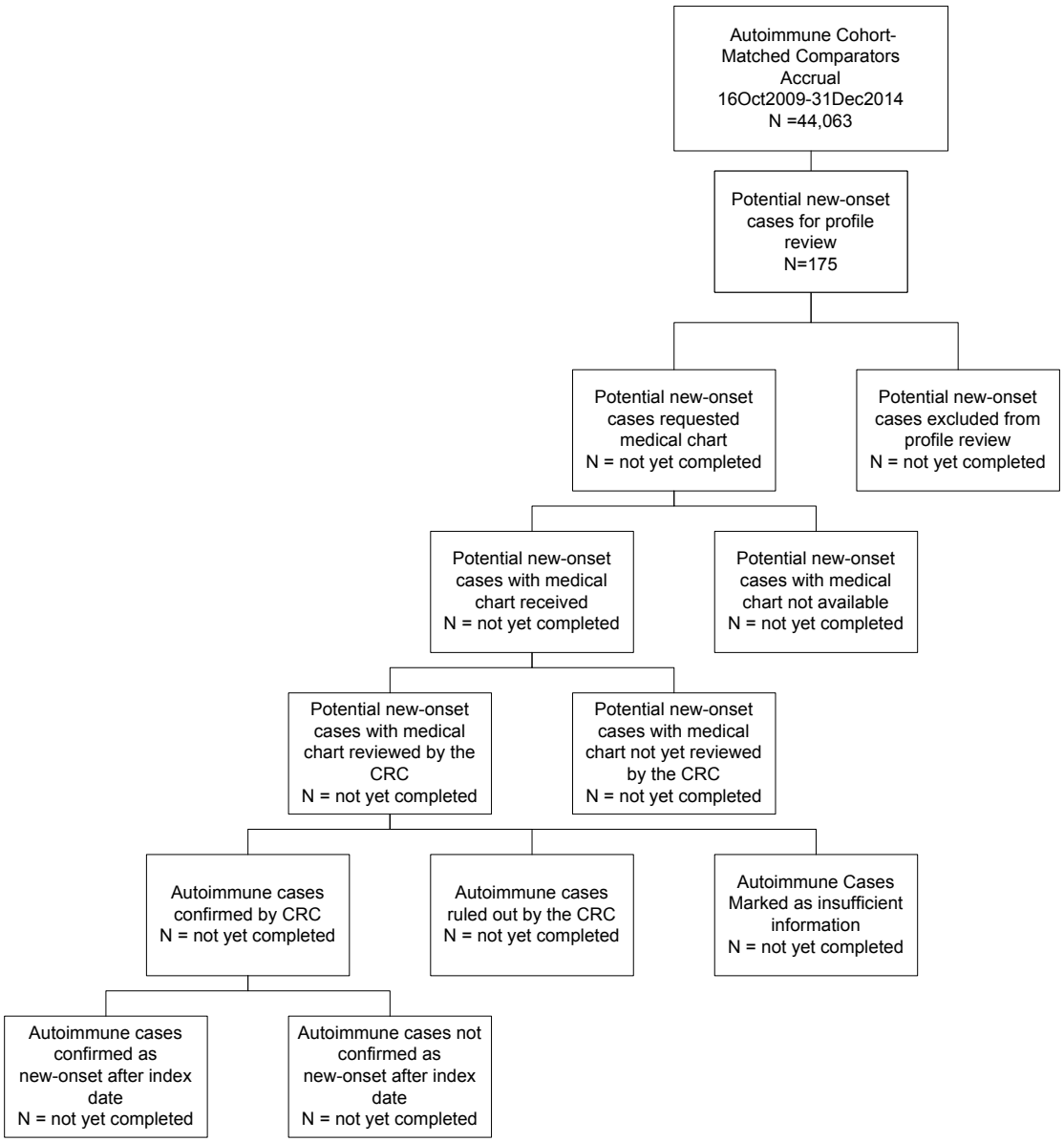
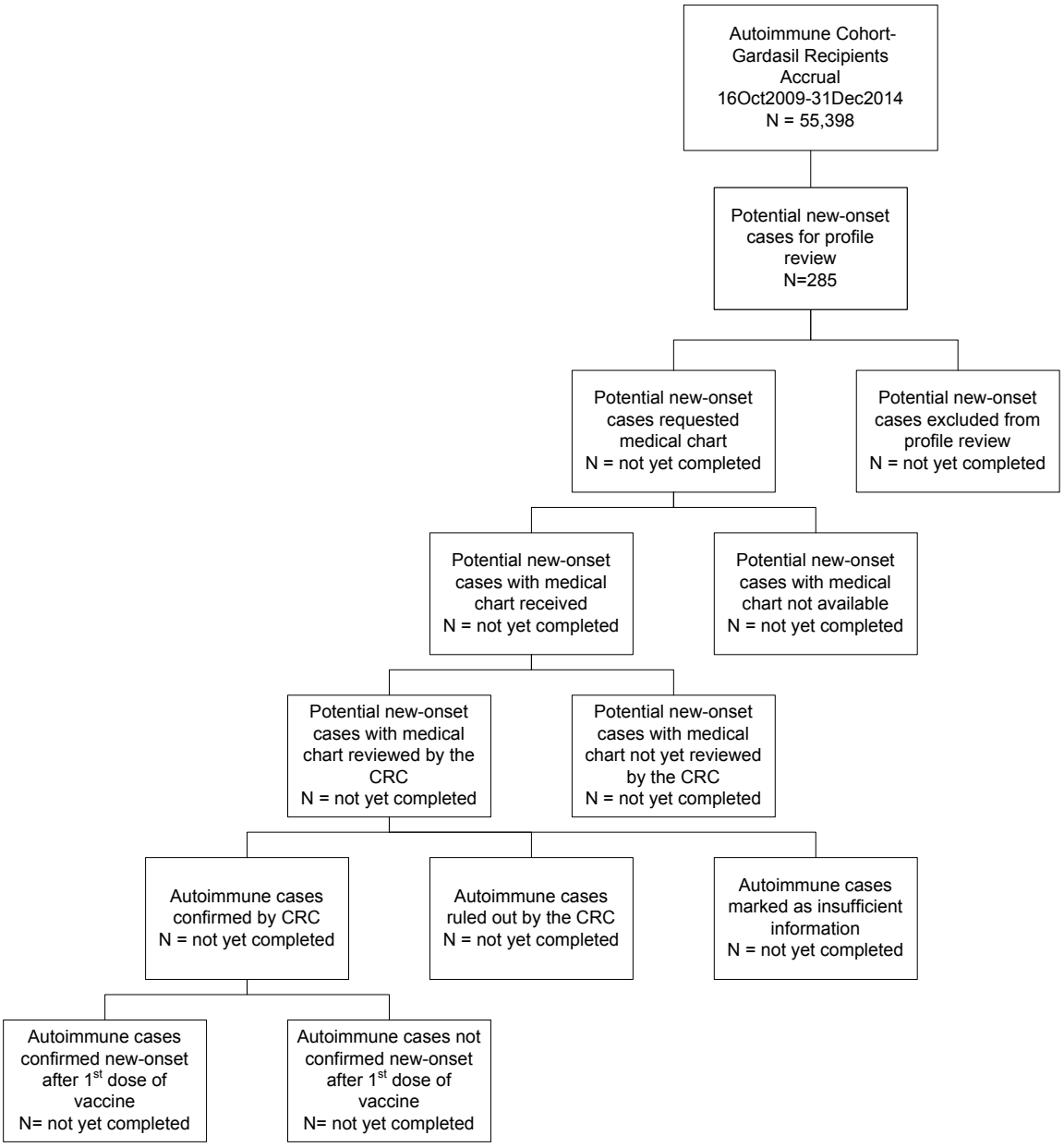


Figure H. Medical Record Abstraction Process - All Initiators of the Autoimmune Cohort through 31-December-2014



10. RESULTS SUMMARY/DISCUSSION

This Annual Interim Report reflects patient accrual from 16-October-2009 through 31-December-2015 with follow-up for outcomes through 29-February-2016 (i.e., follow-up extends for approximately 2 months after the end of patient accrual).

There were 106,110 males who received at least one dose of GARDASIL®, 55,371 males who received at least 2 doses of the vaccine, and 28,411 males who received at least 3 doses of the vaccine, for a total of 189,892 doses of GARDASIL® administered to 106,110 males. The age distribution of the males receiving GARDASIL® reflects the population for which the vaccine is indicated (most common age range, 11 to 18 years). There continues to be a relatively low percentage of regimen initiators who complete the 3 dose schedule. This may be due to incomplete adherence to the vaccine series, which requires 3 separate visits to a physician's office in a population that tends to have limited healthcare use, as observed in other US studies. The high health plan turnover may also play an important role: among initiators in the autoimmune matched cohort, 67% remain in the health plan after 12 months; 46% after 24 months; and 32% after 36 months. Of males receiving 3 doses of the vaccine, 69% (19,610/28,411) were included in the regimen completer cohort (ages 9 and 26 years at first dose, continuously enrolled throughout their GARDASIL® series). The number of regimen completers observed is the same at the end of the third and fourth quarters in 2015 and only slightly higher than at the end of the second quarter in 2015. A similar plateau is observed among the regimen initiators with 3 doses of the vaccine. The plateau observed in the number of regimen completers and regimen initiators with 3 doses of the vaccine is due to incomplete follow-up so that receipt of a third vaccine dose is not yet observed. Future analyses will allow for additional follow-up time to observe administration of Dose 2 and Dose 3. Receipt of Dose 2 and Dose 3 takes more follow-up time than the recommended schedule, and initiation at an earlier age would more likely ensure series completion. When stratified by year of initiation, series completion was slightly lower in 2013 and 2014 as compared to 2012, most likely due to insufficient follow-up time for series completion among individuals who received their 1st dose of Gardasil in 2013 and 2014. These descriptive results on the pattern of GARDASIL® use among males in the PPD were presented at the 31st International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ISPE) in August 2015.[15]

The duration of self-comparison periods is truncated in this Interim Report, resulting in a slight imbalance in the follow-up time observed in the risk and self-comparison periods. However, IRs and RR provided for general safety analyses account for varying follow-up time. To aid in the interpretation of counts of VTE outcomes, the sum of risk period and self-comparison period days were calculated for the Day 1-60 and Day 1-14 analyses. For the Day 1-60 all doses combined analysis, the ratio of risk period days to self-comparison period days was 1.18. This means that there was 18% more risk days than self-comparison days. For the Day 1-14 all doses combined analysis, the ratio of risk period days to self-comparison days was 1.14. This means that there was 14% more risk days than self-comparison days.

The study design aims to address certain limitations of the study setting. This study involves the description and follow-up of patients who receive GARDASIL® (and select comparators) in routine patient care settings. The identification of study exposures is based on health insurer claims and reflects interactions between patients and the health care system for which payment is sought. Some of the study findings may be influenced by the nature of these source data. For example, the described patient characteristics are based on claims associated with intermittent services arising from the complex interplay between patients and caregivers, and include a combination of actual patient characteristics, “rule-out” diagnoses that are submitted to the insurer in order to justify a service, and other uncertainties about what aspects of a healthcare service are coded when a claim for reimbursement is submitted. The data generation mechanism that serves as a foundation for this study requires a translation from the sequence of insurance claims present in the data into a patient’s medical history at a particular point in time, and similarly into a distinction between acute events and chronic conditions.[14] The complexity of this data source that arises from administrative capture of routine healthcare provides a strength in that the study results will be most generalizable to typical use of GARDASIL®, permitting direct inferences to patients. However this complexity is also associated with challenges including uncertain diagnoses and timing of those diagnoses, and potentially incomplete recording of medical services, including receipt of vaccinations outside of the health plan.[16-18] This study includes several features that aim to address these uncertainties, including confirmation of both the diagnosis and timing of study outcomes through select medical record confirmation (for

autoimmune, VTE, select Day 0 events, and death outcomes) and a mix of self-controlled and concurrent cohort designs.

General safety outcomes were evaluated during follow-up in the 139 pre-specified HCUP categories. Overall, there were 8 HCUP categories that showed a significant increase in rate during the vaccination risk period. Following adjustment for multiple comparisons, 4 HCUP categories retained a significantly increased RR: 'ear conditions' (HCUP 6.8); 'otitis media' (HCUP 6.8.1); 'cellulitis and abscess of arm' (HCUP 12.1.1.3); and 'concussion' (HCUP 16.4.1). Of the 8 HCUP categories with elevated RRs, one was in the Days 1-14 risk period, and 7 were in the Days 1-60 risk period (one was elevated in both). Of these 8 HCUP categories with elevated RRs, 4 HCUP categories were not embedded in an already represented HCUP category and corresponded to: 'coma; stupor; and brain damage' (HCUP 6.6); 'ear conditions' (HCUP 6.8); 'cellulitis and abscess of arm' (HCUP 12.1.1.3); 'injury and poisoning' (HCUP 16).

The general safety results for this 5th Annual Interim Report were compared to those of the 4th Annual Interim Report, and the majority of HCUP categories that had either increased or decreased RRs were observed in both reports. In the current report, there were 8 HCUP categories with at least one significantly elevated RR in either risk interval (Days 1-60 or Days 1-14) or dose level (all doses combined or Dose 1 only). In last year's report there were 8 HCUP categories with at least one significantly elevated RR; with overlap in 6 of the HCUP categories between the 2 reports. There were 26 HCUP categories with significantly decreased RRs. Following multiplicity adjustment, 4 HCUP categories retained a significantly decreased RR: 'mental illness' (HCUP 5); 'diseases of musculoskeletal system and connective tissue' (HCUP 13); 'intracranial injury' (HCUP 16.4); and 'concussion' (HCUP 16.4.1). While in the current report, 26 HCUP categories were identified with at least one significantly decreased RR, in the 4th Annual Interim Report there were 32 HCUP categories with decreased RRs, with overlap for 18 of the categories. The specific diagnosis codes within the HCUP categories and their pattern of occurrence suggest expected healthcare among this population comprised mostly of adolescent boys.

Through December 2015 in the regimen initiator cohort, there were 31 VTE outcomes (i.e., claims-identified VTE cases) identified in the risk period among 21 unique males, and 16 VTE outcomes identified in the self-comparison period among 10 unique males

for the Days 1-60 all doses combined analysis. The 17 outcomes with charts available were reviewed by physician specialists to confirm the VTE diagnosis: 11 potential VTE outcomes were confirmed, 5 were not confirmed as VTE, and one was marked as having insufficient information. Of the 11 chart-confirmed VTE outcomes, 5 occurred during the risk period, 2 occurred in the self-comparison period, 2 occurred in neither the risk nor the self-comparison period, and 2 occurred prior to the first dose. If eligible for medical chart review, an additional medical chart will be sought for the male with the undetermined VTE outcome and the information will be included in the next round of claims-profile review and medical record abstraction. Lastly, new potential VTE events electronically identified as part of this report will be included in the next round of claims-profile review and medical record abstraction, and results will be presented in the future reports.

For the Day 0 analysis, a matched comparison group of males receiving other vaccines was available for a high percentage (80%, n=152,814) of the GARDASIL® doses, and there were slightly more counts of emergent Day 0 events in the matched controls than in the regimen initiators: 597 among the regimen initiators and 633 among the males who received a dose of a vaccine other than GARDASIL® during a physician office visit. However, a certain category, 995.20 (other and unspecified adverse effect of drug, medicinal and biological substance, includes allergic reaction) had a higher number of events among the regimen initiators as compared to comparators. To further investigate the imbalance in this category, the co-occurrence of 995.20 and a related category 995.3 (allergy, unspecified not elsewhere classified) was evaluated separately among the regimen initiators and concurrent controls with other vaccine visit. There was no overlap between these 2 codes in either cohort, i.e., a male did not have claims for both codes on Day 0. As a follow-up step, the SRC suggested generating claims-profiles for the males (n=67 initiators and n=5 comparators) with Day 0 events identified by ICD-9 code 995.20 to evaluate the treatment patterns following the Day 0 event. The results of the profile review suggested that these events were limited to Day 0 without treatment or services suggestive of anaphylaxis. The SRC concluded that Day 0 events identified with ICD-9 code 995.20 do not seem to correspond to serious allergic reactions. The SRC recommended conducting a similar claims-profile review for other allergic reaction codes that may represent serious reactions, such as ICD-9 code 519.11 (acute bronchospasm), ICD-9 995.0 (other anaphylactic shock not elsewhere classified,

includes adverse effect of medicinal substance), and ICD-9 code 995.1 (angioneurotonic edema, Quincke's edema). The findings of this claims-profile review will be presented in future reports.

The SRC also requested an assessment of concomitant vaccine use on Day 0 for both the GARDASIL® regimen initiator cohort and the matched comparison group of males receiving other vaccines in order to inform future analyses. The results showed that 70% of the regimen initiators received GARDASIL® alone on Day 0 while 78% of the matched comparators received a single vaccine on Day 0 (39% influenza, 22% meningococcal, and 17% Td/Tdap).

A total of 62,615 males were eligible for the autoimmune cohort (62,615 of the 106,110 in the initiator cohort, 59%), and 84% were able to be propensity-score matched (N=52,679) to an equal number of comparators with a physician visit. The autoimmune cohort is a subset of the regimen initiator cohort required to have 12 months of continuous enrollment prior to the first dose of GARDASIL®. This baseline enrollment requirement excludes 41% of the regimen initiator cohort, reflecting the turnover within this open cohort sourced from a commercial health insurer. In addition, approximately 16% of GARDASIL® recipients in the autoimmune cohort could not be matched to a suitable comparator (one with a close enough propensity-score) and therefore did not contribute to the comparative autoimmune analyses. However, all of the autoimmune outcomes occurring among GARDASIL® recipients in the autoimmune cohort are reported, irrespective of whether they are subsequently used in the comparative analyses. Overall, 214 potential new-onset autoimmune diagnoses were electronically identified among the matched vaccinated cohort, and 279 potential new-onset autoimmune diagnoses were electronically identified in the matched nonvaccinated cohort during the accrual period 16-October-2009 to 31-December-2015. The Final Report will include RRs for chart-confirmed autoimmune outcomes which will account for the person-time in each of the cohorts.

Since the last annual report, improvements have been made to the CRC SOP to reduce many of the limitations that arise from administrative claims data. First, the number and structure of the CRCs were revised to now include a separate CRC for each of the 4 specialties (endocrinology, rheumatology, neurology, and gastroenterology), each comprised of 3 or more specialists. Second, the autoimmune diagnostic criteria provided

in the adjudication procedures were revised to align with the most current published guidelines as presented in the study CRC SOP. Third, medical records were requested from multiple providers related to: 1) the diagnosis of the autoimmune outcome; 2) the first vaccination date for initiators, or day of physician office visit for matched comparators; and 3) any medical records that may have additional details related to the date of outcome occurrence or onset of the condition. Additional blinding of all vaccines in the medical records prior to adjudication was also completed. Currently, a sample of potential cases of autoimmune outcomes is being reviewed by the 4 CRC subcommittees. Narratives were completed for the sample of endocrinology outcomes and reviewed by the SRC. The SRC approved the narratives for these outcomes, and adjudication can be initiated for all potential new-onset endocrinology outcomes. Once the narratives are prepared for the sample of rheumatology, neurology, and gastroenterology outcomes, they will be reviewed by the SRC for final evaluation of the updated CRC SOP. Following the successful completion of this pilot review, the adjudication of all potential new-onset autoimmune cases in the study will be undertaken. The autoimmune analysis is on schedule for inclusion in the final study report.

Nine claims-based deaths were identified among males vaccinated with GARDASIL® (including 7 already reported in the previous annual report). Of the 9 potential deaths, medical records indicated death for 3 males, death was not indicated in the medical records for 3 males, the medical chart was unavailable to review for one death outcome, and medical records will be sought for the 2 potential deaths identified in this report. An NDI Plus search was conducted at the request of the study SRC on the potential deaths through last year's report. The NDI search indicated a low probability of death for one case, and a true death match for 5 claims-based deaths; one death identified in the claims database was ineligible for the NDI search. No attribution of death to GARDASIL® was observed in the charts. The number of potential deaths observed so far in this study (9) is identical to the expected number of deaths obtained by applying age-, sex-, and race-standardized national death rates to the amount of follow-up time among the GARDASIL® initiator cohort. These results are limited by the small numbers of deaths and will continue to be monitored.

During the study period covered by this 5th Annual Interim Report, there was a change (in October 2015) from the use of ICD-9 codes to the use of the ICD-10 codes for

diagnoses and some procedures. For the general safety analysis, the HCUP categories and their mapping to ICD-9 codes was updated by the Centers for Medicare & Medicaid Service (CMS) to ICD-10. This conversion resulted in the loss of Level 3 and Level 4 HCUP categories which were not mapped by CMS due to the significantly larger number of ICD-10 codes that contribute to each category and changes in the coding structures. In order to follow-up on findings observed in previous interim reports, custom HCUP Level 3 and 4 categories were created for those conditions that were observed to be associated with GARDASIL® use in previous reports. The results of the current annual interim report are consistent with the previous year's report. While this consistency in reporting is reassuring, the change in coding practice occurred relatively late in the current analyses accrual period. Therefore, future reports where ICD-10 is used for a longer time period will more fully evaluate the effect of this change in coding practice on study results.

Study accrual and conduct of this observational GARDASIL® safety study is proceeding in a manner consistent with the protocol. Based on the last several months of accrual, the projected 3 years between December 2015 and when study accrual reaches the targeted size of 135,000 initiators (end of 2018) suggests that reaching this numerical target before the planned time-based stopping point (June 2017) may not be feasible. In addition, the new HPV vaccine, GARDASIL®9 (approved in December 2014), may be used in place of GARDASIL® and gradually replace it, which could substantially alter accrual. Although this will likely mean that this study does not meet either of its numerical stopping points (135,000 regimen initiators or 44,000 regimen completers) before its planned time-based stopping point (6 years from start), the study has already accrued more GARDASIL® doses (189,892) than assumed in the protocol power calculation (132,000).

In conclusion, the general safety outcome analyses suggest only chance findings or the consequences of vaccine timing relative to other healthcare services. The small elevations observed in a few RRs for the general safety outcomes could be attributed to uncontrollable artifacts or other possible explanations, such as seasonality (e.g., timing of the risk period relative to the self-comparison period with respect to the increased number of injuries during the summer), chance, or pre-existing conditions. The observed decreased RRs for the general safety analyses may represent delayed workup for possible conditions identified at the vaccine visit, or the healthy vaccinee effect. The VTE

and autoimmune analyses are ongoing and results will be included in future study reports. The study data overall do not suggest an alteration in the existing safety profile of GARDASIL®.

The SRC reviewed this report's data at several meetings in the second half of 2016, issued requests for additional information and recommendations, and reviewed the final version of this 5th Annual Interim Report. Overall, the SRC concluded that it had identified no safety concerns related to GARDASIL® through the results generated by this study.

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