SENTINEL CBER/PRISM SURVEILLANCE PLAN

A SAFETY STUDY OF GARDASIL 9 IN PRISM/SENTINEL USING SEQUENTIAL ANALYSIS

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The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.

History of Modifications

Version	Date	Modification	By
V2	9/27/2017	• Section II: Added mention of Advisory Committee on Immunization Practices (ACIP)'s December 2016 recommendations for use of a 2-dose schedule. • Section II and References: Added mention of a few additional safety studies. • Section III.B.: Explained why 70 days of post-vaccination follow-up is being required, instead of just 56 days. • Section III.C.: Added that NDC codes are being used to identify exposures in addition to CPT codes. • Section III.F.: Stated that doses administered from 1/1/2015 on are being included. • Section III.F.: Removed projected timeline covering period that is now past. • Section III.F.: Revised projection of how many more years are needed to accumulate 3 million doses. • Section III.G.2.: Added some information about SCRI parameters. • Section III.H.: Based on initial data obtained for the study, which included a period in the ICD-10 era, revised ADEM power estimates. (Power apparently higher than previously estimated.) • Appendix: Changed title to reflect fact that cases will now be ascertained in ICD-9 era (given that doses administered in all of 2015 are now being included). • Made a few small clarifying edits throughout.	Katherine Yih
V3	1/17/2018	• FDA's decision to discontinue the Sequential Analysis of Gardasil 9 Safety activity in Sentinel is explained in the Addendum	FDA

Sentinel CBER/PRISM Surveillance Plan

A Safety Study of Gardasil 9 in PRISM/Sentinel Using Sequential Analysis

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I. INTRODUCTION

Not all safety issues can be fully evaluated in prelicensure phases of vaccine evaluation. A complete safety profile may not be apparent until after a vaccine is administered to a general population, unconstrained by the strict inclusion and exclusion criteria in clinical trials. In the course of evaluating biologics license applications (BLA) for new vaccines, regulators often decide that, while no definitive safety signal exists to require a manufacturer-sponsored postmarketing study, additional safety data would nevertheless be valuable. There are many reasons to collect additional postlicensure safety data: (a) to better understand the risk of outcomes too rare to fully assess in prelicensure clinical trials, (b) to further investigate minor imbalances that were considered most likely due to chance or potentially to artifacts of randomization, (c) to investigate uses recommended by the Advisory Committee on Immunization Practices (ACIP) that may not have been fully evaluated in clinical trials (e.g., influenza vaccination in pregnancy), (d) to help buttress public confidence in the face of clusters of passively reported adverse event reports that would be expected to occur but nevertheless raise safety questions among the general public.

At the time of approval of many vaccines, manufacturers have made postmarketing commitments (PMC) to conduct general safety studies to enhance the prelicensure safety database. However, the ability of these studies to detect adverse events, particularly rare ones, can be limited by sample size.

As part of FDA's ongoing vaccine postmarket safety surveillance activities, this study seeks to provide postmarketing safety data for the human papillomavirus (HPV) vaccine Gardasil 9 in Sentinel, the largest vaccine safety surveillance system in the U.S. We will monitor the safety of this vaccine with respect to several pre-specified health outcomes of interest, using sequential analysis methods. The study represents the second component of a general approach to postmarketing vaccine safety surveillance taken by the Postlicensure Rapid Immunization Safety Monitoring (PRISM) subsystem of the Sentinel system. The general vaccine safety surveillance approach includes: (1) surveillance for unexpected adverse events, (2) surveillance for suspected or biologically plausible specified adverse events, and (3) highly customized protocol-based assessment of the association between a vaccine and a specified adverse event where, based on findings of prior studies or surveillance, concern about an association exists. The purpose of the first two components is to identify signs of possible safety concerns and then determine if any indication of an association is sufficiently strong or worrisome as to merit a formal in-depth evaluation (the third component) or possibly some form of regulatory action. This general approach provides a framework for monitoring vaccine safety that can be applied to any new vaccine after licensure, although the framework will necessarily evolve as new methods and other features become available for use in PRISM/Sentinel.

Sequential analysis methods have been used for vaccine safety surveillance twice before by PRISM, although for different vaccines and with different data architectures and somewhat different sequential analysis methods than those featured in this surveillance plan. The first time was for the 2009 pandemic H1N1 influenza vaccine, before PRISM became part of Mini-Sentinel.[1,2] The second time was for influenza vaccines in subsequent seasons.[3]

II. VACCINE AND OUTCOMES OF INTEREST

As one of the first vaccines to be licensed by FDA and broadly recommended by the Advisory Committee on Immunization Practices (ACIP) since the availability of this approach in PRISM/Sentinel, Gardasil 9 is the subject of this safety surveillance plan. Gardasil 9 is a 9-valent HPV vaccine approved by the FDA in December 2014. In girls and women 9 through 26 years of age, it is indicated for the prevention of cancerous and precancerous lesions of the cervix, vulva, vagina, and anus caused by HPV types 16, 18, 31, 33, 45, 52, and 58, as well as genital warts and precancerous lesions of the cervix, vulva, vagina, and anus caused by HPV types 6 and 11. In boys and men 9 through 26 years of age, it is indicated for the prevention of anal cancers/precancerous lesions caused by HPV types 16, 18, 31, 33, 45, 52, and 58, as well as genital warts and anal precancerous lesions caused by HPV types 6 and 11. It was originally administered in a 3-dose schedule, with the second dose administered 2 months after the first, and the third dose 6 months after the first.[4] Gardasil 9 is one of three HPV vaccines routinely recommended by ACIP for females and males aged 11–12 years, but it can be administered as young as age 9 years.[4] Catch-up vaccination is recommended for females aged 13–26 years and for males aged 13-21 years who have not been previously vaccinated; ACIP also recommends vaccination through age 26 for men who have sex with men and for immunocompromised persons who have not been vaccinated previously or have not completed the 3-dose series.[5] On 12/16/2016, ACIP published new recommendations for use of a 2-dose schedule for girls and boys who initiate the vaccination series at ages 9 through 14 years.[6]

FDA approved Gardasil 9 after reviewing results on safety, efficacy, and immunogenicity. HPV9's safety was evaluated in 7 randomized controlled trials involving approximately 23,000 males and females aged 9–26 years, including approximately 15,700 who received Gardasil 9. These clinical studies found injection site reactions to be higher among Gardasil 9-vaccinated persons than among quadrivalent Gardasil recipients.[4] However, rates of systemic reactions, new-onset medical conditions, serious adverse events, and deaths following vaccination were comparable between Gardasil 9 and quadrivalent Gardasil recipients. No serious safety issues were identified in prelicensure studies of Gardasil 9.

FDA's routine postmarketing safety monitoring for Gardasil 9 has not identified any safety issues since licensure. However, FDA seeks to make use of PRISM/Sentinel's sequential analysis capability to conduct surveillance for a limited number of potential adverse events:

- **Complex regional pain syndrome (CRPS):** CRPS is a clinical syndrome that affects one or more extremities and is characterized by persistent pain and swelling disproportionate to any known inciting event, and at least one sign of autonomic dysfunction in the affected limb(s). The pathogenesis of this syndrome is poorly understood, but its onset is often precipitated by a physical injury, such as minor trauma, fracture, infection, or a surgical procedure. Published literature suggests that time between the precipitating event and CRPS symptom onset can vary widely; however, a review of available studies indicated that symptom onset typically occurs within 6 months of the injury.[7] In June 2013, the Japanese Ministry of Health, Labor, and Welfare suspended its recommendation of routine immunization with HPV vaccine in girls and women following post-vaccination reports of serious chronic pain and concern about a possible association with HPV.[8] In early November 2015, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee completed a detailed scientific review of the evidence related to a possible association between HPV vaccines and CRPS. The Committee concluded that the evidence did not support a causal link between the vaccines and the syndrome.[9] Although U.S. vaccine safety information sources such as the Vaccine Adverse Event

Reporting System (VAERS) have not suggested an increased risk of CRPS following HPV vaccination either, some post-HPV-vaccine cases have been reported to VAERS.

- **Uveitis:** Uveitis is characterized by inflammation of the uvea, or middle layer of the eye. Frequently occurring in association with systemic medical conditions such as infections and inflammatory diseases, uveitis has been noted in the literature as occurring sporadically following HPV vaccination. In a case series of 24 such reports published in 2014, the median time to symptom onset was 30 days after vaccination, with a range of 0-476 days.[10] Two earlier population-based observational studies evaluated the risk of uveitis[11] or "eye disorders"[12] after Gardasil vaccination and found no association.

- **Acute disseminated encephalomyelitis (ADEM):** ADEM is a demyelinating disease of the central nervous system that typically follows an infection. Clinical features include multifocal neurologic signs, including motor, sensory, cranial nerve, and brainstem deficits, as well as nonspecific symptoms such as headache, malaise, and altered mental status. Certain vaccinations have already been shown to precipitate ADEM on rare occasion[13]. Reports of ADEM following HPV vaccination can be noted in the VAERS database and have been published in the literature. A 2014 publication summarizing case reports of demyelinating syndromes occurring after various vaccinations including HPV vaccination noted a mean symptom onset interval of 14 days; however, there were cases where the clinical presentation was delayed up to and beyond three weeks.[14] Four population-based observational studies examined the risk of ADEM after Gardasil vaccination and found no association.[11,15,16,17]

- **Pericarditis:** Pericarditis is characterized by inflammation of the pericardium; clinical features can include chest pain, electrocardiogram abnormalities, a pericardial friction rub, and a new or worsening pericardial effusion.[18] Cases of pericarditis following vaccination have been documented in the literature, with mean time to symptom onset after vaccination noted as 11 days (range 2-42 days).[19] Klein et al. [2012] evaluated the risk of "diseases of the heart" after Gardasil vaccination and found no association.[12] However, reports following HPV vaccination have been noted by international health agencies, as well as in the VAERS database.

Note about terminology: Because a clear distinction needs to be made between the quadrivalent and 9-valent HPV vaccines in this surveillance plan, we use the term "HPV4" for quadrivalent Gardasil and "HPV9" for Gardasil 9 in the remainder of the document. The terms "risk interval," "risk window," and "RW" are used interchangeably, as are "comparison interval," "comparison window," "control interval," "control window," and "CW." Throughout the document, the words "signal," "signals," and "signaling" refer to *statistical* signaling, whether or not the adjective is used.

III. METHODS

A. OVERVIEW OF STUDY DESIGNS AND SEQUENTIAL ANALYSIS METHODS

We will use a cohort design for CRPS and uveitis, because the long putative risk interval relative to the typical spacing of Doses 1 and 2 (2 months) makes the self-controlled risk interval (SCRI) design unfeasible. For these outcomes, the comparison will be between HPV9 vaccinees and concurrent controls receiving tetanus-diphtheria-acellular-pertussis combination vaccine (Tdap) and/or meningococcal (groups A, C, Y, and W-135) conjugate vaccine (MCV4). For ADEM and pericarditis, we will use a SCRI design, and the comparison will be between exposed and unexposed person-time for the

same HPV9 vaccinees. The designs are further elaborated in Table 1 below, with their corresponding sequential analysis methods, which are described in Section III.G.

Table 1. Designs and analysis methods

Outcome	Design	Intervals compared	Confounding adjustment	Sequential analysis method
CRPS Uveitis	Cohort	Days 1-56 after HPV9 vs. Days 1-56 after Tdap or MCV4	By means of stratification by covariates of interest	Conditional sequential sampling procedure (CSSP), group sequential with a pre-specified number and frequency of interim tests[20,21]
ADEM Pericarditis	Self-controlled risk interval (SCRI)	Days 1-28 vs. Days 29-56 after HPV9; each vaccinee contributes both periods	By means of self-controlled design	Binomial maximized sequential probability ratio test (maxSPRT)[22], group sequential[23,24]

1. Cohort Design

For CRPS and uveitis, we will use a cohort design with concurrent controls. We will compare the rate of each outcome occurring during Days 1-56 after HPV9 vaccination (whether with or without other vaccines) to the rate in the same period after Tdap or MCV4 vaccination without HPV9 vaccine. (Tdap and MCV4 are considered equivalent for the purposes of this analysis.) We will adjust for confounding bias by stratifying by Data Partner, sex, and age group (9-11, 12-14, 15-17, 18-20, 21-23, 24-26 years of age). Within each stratum (defined by unique combination of Data Partner, sex, and age group), the number of incident events (i.e., cases of CRPS or of uveitis) among HPV9 vaccinees follows a binomial distribution, with the number of trials being the total number of events among all those vaccinated with HPV9, Tdap, or MCV4. Under the null hypothesis of no elevated risk, the binomial probability equals the proportion of eligible HPV9 doses among all the eligible HPV9, Tdap, and MCV4 doses. If the observed number of events among HPV9 vaccinees is statistically significantly larger than the expected number of events under the null hypothesis, it indicates a potentially elevated risk due to HPV9 vaccination.

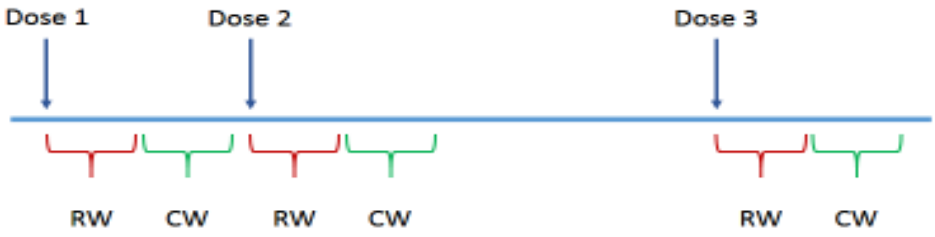
All eligible HPV9 doses will be included in the analysis and treated as equivalent.

2. Self-Controlled Risk Interval (SCRI) Design

For ADEM and pericarditis, we will use a self-controlled risk interval (SCRI) design,[25,26] shown schematically in Figure 1. This design makes use of only vaccinated cases occurring in pre-specified risk or control windows. A particular strength of self-controlled designs is that they control for fixed potential confounders (e.g., sex, genetic factors, socio-economic status), whether they are known or not, since individuals serve as their own controls. In addition, in using only vaccinated cases the SCRI design avoids the bias that can affect cohort studies when vaccinated subjects are misclassified as unvaccinated. The null hypothesis is that the risk of the outcome in question on an average day during the pre-defined risk interval after HPV9 is the same as the risk of the outcome on an average day during the pre-defined control interval.

No dose-specific analyses will be done; rather, all doses will be treated as equivalent.

Figure 1. Self-controlled risk interval (SCRI) design. Paired risk and comparison windows (RW and CW) follow each dose. Each vaccinee contributes person-time in both intervals. Only vaccinated cases occurring in these intervals are used in the analysis.



B. STUDY POPULATION AND ENROLLMENT CRITERIA

The study population will consist of females and males enrolled in Aetna, Harvard Pilgrim Health Care, HealthCore, Humana, and Optum, who are 9-26.99 years of age at the time of vaccination. To be included in analysis, a vaccine dose must have occurred on or after 1/1/2015, be preceded by ≥ 183 days of continuously enrolled time, and be followed by ≥ 70 days of continuously enrolled time. (We require 70 days instead of only 56 days, in case we need to obtain claims profiles of case-patients for signal follow-up—requiring 70 days of post-exposure enrollment gives 2 weeks more of post-diagnosis time in which to examine claims, which could be useful, especially for cases occurring toward the end of the Days 1-56 period.) In determining "continuously enrolled time," apparent gaps in enrollment of up to 45 days duration will be bridged, i.e., treated as continuously enrolled time.

C. EXPOSURES

HPV9, Tdap, and MCV4 vaccine exposures will be ascertained by means of CPT codes 90651, 90715, and 90734, respectively, in claims data as well as by means of NDC codes (not listed because proprietary). All HPV9 doses meeting the criteria in Section B will be included in analysis as HPV9-exposed, regardless of whether other vaccines were given on the same day, unless there was a dose of any HPV vaccine (CPT codes 90649, 90650, or 90651 and NDC codes) given in the prior 56 days. All doses of Tdap or MCV4 meeting the criteria in Section B will be included in analysis as the comparison group, unless (a) the dose was given on the same day as HPV9, (b) there was a dose of any HPV vaccine given in the prior 56 days, or (c) the dose was followed by HPV9 within 56 days.

D. OUTCOMES AND RISK AND COMPARISON INTERVALS

Algorithms and risk and control intervals for outcomes to be monitored are shown in Table 2. For CRPS and uveitis, which will be studied using the cohort design, we will use a risk interval of Days 1-56 after vaccination ("Day 0" is the day of vaccination). If there is an association between HPV9 vaccination and either of these outcomes, this Days 1-56 interval may not capture all of the vaccine-associated cases (see Section II), but since the comparison is between Days 1-56 after HPV9 and the same period after the comparison vaccines, the design has the capability of detecting an increased risk after HPV9 as long as at least part of the period of increased risk is during Days 1-56. (It is not practical to use a longer risk interval because of the typical 2-month spacing between Doses 1 and 2.) Only instances of CRPS and uveitis that are the first-ever to occur in all enrolled time (with a minimum of 183 days of enrolled time prior to HPV9 vaccination) will be included in analysis. For ADEM and pericarditis, which have shorter putative risk intervals and will be studied using the SCRI design, we will use a risk interval of Days 1-28 and a control interval of Days 29-56 after vaccination. If there is an association between HPV9

vaccination and either of these outcomes, the Days 1-28 risk interval is expected to capture most of the vaccine-associated cases (see Section II). To the extent that a vaccine-associated risk of either outcome extends beyond Day 28, there will be some attenuation of the risk detected. Only instances of ADEM and pericarditis that are the first to occur in a 183 days period of time will be included in analysis.

Table 2. Algorithms and risk and control intervals (RW and CW) for health outcomes of interest (HOIs) to be monitored. ICD10 codes for the HOIs are shown in the Appendix, along with ICD9 codes to be used to determine whether the event was the first ever or first in 183 days

#	HOI	Exclusions	Settings	First in what period	RW	CW
1	Complex regional pain syndrome (reflex sympathetic dystrophy) (CRPS)	None	Inpatient, ED, outpatient	First ever	Days 1-56	Days 1-56 after Tdap or MCV4
2	Uveitis	None	Inpatient, ED, outpatient	First ever	Days 1-56	Days 1-56 after Tdap or MCV4
3	Acute disseminated encephalomyelitis (ADEM)	ICD10 code G35 or ICD9 code 340*: multiple sclerosis, ever, in all previous enrolled time (including beyond (i.e., before) -183 days) through 56 days post-exposure	Inpatient, ED	183 d	Days 1-28	Days 29-56
4	Acute pericarditis	None	Inpatient	183 d	Days 1-28	Days 29-56

E. DATA EXTRACTION

Programmers at the Data Partners will use the Sentinel Cohort Identification and Descriptive Analysis (CIDA) Tool on each newly refreshed and quality-checked batch of data (typically called an "ETL," which stands for "extract, transform, and load," referring to the process of pulling data out of the source systems and placing it into a data warehouse) in the Common Data Model (CDM) to produce an aggregate dataset for sequential analysis. In order to ensure data completeness, the aggregate dataset may need to be truncated, i.e., if data from recent months are determined to be less than 90% complete (which is often the case, due to data-lag), those months of data will be excluded. In the *subsequent* aggregate dataset for the respective Data Partner, to be created from the Data Partner's next ETL, data for those excluded months will mostly likely be complete and thus be included. For each of these aggregate datasets, in order to adhere to the requirements of the statistical method, the period of admissible exposures will not overlap with the period of exposures in the prior aggregate dataset for that Data Partner. For example, if the first aggregate dataset obtained from Data Partner A included vaccine exposures during 1/1/2015-12/31/2015 and no later, this Data Partner's second aggregate dataset (obtained only after they had accumulated additional data and created a new ETL) would include only exposures on or after 1/1/2016. Analyzed data will not be revised or reanalyzed.

The cohort-design data to be analyzed will consist of the number of HPV9 doses, the number of Tdap or MCV4 doses, the number of events following HPV9 vaccination, and the number of events following Tdap or MCV4 vaccination. Within the dataset, these will be stratified by Data Partner, sex, and age

group. If a patient has one of the health outcomes of interest (CRPS or uveitis), all subsequent doses of HPV9, Tdap, and MCV4 will be censored, because the first-ever requirement for those outcomes means that no subsequent event would be eligible for analysis.

The SCRI-design data to be analyzed will consist of simply the number of cases in the risk interval and the number in the control interval after HPV9 vaccination. No censoring of doses will be done, because there is no first-ever requirement for the outcomes to be studied using the SCRI design (ADEM and pericarditis).

Both the cohort and SCRI datasets will include Data Partner, sex, age group, year, year-month, and time-to-event (number of days between exposure and event), allowing subgroup analysis and time-to-event analysis using temporal scan statistics in the event a signal is detected.

F. TIMING OF ANALYSIS

Data extraction and sequential analysis will begin in the fall of 2016, include vaccine doses since 1/1/2015, and continue until 3 million doses of HPV9 have been included in the analysis. (We are stipulating the same stopping point (in the absence of a signal) for all four outcomes for practicality; the statistical power will differ among the four outcomes because of the frequency of the outcome and the two statistical methods being used (see Section H).) However, it should be noted that the study may be stopped if the rate of vaccine uptake is low and the total number of doses is not accumulated within a reasonable period of time.

We will extract data using CIDA each time a Data Partner updates their data, i.e., produces an ETL that is quality-checked and approved by the Sentinel program. For CRPS and uveitis, we will run CSSP analyses if, and only if, the number of doses of HPV9 accrued is approximately 250,000 more than at the last look (or at least 250,000 more, if the influx is great) and there are new cases of the outcome. For ADEM and pericarditis, we will run SCRI binomial maxSPRT analyses if, and only if, there are new cases of the outcome. This means that analyses for the four outcomes may occur on different schedules.

Based on initial data obtained for the current study, we estimate that the target of 3 million doses could be reached in about 2.5 more years, as of this writing (6/2017), although the new 2-dose ACIP recommendation published in 12/2016 could extend the period somewhat.

G. STATISTICAL ANALYSIS

1. Cohort Design

With the cohort design with concurrent controls, we will use the conditional sequential sampling procedure (CSSP) for sequential analysis.[20,21] This is a group sequential analytic method to test whether there is an elevated risk for a selected adverse outcome (CPRS or uveitis in this case) following exposure to the vaccine of interest (HPV9) compared to selected comparator vaccine(s) (Tdap, MCV4). The CSSP adjusts for possible confounding bias between the two exposure groups by stratifying on important covariates (Data Partner, sex, and age group). The test statistic is the cumulative number of events among HPV9 vaccinees, which is the sum across all covariate strata from the beginning of surveillance through the current interim test. Within each covariate stratum, the number of new events among HPV9 vaccinees added at each interim look follows a binomial distribution with the number of trials being the number of newly added events from both the exposure and control groups. The binomial probability under the null hypothesis is the proportion of eligible HPV9 doses among the number of eligible HPV9, Tdap, and MCV4 doses.

Three inputs to the sequential analysis must be pre-specified: 1) The alpha level: We will choose the conventional alpha level of 0.05. 2) The upper limit on surveillance, defined as the maximum number of interim looks: We will take 12 looks. 3) The alpha spending function, which allocates the overall alpha of 0.05 among the interim tests: We will use a linear function.

At each interim test, the probability of observing "more or equally extreme" scenarios under the null hypothesis will be calculated via Monte Carlo simulation, as the distribution of the test statistic does not exist in simple, analytic form. This conditional probability will be compared to a cut-off p-value that is determined by the overall alpha level and the alpha spending function. If the conditional probability is less than or equal to the cut-off p-value, then a signal is raised, indicating the possibility of an elevated risk of the outcome following HPV9 vaccination. At that point, surveillance for the outcome in question formally ends, in keeping with the dictates of sequential analysis.

One-tailed tests will be used, since we are looking only for elevated risks from vaccination rather than for protective effects.

2. SCRI Design

For the sequential SCRI analyses, we will use the maximized sequential probability ratio test (maxSPRT) for binomial data to compare the cumulative numbers of events in risk and control intervals.[22] The maxSPRT adjusts for the repeated looks at the accumulating data entailed in sequential analysis. The test statistic is the log-likelihood ratio (LLR). We will use group sequential analysis[23,24] rather than continuous sequential analysis, since the data are expected to arrive in large chunks.

Three inputs to the sequential analysis must be pre-specified: 1) The alpha level: Again, we will choose the conventional alpha level of 0.05. 2) The upper limit on surveillance: In contrast to the cohort/CSSP method above, for the SCRI/binomial maxSPRT method the upper limit is the cumulative number of observed cases in risk and control intervals combined at which surveillance will end. The concept is the same, however, namely that if surveillance continues beyond our pre-specified upper limit, then our chance of getting a false positive (Type I error) over the course of surveillance exceeds 0.05. We choose upper limits based on the approximate cumulative number of cases that are expected to occur in the risk plus control intervals over the duration of surveillance (i.e., until 3 million doses have been administered to the study population). The upper limit for ADEM will be 20 and for uveitis 12 (see Section H.2. below). The critical value of the LLR is the signaling threshold, expressed as the cumulative number of cases needed in the risk window in order to reject the null hypothesis, which changes with each sequential analysis. The critical value is dictated by the matching ratio (ratio of risk interval length to control interval length, 1 in our case), the alpha level, and the upper limit. 3) The minimum number of cases needed in order to conduct the first analysis: For a binomial maxSPRT with equal-length risk and control intervals, no signal is possible with fewer than 6 total cases in the two intervals. However, one may wish to conduct an analysis with fewer than 6 cases in order to monitor the LLR and RR. In this surveillance, we will begin SCRI analysis when there are at least 4 cases in risk and control intervals combined.

The null hypothesis is that the risk on an average day in the risk interval is the same as the risk on an average day in the control interval. The null hypothesis is rejected if, in a sequential analysis, the LLR reaches the critical value; this constitutes a statistical signal. The null hypothesis is not rejected if the upper limit of observed cases in risk and control intervals is surpassed without a signal arising, or if surveillance ends without this upper limit being surpassed.

As with the CSSP, one-tailed tests will be used, since we are looking only for elevated risks from vaccination, not protective effects.

H. STATISTICAL POWER

With these quite rare outcomes, statistical power is a concern. The plan to continue surveillance until 3 million doses have been administered (and data in their follow-up periods are estimated to be relatively complete) seeks to address this.

1. Cohort Design

For CRPS, we expect to have 100% power to detect a signal even if the true RR is as low as 2. For uveitis, we expect to have 95% power to detect a signal if the true RR is 2.5 and 70% power if the true RR is 2.

2. SCRI Design

For ADEM, an upper limit of 20 cases will be selected. This is based on initial data obtained for the current study, which included a period in the ICD-10 era. As shown in Table 3, if we were to continue surveillance until 20 cases had accrued in risk and control intervals, we would have approximately 60% power to detect a signal if the true RR were 3, 80% power to detect a signal if the true RR were 5, and close to 100% power to detect a signal if the true RR were 10. For acute pericarditis, an upper limit of 12 will be selected, corresponding to the approximate number of cases projected to be observed (based on descriptive data from a PRISM study involving HPV4), under the null hypothesis, in risk and control intervals by the time 3 million doses have been administered. With this upper limit, we would have 40% power to detect a signal if the true RR were 3, 70% power to detect a signal if the true RR were 5, and 90% power to detect a signal if the true RR were 10.

Table 3. Relationship between statistical power and pre-specified upper limits on surveillance for the binomial maxSPRT (SCRI design) with equal-length risk and control intervals, for three hypothesized true relative risks. The numbers in the body of the table represent alternative upper limits on surveillance in terms of the cumulative number of observed cases. Surveillance stops and the null hypothesis is not rejected if and when the cumulative number of events occurring in risk and control intervals reaches the upper limit with no statistical signal arising.

Power	RR=10	RR=5	RR=3
0.1	6	6	6
0.2	6	6	6
0.3	6	6	9
0.4	6	6	12
0.5	6	9	16
0.6	6	12	22
0.7	9	12	28
0.8	9	19	36
0.9	12	25	49
0.95	16	30	58
0.99	22	41	80

I. SIGNAL FOLLOW-UP

If a signal appears, we will follow established procedures for investigating sequential analysis signals.[27,28] Specifically, we will take some of the following steps, although not necessarily in this order:

1. If the signal is for ADEM or pericarditis, double-check that periods during which data were incomplete were excluded from analysis for all sequential analyses conducted to date. If this did not happen, there would tend to be fewer cases in the later observation interval than in the earlier one, which could produce a spurious signal for those two outcomes.
2. Examine the demographic features of the cases (i.e., the stratification variables). This could reveal, for example, that most of the cases in the risk interval are from one site, which might indicate a data quality or coding problem there, or that most are in a specific age group, which might suggest a true risk but only for that age group.
3. Conduct a temporal scan statistical test on the timing of cases' diagnoses in the 56 days after HPV9 vaccination. Statistically significant clustering of diagnoses would lend credibility to the signal.
4. Obtain and qualitatively evaluate claims profiles (listings of health insurance claims for medical encounters, including diagnosis and procedure codes) for a defined period from X days prior to exposure through Y days after exposure for patients contributing to signals, to determine more about their clinical presentation. This is a much quicker and cheaper way to gain clinical insight into the cases than medical chart review.
5. Consider the possibility of confounding by seasonality. (HPV vaccination has a seasonal pattern, being more common in the late summer prior to school entry. ADEM, uveitis, and pericarditis can be caused by infections, some of which also have a seasonal pattern. If an outcome occurs more frequently in early fall than at other times of year, the specific seasonality of both exposure and outcome could lead to a spurious signal.) Examine all the diagnosis codes of the cases to evaluate in how many of the cases the event might have been caused by an infectious agent with a seasonal pattern that could have produced a bias toward signaling. Conduct some simple quantitative bias analysis by, for example, removing those cases or randomly reassigning them to risk and control intervals and repeating the analysis.
6. Request that FDA examine VAERS data for disproportionate reporting of the outcome.
7. To gain power at the expense of some control for confounding, conduct a logistic regression analysis comparing rates of the outcome in HPV9 vaccinees and in patients receiving other vaccines, such as MCV4, Tdap, and/or varicella. This could be done either using potential cases identified in the administrative data or, with additional funding, using chart-confirmed cases. The analysis could make use of a fixed number of controls (recipients of other vaccines) for each HPV9 vaccinee, matching on Data Partner, sex, year of age, and year-and-month of vaccination, or adjust for these covariates in the analysis. A disadvantage of the matched approach is that in the random selection of controls, some cases of the outcome might not be used, constituting a loss of information that is especially problematic if the outcome is rare. A disadvantage of the unmatched but adjusted approach is that the number of covariates to be adjusted for will consume degrees of freedom and reduce power, and there could be cells containing 0 counts, which could prevent the model from converging. The decision of which approach to take, if this kind of analysis is undertaken at all, will take into consideration how rare the outcome is.

IV. STRENGTHS AND LIMITATIONS

A major strength of the study is its use of sequential analysis to allow ongoing safety monitoring, while adjusting for the repeated looks at the accumulating data. The cohort design (for CRPS and uveitis), using the CSSP for sequential analysis, which has not been used by PRISM previously, does not waste control data as designs with fixed matching ratios do, but rather incorporates information from all comparison vaccinees in each stratum, while controlling for the covariates defining the strata (Data Partner, sex, and age group). This design is a better choice than the SCRI design for these outcomes, given that the long putative risk interval relative to the recommended spacing of Doses 1 and 2 makes the SCRI design unfeasible. The self-controlled design (for ADEM and pericarditis) has the virtue of controlling for all time-invariant potential confounders.

The main limitation is that statistical power to detect modest increases in risk within the time-frame of the planned surveillance will be low for pericarditis and ADEM. However, we may well be able to detect increased risks of sufficient magnitude to matter for public health. Another limitation is the possibility of some confounding. With the cohort design, we will adjust for potential confounding by Data Partner, sex, and age group by stratifying on those covariates, but there could be residual confounding. With the SCRI design, seasonality could introduce bias, given seasonal patterns in HPV9 vaccination and in some of the infectious causes of the outcomes. An additional limitation is that if any of the prespecified risk windows (Days 1-56 or 1-28) are too long or too short with respect to the true period of risk (if any), signals may be obscured or risk estimates attenuated. This limitation is shared with all study designs using a prespecified risk window.

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VI. APPENDIX

Table 4. ICD-10 and ICD-9 codes to be used in case-finding algorithms, including in the look-back to determine incidence (first ever or first-in-183-days occurrence)

ICD10 code	ICD10 code label	ICD9 code	ICD9 code label
Complex regional pain syndrome			
G90.50	Complex regional pain syndrome I, unspecified	337.20 337.21 337.22 337.29	Reflex sympathetic dystrophy, unspecified Reflex sympathetic dystrophy of the upper limb Reflex sympathetic dystrophy of the lower limb Reflex sympathetic dystrophy of other specified site
G90.511	Complex regional pain syndrome I of right upper limb		
G90.512	Complex regional pain syndrome I of left upper limb		
G90.513	Complex regional pain syndrome I of upper limb, bilateral		
G90.519	Complex regional pain syndrome I of unspecified upper limb		
G90.521	Complex regional pain syndrome I of right lower limb		
G90.522	Complex regional pain syndrome I of left lower limb		
G90.523	Complex regional pain syndrome I of lower limb, bilateral		
G90.529	Complex regional pain syndrome I of unspecified lower limb		
G90.59	Complex regional pain syndrome I of other specified site		
Uveitis			
H44.131	Sympathetic uveitis, right eye	360.11 363.00 363.01 363.03 363.04 363.05 363.06 363.07 363.08 363.10 363.11 363.12 363.13 363.14 363.20 364.00 364.01 364.04 364.3	Sympathetic uveitis Focal chorioretinitis, unspecified Focal choroiditis and chorioretinitis, juxtapapillary Focal choroiditis and chorioretinitis of other posterior pole Focal choroiditis and chorioretinitis, peripheral Focal retinitis and retinochoroiditis, juxtapapillary Focal retinitis and retinochoroiditis, macular or paramacular Focal retinitis and retinochoroiditis of other posterior pole Focal retinitis and retinochoroiditis, peripheral Disseminated chorioretinitis, unspecified Disseminated choroiditis and
H44.132	Sympathetic uveitis, left eye		
H44.133	Sympathetic uveitis, bilateral		
H44.139	Sympathetic uveitis, unspecified eye		
H20.00	Unspecified acute and subacute iridocyclitis		
H20.011	Primary iridocyclitis, right eye		
H20.012	Primary iridocyclitis, left eye		
H20.013	Primary iridocyclitis, bilateral		
H20.019	Primary iridocyclitis, unspecified eye		
H20.041	Secondary noninfectious iridocyclitis, right eye		
H20.042	Secondary noninfectious iridocyclitis, left eye		
H20.043	Secondary noninfectious iridocyclitis, bilateral		
H20.049	Secondary noninfectious iridocyclitis, unspecified eye		
H20.9	Unspecified iridocyclitis		

ICD10 code	ICD10 code label	ICD9 code	ICD9 code label
H30.001	Unspecified focal chorioretinal inflammation, right eye		chorioretinitis, posterior pole Disseminated choroiditis and chorioretinitis, peripheral Disseminated choroiditis and chorioretinitis, generalized Disseminated retinitis and retinochoroiditis, metastatic Chorioretinitis, unspecified Acute and subacute iridocyclitis, unspecified Primary iridocyclitis Secondary iridocyclitis, noninfectious Unspecified iridocyclitis
H30.002	Unspecified focal chorioretinal inflammation, left eye		
H30.003	Unspecified focal chorioretinal inflammation, bilateral		
H30.009	Unspecified focal chorioretinal inflammation, unspecified eye		
H30.011	Focal chorioretinal inflammation, juxtapapillary, right eye		
H30.012	Focal chorioretinal inflammation, juxtapapillary, left eye		
H30.013	Focal chorioretinal inflammation, juxtapapillary, bilateral		
H30.019	Focal chorioretinal inflammation, juxtapapillary, unspecified eye		
H30.021	Focal chorioretinal inflammation of posterior pole, right eye		
H30.022	Focal chorioretinal inflammation of posterior pole, left eye		
H30.023	Focal chorioretinal inflammation of posterior pole, bilateral		
H30.029	Focal chorioretinal inflammation of posterior pole, unspecified eye		
H30.031	Focal chorioretinal inflammation, peripheral, right eye		
H30.032	Focal chorioretinal inflammation, peripheral, left eye		
H30.033	Focal chorioretinal inflammation, peripheral, bilateral		
H30.039	Focal chorioretinal inflammation, peripheral, unspecified eye		
H30.041	Focal chorioretinal inflammation, macular or paramacular, right eye		
H30.042	Focal chorioretinal inflammation, macular or paramacular, left eye		
H30.043	Focal chorioretinal inflammation, macular or paramacular, bilateral		
H30.049	Focal chorioretinal inflammation, macular or paramacular, unspecified eye		
H30.101	Unspecified disseminated chorioretinal inflammation, right eye		
H30.102	Unspecified disseminated chorioretinal inflammation, left eye		

ICD10 code	ICD10 code label	ICD9 code	ICD9 code label
H30.103	Unspecified disseminated chorioretinal inflammation, bilateral		
H30.109	Unspecified disseminated chorioretinal inflammation, unspecified eye		
H30.111	Disseminated chorioretinal inflammation of posterior pole, right eye		
H30.112	Disseminated chorioretinal inflammation of posterior pole, left eye		
H30.113	Disseminated chorioretinal inflammation of posterior pole, bilateral		
H30.119	Disseminated chorioretinal inflammation of posterior pole, unspecified eye		
H30.121	Disseminated chorioretinal inflammation, peripheral right eye		
H30.122	Disseminated chorioretinal inflammation, peripheral, left eye		
H30.123	Disseminated chorioretinal inflammation, peripheral, bilateral		
H30.129	Disseminated chorioretinal inflammation, peripheral, unspecified eye		
H30.131	Disseminated chorioretinal inflammation, generalized, right eye		
H30.132	Disseminated chorioretinal inflammation, generalized, left eye		
H30.133	Disseminated chorioretinal inflammation, generalized, bilateral		
H30.139	Disseminated chorioretinal inflammation, generalized, unspecified eye		
H30.891	Other chorioretinal inflammations, right eye		
H30.892	Other chorioretinal inflammations, left eye		
H30.893	Other chorioretinal inflammations, bilateral		
H30.899	Other chorioretinal inflammations, unspecified eye		
H30.90	Unspecified chorioretinal inflammation, unspecified eye		

ICD10 code	ICD10 code label	ICD9 code	ICD9 code label
H30.91	Unspecified chorioretinal inflammation, right eye		
H30.92	Unspecified chorioretinal inflammation, left eye		
H30.93	Unspecified chorioretinal inflammation, bilateral		
ADEM			
G04.00	Acute disseminated encephalitis and encephalomyelitis, unspecified	323.51 323.52 323.61 323.62 323.81 323.9	Encephalitis and encephalomyelitis following immunization procedures Myelitis following immunization procedures Infectious acute disseminated encephalomyelitis (ADEM) Other postinfectious encephalitis and encephalomyelitis Other causes of encephalitis and encephalomyelitis Unspecified causes of encephalitis, myelitis, and encephalomyelitis
G04.01	Postinfectious acute disseminated encephalitis and encephalomyelitis (postinfectious ADEM)		
G04.02	Postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis		
G04.30	Acute necrotizing hemorrhagic encephalopathy, unspecified		
G04.31	Postinfectious acute necrotizing hemorrhagic encephalopathy		
G04.32	Postimmunization acute necrotizing hemorrhagic encephalopathy		
G04.39	Other acute necrotizing hemorrhagic encephalopathy		
G04.81	Other encephalitis and encephalomyelitis		
G04.90	Encephalitis and encephalomyelitis, unspecified		
Pericarditis			
B33.23	Viral pericarditis	074.21 420.90 420.91 420.99	Coxsackie pericarditis Acute pericarditis, unspecified Acute idiopathic pericarditis Other acute pericarditis
I30.0	Acute nonspecific idiopathic pericarditis		
I30.1	Infective pericarditis		
I30.8	Other forms of acute pericarditis		
I30.9	Acute pericarditis, unspecified		

VII. ADDENDUM

After conducting two rounds of sequential analysis, monitoring the accumulation of vaccine doses administered since the vaccine approval in December 2014 and its launch in summer 2015, and factoring in that all available data for this study at any given time are about 9-12 months old, the Center for Biologics Evaluation and Research (CBER) decided to discontinue this study as of December 2017. The uptake rate of HPV9 vaccine has been slower in the population than CBER anticipated at the time of the design of this study. The study protocol stated that surveillance was to continue until three million doses were included in analysis. Hence, according to the protocol, the study would end after accumulation of three million doses of vaccine if no statistically significant results were detected for any of the outcomes prior to that date. However, based on the observed rate of vaccine accumulation, it would have taken several more years to accumulate three million doses of the vaccine in the data. Even if three million doses had accumulated, power calculations indicated that the statistical power to detect elevated risks would have been sub-optimal for two of the four outcomes to be analyzed unless relative risks were at least 5. In addition, the Global Advisory Committee on Vaccine Safety (GACVS) has conducted several reviews of the safety of HPV vaccines and has published a recent safety update.[1] The GACVS continues to conclude that HPV vaccines are safe.