MINI-SENTINEL CBER/PRISM SURVEILLANCE PROTOCOL

MONITORING FOR VENOUS THROMBOEMBOLISM AFTER GARDASIL VACCINATION

Version 2.1

Prepared by: Michael D. Nguyen, MD[1], Sharon K. Greene, PhD, MPH[2], W. Katherine Yih, PhD, MPH[2], Martin Kulldorff, PhD[2], Tracy A. Lieu, MD, MPH[2], Ruth Gil Prieto, PhD, MPH[2], Nandini Selvam, PhD, MPH[3], Vinit Nair, BS Pharm, MS, RPh[4], Cheryl N. McMahill-Walraven, MSW, PhD[5], Jill de Jong, MD, PhD[6], David B. Martin, MD, MPH[1]

Author Affiliations: 1. Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD; 2. Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; 3. HealthCore Inc, Alexandria, VA; 4. Comprehensive Health Insights, Humana Inc., Louisville, KY; 5. Aetna Informatics, Aetna, Blue Bell, PA; 6. Department of Pediatrics, The University of Chicago, Chicago, IL

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multifaceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

History of Modifications

Version	Date	Modification	By
V2.0	2/4/2014-4/1/2014	• Incorporated two more Data Partners (DPs) in order to increase statistical power • Modified Table **3** to add those DPs and to revise some data start and end dates • Changed pre-HPV minimum enrollment requirement from 13 mo. to 4 mo., so as to include more cases and gain statistical power • Included discussion of a limitation of this change from 13 to 4 mo. of minimum enrollment • Recalculated statistical power • Shortened washout and control intervals and removed plan to truncate post-vaccination observation time at subsequent dose, to avoid bias • Stated the intention to look at Doses 2 and 3 separately (as secondary analyses), in addition to looking at Dose 1 and all-doses combined (as primary analyses) • Stated that possible effect modification would be examined by including interaction term(s) in model (rather than only by stratifying analyses) • Restricted VTE cases for analysis to first-ever rather than also first-in-one-year cases • Eliminated exploratory analyses of chronic VTE • Changed from one primary and two secondary analyses to three co-primary analyses • Changed point in combined hormonal contraceptive (CHC) duration of use after which VTE risk would be treated as flat from 12 mo. to 9 mo. • Added fuller account of how CHC-VTE risk would be modeled, what the minimum required enrollment period would be, what the criteria for determining best fit would be, and the fact that the model and curve would be chosen before any analyses of HPV-VTE risk are done • Removed the small signal investigation section, because in a sense the whole study is a signal investigation • Made small changes to chart review section, e.g. added criteria used to rank HPV (exposure) charts to be sought, modified how PPV would be calculated • Made changes to the non-CHC risk factors being considered; to the risk factor definitions, including pregnancy; and to the risk factor grouping • Removed mention of brand-specific CHC analyses • Made many less substantive changes in the interests of completeness, accuracy, flow, and the like • Removed Appendix 4, which was thought to be difficult to understand and unnecessarily elaborate	Mini-Sentinel PRISM HPV Workgroup

Version	Date	Modification	By
V2.1	11/15/2014	• Changed maximum apparent CHC usage gaps to bridge (ignore) from 7 days to 14 days, as 7 days seemed too stringent-- apparent gaps of 1-14 days seem unlikely to represent true interruptions in use. This appears on the page labeled "8," which is electronic p. 12.	Mini-Sentinel PRISM HPV Workgroup

MINI-SENTINEL CBER/PRISM SURVEILLANCE PROTOCOL

Monitoring For Venous Thromboembolism After Gardasil Vaccination

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I. INTRODUCTION

A. CONTEXT OF SAFETY CONCERN

Gardasil is a quadrivalent vaccine indicated for the prevention of anogenital cancers and genital warts caused by infection with human papillomavirus (HPV) types 6, 11, 16, and 18. Gardasil is routinely recommended for females aged 11–12 years in a three dose series (0, 2, and 6 months) but can be administered as young as age 9 years; catch-up vaccination is recommended for females aged 13–26 years who have not been previously vaccinated.[1] FDA approved Gardasil in June 2006 based on 12 randomized controlled studies involving approximately 21,000 males and females aged 9–26 years in support of its safety and efficacy. In these clinical studies, injection site reactions were found to be higher among Gardasil vaccinated persons.[2, 3] However, rates of systemic reactions, new onset medical conditions, serious adverse events and deaths following vaccination were comparable between vaccine and placebo recipients. No safety issues were identified in prelicensure studies of Gardasil.

Postlicensure surveillance identified disproportional reporting of venous thromboembolism (VTE) after Gardasil vaccination. An analysis of the first 2.5 years of passive surveillance in VAERS found that VTE was reported more frequently than expected compared with other vaccines.[4] The median age of reported VTE cases was 20 years (range 15–39 years) and the median onset interval was 23 days (range 0–306 days). However, 90% of the reported cases had at least one preexisting risk factor for VTE, suggesting that confounding may explain a substantial proportion of the cases. Due to the known limitations of passive surveillance, disproportional reporting alone is not sufficient to demonstrate a causal relationship between VTE and Gardasil.

To supplement passive surveillance, the Vaccine Safety Datalink (VSD) monitored 600,558 Gardasil doses to females aged 9–26 years for the first 3 years after licensure (August 2006 to October 2009). During this period, VSD monitored 8 outcomes using rapid cycle analyses, and no safety signals were detected based upon predefined criteria.[5, 6] However, a statistically non-significant relative risk of 1.98 for VTE (defined using ICD-9 codes 415.1x and 453.x) after Gardasil administration in females aged 9–17 years was found compared with a historical comparison group of females of the same age. Eight VTE cases in females aged 9–17 years were electronically identified 1–42 days postvaccination and five cases were chart-confirmed. The VTE diagnosis in four of the five confirmed cases occurred within 1-7 days after vaccination; the fifth occurred on Day 32. All five cases had at least one known risk factor, including hormonal contraceptive use, coagulation disorders, smoking, obesity or prolonged hospitalization. No elevated risk was detected after Gardasil vaccination among adult females aged 18–26 years.

In December 2010, this information was presented to the FDA Pediatric Advisory Committee as part of a routine safety review.[7] The committee recommended that additional surveillance studies be conducted to further evaluate the potential risk of VTE following Gardasil vaccination. This protocol describes the methods used to monitor VTE after Gardasil vaccination in the PRISM program.

B. VENOUS THROMBOEMBOLISM IN CHILDREN

Venous thromboembolism consists of deep vein thrombosis and pulmonary embolism. VTE can be clinically categorized by etiology (idiopathic/risk-associated), anatomic location (proximal/distal; superficial/deep), organ system involvement (e.g. pulmonary, cerebral, extremity), or recurrence (primary/recurrent).

The annual incidence of VTE in children <18 years is estimated to be 0.7–13.4 per 100,000 children, although rates vary by age (see Table 1 and Table 2 below).[6, 8-10] The incidence of VTE increases sharply with age, with adults having VTE at a rate of 300–5,000 per 100,000.[11] More than 90% of pediatric VTE cases have ≥2 risk factors.[11, 12] Common risk factors include immobility, malignancy, infection, cardiac disease, surgery, trauma, and congenital prothrombotic disorders (Factor V Leiden, prothrombin gene mutation, antithrombin III deficiency, Protein C and S deficiency, and elevated homocysteine). In the target population for Gardasil, there are additional environmental and behavioral risk factors, including: combined hormonal contraceptive (CHC) use, smoking, and obesity. In particular, CHC use is estimated to increase VTE risk by 3–6 fold due to an estrogen mediated procoagulant state.[13] Some studies have shown a higher risk in the first year of use[14, 15] (especially the first 3 months) and with contraceptives containing drospirenone, desogestrel and gestodene, compared with levonorgestrel.[16-19] It is plausible that health visits where Gardasil is administered are also visits when contraception is initiated. The possibility that the increases in risk observed after Gardasil are due to confounding by contraceptive use or are exacerbated by contraceptive use (effect modification) has not yet been systematically evaluated and is one of the objectives of this safety evaluation.

Table 1. Venous Thromboembolism, National Hospital Discharge Survey (1979–2001)

Venous Thromboembolism, National Hospital Discharge Survey (1979–2001)			
	Incidence rate (per 100,000 person-years)		
Age Group (years)	**Males**	**Females**	**All**
0–1	11.3	9.7	10.5
2–14	2.3	2.6	2.4
15–17	8.1	14.9	11.4
All	4.3	5.5	4.9

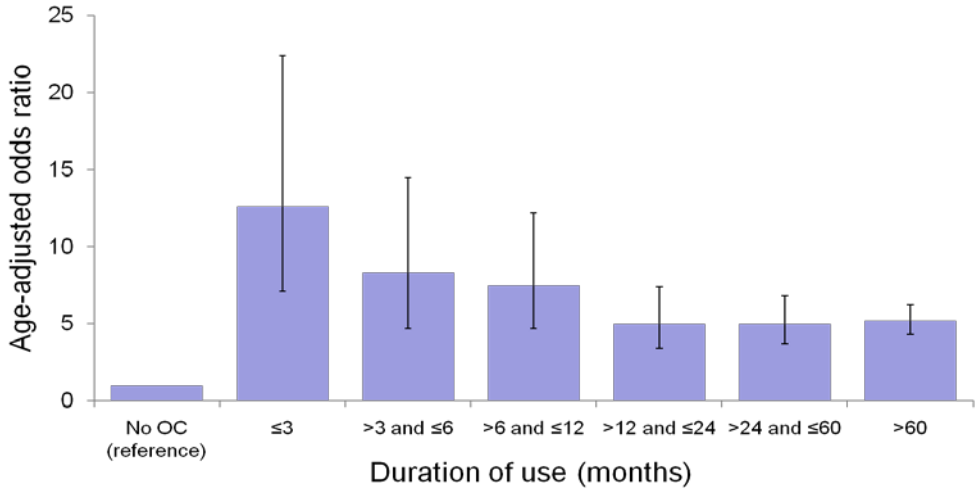
Source: Stein. J Pediatr 2004; 145:565-5

Table 2. Venous Thromboembolism, Vaccine Safety Datalink (2006–2009)

Venous Thromboembolism, Vaccine Safety Datalink (2006–2009)	
Age Group (years)	**Incidence rate* (per 100,00 person-years)**
9–13	3.2
14–17	13.4
18–26	73.6

Source: Gee. Vaccine 2011;29(46):8279-8284.
*VSD did not include 451.x in their VTE definition. If this code had been included (as we are doing in PRISM), then these rates would be higher.

Figure 1. VTE Risk by Duration of Combined Hormonal Oral Contraceptive Use



Vlieg et al. *BMJ* 2009;339:b2921

C. HYPERCOAGULABLE STATES AND RATIONALE FOR RISK INTERVAL

There is no specific biologic mechanism linking VTE to Gardasil vaccination. The Institute of Medicine recently reviewed the general coagulation pathways and hypercoagulable states that might plausibly be involved, but the biologic mechanisms were not specific to vaccination.[20] Furthermore, no imbalances were noted in the rates of thromboembolic events in clinical trials, and the majority of cases identified in postmarketing surveillance have had underlying risk factors that increase the propensity for thrombosis.

Hypercoagulable states occur as a result of any number of transient or permanent conditions that increase the tendency for blood clot formation.[21] Although the risk increases with the number of risk factors, a person with a confirmed hypercoagulable state does not necessarily develop thrombosis. The final common pathway to thrombosis in many acquired hypercoagulable states is marked by a conversion from a normally nonthrombotic endothelial surface to a prothrombotic, proinflammatory phenotype associated with increased leukocyte adhesion molecules, increased expression of macrophages, tumor tissue factor, or inhibition of the protein C system.[21] Myriad other factors also influence the propensity for thrombosis including increases in coagulation factors, decreases in antithrombotic factors, venous stasis, increased blood viscosity, presence of an indwelling catheter, and mechanical compression or obstruction.

However, not all hypercoagulable states are the same, and the timing of clot formation depends on the underlying factors. For transient hypercoagulable states such as pregnancy, risk begins in the first trimester and persists for up to 42 days postpartum.[22] Patients undergoing same-day or inpatient surgery are at highest risk during the 6 weeks after surgery, but patients may remain at risk for a total of 12 postoperative weeks.[23] The risk of travel-related VTE is typically observed in the first 2–4 weeks after long haul travel.[24] For inherited conditions, the first thrombotic event can present as early as adolescence (Factor V Leiden), or much later in adulthood (prothrombin 20210 gene mutation).[11]

For this study, defining the risk interval following Gardasil vaccination is challenging without a theoretical mechanism. We estimate that the period of increased risk, if any, would most likely occur

immediately following vaccination, be short-lived and presumably return to baseline after each vaccination. This is consistent with the findings in the VSD VTE evaluation. With these assumptions, we have selected 2 risk intervals: days 1-28 post-vaccination (primary) and days 1-7 post-vaccination (secondary).

II. OBJECTIVES

1. To determine the existence and magnitude of any increased risk of VTE in the 1 or 4 weeks following Gardasil vaccination compared with unexposed person-time among vaccinees and to assess the role of combined hormonal contraceptives (CHCs) as a potential confounder or effect modifier
2. To determine through medical chart review the positive predictive value of an ICD9 code based algorithm for identifying VTE

III. METHODS

A. STUDY POPULATION AND DATA SOURCES

The Data Partners participating in PRISM are HealthCore, Humana, Aetna, Optum Insight, and Tennessee Medicaid (Vanderbilt). We added Optum Insight and Tennessee Medicaid (Vanderbilt) to increase the study's statistical power. The study population will consist of Gardasil vaccinees who were members of any of these Data Partners during the period of interest and who meet other enrollment criteria (Table **3**).

The maximum study period will be from June 2006 (the licensing date of Gardasil) to March 2013. The period of data availability varies by Data Partner. The start and end-dates of data to be included are shown below:

Table 3. Periods of Data to be Used in HPV Analyses

Data Partner	Start	End		No. of years
HealthCore	6/2006 (HPV licensure)	5/2011		5
Humana	10/2007*	8/2011		~ 4
Aetna	5/2008*	12/2012		~3.5
Optum Insight	5/2008*	3/2013		~5
Tennessee Medicaid	6/2006 (HPV licensure)	12/2012		~6.5

* Start date shown takes into consideration the requirement of 4 months of pre-HPV enrollment so is 4 months after the actual first care date available in the Data Partner's data.

Within these data, only the following population will be included in the analyses: females age 9-26 years old with medical and pharmacy coverage who were exposed to ≥1 dose of Gardasil, and continuously enrolled in the health plan from 4 months prior to the 1st dose of Gardasil through at least 70 days after the 1st dose of Gardasil. Continuously enrolled person-time will be included, with the following proviso: If a vaccinee has incomplete person-time during 0-70 days after Dose 2 or 3 of Gardasil, his/her person-time on and after the day of that dose will be excluded in order to avoid possible bias. For example, if a vaccinee gets Dose 1 at 12 years 0 months of age and Dose 2 at 12 years 2 months and then disenrolls at 12 years 3 months, only the person-time through the day before Dose 2 will be included. Enrollment gaps of up to 14 days at any time in the 4 months prior to the first dose will be permitted, but no such enrollment grace period will be used from day 0 through day 70 of the first dose. Similarly, the second and third doses will be included, respectively, only if there are no enrollment gaps from day 0 through day 70 of these doses. These enrollment criteria exclude patients who disenroll or die after their Gardasil dose but before 70 days elapse.

Sources of immunization records will be claims data from up to three Data Partners and immunization registry data from any of the nine participating registries (also known as immunization information systems, IISs): AZ, FL, MI, MN, NYC, NYS, PA, VA,. The source of VTE diagnosis records will be claims data.

B. STUDY DESIGN, NULL HYPOTHESIS, AND ANALYSIS PLAN

A self-controlled risk interval design (detailed in Table 4 below and shown schematically in Figure 2) is proposed. The null hypothesis is that the risk of VTE onset on a day during the defined risk interval directly after Gardasil is the same as the risk of VTE onset on a day during the unexposed control interval.

Table 4. Analysis Methods, Data Sources, Risk Intervals

Method	Data to use	Notes
Self-controlled risk interval[25, 26] using chart-confirmed data	Outcomes: chart-confirmed subset of vaccinated cases found in claims data, reclassified from diagnosis date to onset date Contraceptives: dispensing, chart review VTE risk factors: claims, chart review	Risk interval (1°): 1-28 days Risk interval (2°): 1-7 days Washout: 29-35 days Comp interval: Dose 1: 36-56, Dose 2 & 3: 36 – 63 days Controls for fixed potential confounders (e.g., genetic factors, SES), and implicitly adjusts for CHC use to the extent that VTE risk from contraceptives does not vary over the 63-day observation period. Analyses for 1st dose and all doses together primary; analyses for 2nd and 3rd doses secondary. Only doses that are informative (with VTE in either risk or comparison interval) will contribute person-time. To assess effect modification, may stratify or (preferred) include interaction terms in model.
Temporal scan statistic using chart-confirmed data	Outcomes: chart-confirmed subset of vaccinated cases found in claims data, reclassified from diagnosis date to onset date	

C. EXPOSURE CODES

- Vaccination: Gardasil vaccination will be identified by means of CPT code 90649 in claims or IIS data and CVX code 62 in IIS data. Gardasil vaccination will be confirmed through review of vaccination records, claims data, and IIS data. To enable exploratory analyses stratified by number and/or type of concomitant vaccines, data will also be collected for non-HPV vaccines administered on the same day.

- Contraceptives: To control for the confounding effect of CHC use and to assess whether such use may be an effect modifier of the association between Gardasil and VTE, the contraceptive use status of all vaccinees will be determined. A list of National Drug Codes (NDCs) will be constructed by querying First Data Bank for the Enhanced Therapeutic Classification categories "Contraceptives Oral," "Contraceptives Intravaginal, Systemic" and "Contraceptives Transdermal." Other contraceptives such as emergency contraceptives, intrauterine devices, implantable devices and injections do not contain estrogen - the ingredient most associated with a net prothrombotic state. To ensure that this list is complete, the identified generic names will be shared with each participating Data Partner, which will add any missing or homegrown codes for these generic names to the list.

  The MSCDM Dispensing file will be used to identify contraceptive exposure status for all Gardasil vaccinees, for up to four dates of interest: as of each of the three Gardasil doses and as of VTE diagnosis. Vaccinees will be considered exposed to contraceptives if the dispensing date + days supplied (RxDate+RxSup) includes the date of interest, with the following proviso. Suppose there are two consecutive contraceptive dispensings, A & B, with their respective RxDate + RxSup. If $RxDate_B$ falls within the period $RxDate_A + RxSup_A$, then we will assume Dispensing B was filled early, in which case the timing for dispensing B should instead be determined as $RxDate_A + RxSup_A + RxSup_B$. This process will be repeated as needed for any number of consecutive dispensings filled early. Contraceptive exposure status at the time of VTE will also be determined for all VTE cases within 9 months of contraceptive initiation. A limitation is that the RxDate available in the Dispensing file is not necessarily the date the patient actually initiated contraceptives. For instance, a patient may pick up her prescription on Sunday, January 1, but not initiate use until Sunday, January 29, following her next menstrual period. Since we cannot know the timing of each patient's menstrual period and actual contraceptive initiation, we will assume initiation begins on the RxDate, with the result that total length of contraceptive use may be overestimated for some patients by up to around 4 weeks, or longer for patients with irregular periods.

  For current users, the days supplied (RxSup) will be summed for all recent dispensings for the same patient to determine the total duration. If a gap between one (dispensing date + days supplied) and the next (dispensing date + days supplied) is ≤14 days, the gap will be ignored and the gap days will be counted in the total duration. If the gap is >14 days, then the period covered by the prior dispensing and gap will not be counted in the total duration.

  All CHCs (oral, intravaginal and transdermal) will initially be considered as one drug class. We purposely did not identify person-time exposed to progestin-only products in the electronic data; any such person-time will be classified as CHC-unexposed.

- VTE risk factors: The list of codes used to detect the risk factors for VTE is included in Appendix 1: Codes Used to Identify Select VTE Risk Factors. Unfortunately, there are no precise codes for many nonspecific categories of VTE risk factors, such as recent infection, major surgery (requiring general anesthesia >30 minutes), prolonged immobility (bed rest ≥3 days), history of long haul air travel, and

major trauma.[27] Additionally, anatomic venous compression syndromes resulting in VTE (Paget-Schroetter and May-Thurner syndromes) cannot be differentiated using administrative codes and require medical record review.

As seen in Appendix 2, we will identify pregnancy and the post-partum period as a risk factor for VTE using administrative codes signifying a delivery or pregnancy outcome after the index date for VTE, rather than markers of pregnancy prior to the index date. This requires an estimate for the appropriate follow up time for spontaneous abortion, stillbirth and preterm deliveries. Shorter follow-up periods will result in misclassifying some individuals with longer-duration pregnancies as non-pregnant, and longer follow-up times may result in misclassifying some individuals with shorter-duration pregnancies as pregnant prior to VTE onset. Since pregnancy is an important risk factor and our goal is to avoid confounding by pregnancy, we have selected a full 40 week (280 day) follow-up time to maximize our chances for detecting pregnancy as a risk factor.

Important risk factors will also be identified through medical record review of all vaccinated cases with VTE in a risk or comparison interval.

D. OUTCOME DEFINITION

In the first year of the Mini-Sentinel pilot project, systematic evidence reviews were conducted on 20 FDA-identified health outcomes of interest for active surveillance. Using methods outlined by the Observational Medical Outcomes Partnership, teams of investigators assessed the performance characteristics of electronic algorithms to detect health outcomes in administrative databases. Tamariz et al. conducted the review for VTE and identified 345 abstracts from a comprehensive literature search, 65 of which were selected for full-text review, and 10 studies were included in the final evidence tables.[28] For VTE, the performance of multiple PE and/or DVT ICD-9 codes (415.1x, 451.x, and 453.x) reported positive predictive values ranging from 26% to 93%.

In this PRISM surveillance protocol, we will use 415.1x, 451.x, 453.x (see Appendix 3). We are excluding 415.0 (cor pulmonale) because it is not specific to VTE and can have multiple other etiologies. We are using codes for superficial venous thrombosis because recent evidence suggests that superficial venous thrombosis may not be as benign as is commonly believed and may be a marker for more clinically significant thromboembolic risk.[29] Although superficial thrombosis may be evaluated in exploratory analyses, all primary analyses will focus on the outcomes of pulmonary embolism and deep vein thrombosis.

Table 5. VTE Outcome Definition

ICD-9 Codes	Risk Interval	Setting	Adjudication status	Incident Case Definition
415.1x Pulmonary embolism, infarction; 451.x Phlebitis and thrombophlebitis; 453.x Other venous embolism, thrombosis	1°: 1-28 days 2°: 1-7 days	Inpatient, ED, clinic	Definite	First-ever VTE diagnosis

To avoid follow-up visits and restrict to incident cases, we will consider diagnoses that are the first in that patient's record since enrollment. History of VTE will be assessed not only using claims data, but

also during medical record review. Analyses will restrict to first-ever diagnoses, i.e., the first VTE diagnosis since patient enrollment, and with no VTE history found during medical record review. VTE diagnoses for all 1-77 days following each dose will be captured (an additional 14 days was added to the 63 days in the main observation period in case of delays between the symptom onset date and the date of the VTE diagnosis according to the claims data).

E. STATISTICAL ANALYSES

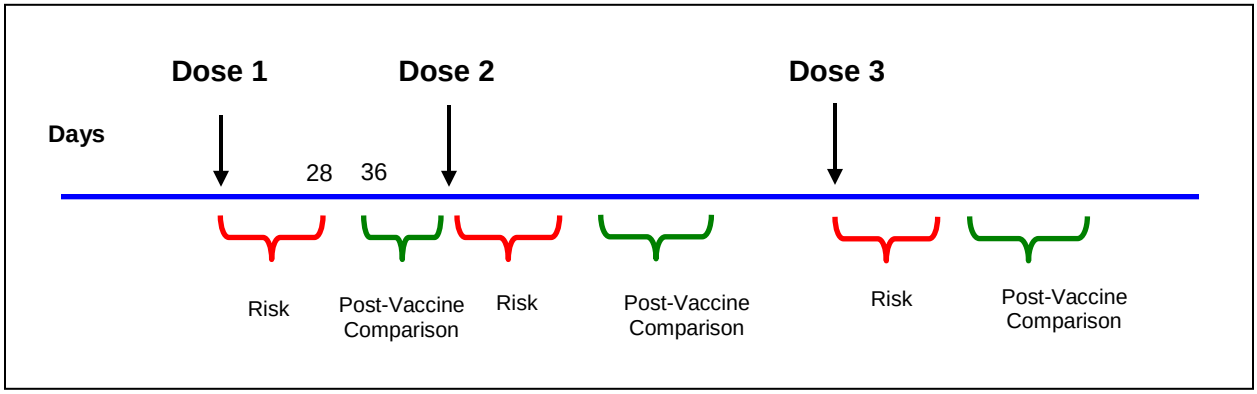
Descriptive analyses

A number of univariate and bivariate descriptive analyses in the form of tables, histograms, and other graphs will be carried out prior to any hypothesis testing in order to characterize the Gardasil and VTE data and to assess the prevalence of contraceptive use and other measureable risk factors for VTE among vaccinees.

Self-controlled analyses

Co-primary analyses. There are 3 co-primary analyses, as described in the paragraphs below. These analyses all use the self-controlled risk interval design,[30, 31] with exposed Days 1-28 (primary) and Days 1-7 (secondary) post-vaccination risk intervals. The unexposed comparison intervals are the same regardless of which risk interval is used and are Days 36-56 post-vaccination for Dose 1 and Days 36 – 63 for Doses 2 and 3 (Figure 2). The comparison interval for Dose 1 is 1 week shorter than for Doses 2 and 3 to avoid potential bias due to Dose 2 frequently being given during Days 57-63 after Dose 1. (Approximately 25% of second doses were given in that 7-day period in the study population.)

Figure 2. Self-Controlled Risk Interval Design



Analysis #1 will include all Gardasil recipients with VTE in either the risk or the comparison interval of a Gardasil dose. It will not explicitly adjust for CHC use; however, it will *implicitly* adjust for CHC use to the extent that VTE risk from CHCs does not vary over the 63-day observation period.

CHC use is a potential time-varying factor that, for some vaccinees, could cause the baseline risk of VTE to be different in the risk vs. control intervals. To lessen this possible effect, two additional analyses will be performed. Although these analyses address time-varying confounding by CHC use, they are not necessarily better than Analysis #1, because Analysis #2 excludes some cases, leading to a loss of statistical power, and Analysis #3 is subject to some degree of misclassification of duration of CHC use and does not account for uncertainty in the CHC-VTE risk function to be used for the adjustment.

Analysis #2 will restrict to vaccinees whose baseline risk of VTE is unlikely to have varied between the risk and comparison intervals due to contraceptive use, i.e., (1) those vaccinees who have no record of contraceptive use as of 63 days after the Gardasil dose ("never-users"), in addition to (2) those vaccinees who have continuously been on contraceptives for at least 9 months as of the day of the Gardasil dose, after which the time-varying risk after contraceptive initiation appears to plateau ("long-term users"). (See *Estimation of VTE risk by duration of CHC use* subsection below for more about the point at which the risk from CHC use is considered to plateau.) This restriction will result in fewer cases included in analysis, reducing power, but will address the time-varying confounding related to contraceptive initiation.

Analysis #3 will not exclude cases, thereby retaining the same power as in analysis #1, and will explicitly adjust for the increased risk of VTE associated with the initiation of CHC use, as data suggest that VTE risk varies within the first several months of initiation. In the logistic regression analysis, an offset term will be used for vaccinees who initiate CHCs between 8.99 months prior to the Gardasil dose and the end of the control interval following the Gardasil dose, as determined by the medical record or inferred from the pharmacy dispensing data, to adjust for the time-varying VTE risk from CHC use. The offset term will be obtained by estimating the risk of VTE by duration of CHC use:

Estimation of VTE risk by duration of CHC use. The time-varying risk of first-ever VTE will be estimated from a risk curve generated from electronic data going back to 2004 from 9-26 year olds with a minimum of 7 months of enrolled time. Requiring a minimum of 7 months of enrolled time optimizes precision (compared to 13 months, for example, which would eliminate a substantial proportion of cases and person-time and produce less stable VTE background rates) and accuracy (compared to 4 months, for example, where misclassification of CHC duration would be somewhat more common). VTE cases within 1-28 days following Gardasil will be excluded.

After a preliminary examination of the risk of VTE by duration of CHC use in the portion of the study population contributed by five Data Partners, we decided, for purposes of the CHC-VTE risk curve to be used for adjusting Analysis #3, to consider the risk from CHC use to plateau starting at 9 months' duration. This was based on the CHC-associated risk appearing to be about the same during the 9-12 months after CHC initiation as beyond 12 months. The decision was subsequently supported by modeling.

Prior to doing any analyses of the risk of VTE after HPV, we will fit the CHC-VTE data using a linear function, then linear + quadratic, then linear + quadratic + cubic, and so on not to exceed a 5^{th} order polynomial function in a Poisson regression model. Goodness-of-fit will be determined based upon a combination of the LLR, p-value, Akaike information criterion (AIC), and biologic plausibility, and the best model will be selected. We will guard against overfitting by using such tools as the AIC, which deals with the trade-off between a model's goodness of fit and complexity. If a polynomial model does not fit, then we will use splines or other methods. We will treat the risk curve as known without error.

Limitations of Analysis #3. One limitation of Analysis #3 is the minimum-enrollment criterion of 4 months prior to Gardasil vaccination for inclusion in Analyses 1-3. (This was first mentioned in Section III.A.) The original protocol specified an inclusion criterion of 13 months of minimum enrollment, the purpose being to allow assessment of the duration of CHC use up to at least 12 months prior to vaccination, thereby covering the full 12-month period since CHC initiation during which the CHC-associated risk of VTE varies (Figure 1). We changed this to 4 months because of the loss of cases and

statistical power that would have resulted from choosing a longer period of minimum enrollment. The possibility of misclassification of long-term CHC use as shorter-term use introduced by this reduction in minimum enrollment from 13 months to 4 months was considered acceptable in light of the following considerations:

1. A descriptive analysis of CHC dispensings to PRISM females aged 9-26 years in the original 3 DPs determined that 100% are given in the form of a ≤ 91 days' supply and approximately 90% are given in the form of a ≤ 28 days' supply. These percentages were consistent across data partners and years of age. Therefore, the great majority (or even all) of those with true durations of CHC usage of < 4 months at the time of vaccination will be correctly classified with the inclusion criterion of at least 4 months of pre-Gardasil enrollment.
2. Those with only 4 months of enrollment prior to vaccination and true durations of CHC usage of ≥ 4 months prior to vaccination will be misclassified as having been exposed for only 3-4 months. However, the existence of clinician documentation of CHC initiation and/or duration of use in some of the medical records allays concerns about this.
3. The period of CHC use where VTE risk varies most quickly and where accurate capture of duration of use is therefore most crucial is the first 3 months after initiation (Figure 1).
4. Sensitivity analyses can be conducted, removing cases with short periods between enrollment and first apparent CHC dispensing (i.e. cases whose duration of CHC use may have been misclassified as shorter than the true duration).

Another limitation of Analysis #3 is that it does not account for patients who discontinue CHCs during the observation period. This may introduce a weak bias toward an association, because patients who discontinue CHCs during the observation period may on average have fewer observed VTE events toward the end of the observation period. However, we will not characterize and adjust for the VTE risk after CHC discontinuation, because dispensing claims data are likely unreliable regarding the true timing of discontinuation. Thus, although a patient may discontinue use any time after a prescription refill, we assume use is ongoing throughout the complete days' supply, which could mischaracterize the VTE risk. Also, a patient who appears to have discontinued CHC use because there are no longer claims for dispensings may have, for instance, switched to paying for CHCs out-of-pocket at Planned Parenthood.

Table 6. Pre-specified self-controlled risk interval analyses*

Dose #	First-ever, Definite VTE Cases	Risk Interval	Adjustment for Time-Varying Risk Following CHC Initiation (all co-1°)
All (1°)	All cases	1°: 1-28 2°: 1-7	No (analysis #1)
	Restricted to never users or those with ≥ 9 months of CHC use	1°: 1-28 2°: 1-7	Not applicable (analysis #2)
	All cases	1°: 1-28 2°: 1-7	Yes (analysis #3)
1 (1°)	All cases	1°: 1-28 2°: 1-7	No (analysis #1)
	Restricted to never users or those with ≥ 9 months of CHC use	1°: 1-28 2°: 1-7	Not applicable (analysis #2)
	All cases	1°: 1-28 2°: 1-7	Yes (analysis #3)
2 (2°)	All cases	1°: 1-28 2°: 1-7	No (analysis #1)
	Restricted to never users or those with ≥ 9 months of CHC use	1°: 1-28 2°: 1-7	Not applicable (analysis #2)
	All cases	1°: 1-28 2°: 1-7	Yes (analysis #3)
3 (2°)	All cases	1°: 1-28 2°: 1-7	No (analysis #1)
	Restricted to never users or those with ≥ 9 months of CHC use	1°: 1-28 2°: 1-7	Not applicable (analysis #2)
	All cases	1°: 1-28 2°: 1-7	Yes (analysis #3)

* All analyses test a single hypothesis about the potential association between VTE and Gardasil vaccination. As such, this examination of the robustness of this potential association does not require adjustment for multiple testing.

Sensitivity analyses. A number of sensitivity analyses will be considered, including analyses that remove VTE cases where the true duration of CHC use could be longer (to be determined by examining the period between enrollment and apparent CHC initiation) and analyses that remove VTE cases receiving concomitant vaccination. The need for additional sensitivity analyses may emerge during the analysis phase.

Additional methods considered but not used

We considered Fireman et al.'s case-centered method to adjust for any seasonality in vaccination and VTE,[32] but it is not necessary because it is not clear that VTE is seasonal.[33] To adjust for the time-varying factor of CHC use status, we will use a self-controlled risk interval design, as described above.

In addition, we considered but decided not to construct a cohort of CHC users, comparing VTE risk post-vaccination (index) date for vaccinees vs non-vaccinees, controlling for age, sex, site, duration of CHC use, and other VTE risk factors. The rationale is that we can more simply assess effect modification by CHC use by restricting self-controlled risk interval analyses to CHC non-users and users ≥ 9 months in analysis #2, and the self-controlled risk interval analysis has the advantage of implicitly controlling for all

measured and unmeasured confounders that do not vary over the risk and control intervals (e.g., genetic predisposition to VTE).

Statistical power

One-sided power calculations for the self-controlled risk interval analysis, alpha=0.05, 1-28 day risk interval, were updated to include the addition of Optum Insight and Tennessee Medicaid (Vanderbilt). Gardasil vaccine dose counts were obtained from descriptive data from the five PRISM Data Partners. Background rates of ICD-9 diagnoses for VTE were obtained from the PRISM initial health outcomes of interest data characterization. For simplicity, these background rates were assumed to be known with certainty. We assumed the matching ratio for the number of days in the risk vs control intervals was 1:1, even though the comparison intervals are different for Dose 1 compared to Doses 2 and 3. Accordingly, because the ratio of the risk and control interval is 4:3 for Dose 1, the power will be slightly less for that dose compared to Doses 2 and 3. The results are shown in Table 7 and can be applied to any/all doses.

Table 7. Power for Self-Controlled Risk Interval Analysis

Millions of doses	RR	Power
1	1.3	17%
1.8	1.3	24%
2	1.3	25%
1	1.5	30%
1.8	1.5	44%
2	1.5	47%
1	2.0	65%
1.8	2.0	86%
2	2.0	89%

Given that there are approximately 1.8 million doses in the PRISM study population, we should have at least 80%, and possibly 86%, power to detect a RR of 2.0 for all doses combined, in the full 9-26-year-old group, if all doses confer an increased risk.

F. DATASET CREATION AND REGISTRY MAPPING

PRISM uses Mini-Sentinel's distributed Common Data Model (MSCDM), by which the Data Partners maintain control over patient-level data. Data Partners periodically extract and organize data from their systems into eight files of standard format, of which the relevant ones for this study are: enrollment, demographics, encounter, diagnosis, procedure, and dispensing (i.e., death and cause of death files will not be used). To obtain immunization data from state immunization registries, Data Partners other than Optum and Vanderbilt will provide them with member identification information to allow the registries to match Data Partner members with registry immunization records. The registries will return immunization data for Data Partner members to the Data Partners, including vaccination date, vaccine code, and (when available) manufacturer and lot number, from which the Data Partners will populate a uniform-format state vaccine file linkable by means of a patient identification number to the other files. Immunization data from the claims-based procedure and state vaccine files will be combined into an intermediate file, eliminating duplicates, by means of a program to be provided by PRISM programmers. Registries will refresh data for the Data Partners once after the initial matching and transmission of data.

PRISM programmers will provide the Data Partners with programs to run on the standard-format patient-level files, which will produce aggregate data on Gardasil vaccination and VTE organized in strata defined by such variables as date of vaccination, type of vaccine, dose number, age, length of contraceptive use, and presence of other VTE risk factors, with a count of patients conforming to the stratum's values of those variables. For example, the aggregate data file on vaccination might have a stratum for 13-year-old current contraceptive users of 0-3.99 months duration with no other VTE risk factors vaccinated with Gardasil Dose 1 on 10/25/2009. The Data Partners will return the aggregate data for analysis, using Mini-Sentinel's secure file transport methods.

G. VTE CASE AND GARDASIL EXPOSURE VALIDATION / POSITIVE PREDICTIVE VALUE CALCULATION

Medical records of all eligible VTE cases diagnosed 1-77 days following Gardasil will be reviewed; an additional 14 days was added to the 63 days in the main observation period in order to account for potential delays between the symptom onset date and the date of the VTE diagnosis according to the claims data. All cases included in analysis will be chart-confirmed. The chart abstraction form developed by VSD will be modified to add additional risk factors. VTE cases will be classified using the criteria developed by the Worcester Venous Thromboembolism Study.[34]

Table 8. VTE Case Validation Criteria

	Pulmonary Embolism	Deep Vein Thrombosis
Definite	Confirmed by pulmonary angiography, spiral CT scan/CT pulmonary angiography, MRI scan or pathology	Confirmed by venography, compression/duplex ultrasound, CT scan or at autopsy
Probable	If above tests not performed or were indeterminate, but ventilation-perfusion scan findings were of high probability	If above tests not performed or were indeterminate, but impedance plethysomography, radionucleotide venography, or radiolabelled fibrinogen scan test results were reported as positive
Possible	If all of the above tests were not performed or were indeterminate and 2 of the following criteria were satisfied: medical record indicates physician-diagnosed DVT, signs or symptoms of DVT were documented and the patient underwent therapy with anticoagulants, or an IVC filter was placed.	If all of the above tests were not performed or were indeterminate and 2 of the following criteria were satisfied: medical record indicates physician-diagnosed DVT, signs or symptoms of DVT were documented and the patient underwent therapy with anticoagulants, or an IVC filter was placed.

In addition, records likely to contain immunization information will be reviewed for vaccinated VTE cases in order to correctly identify Gardasil vaccine exposure. The record associated with the most recent dose prior to the VTE index date will be sought, to confirm or correct the vaccination timing, dose number, and type/manufacturer in the claims data. If no such record is available, the record associated with the subsequent dose will be sought, and so on. If available in the record obtained, immunization *history* will be extracted to help identify the number of the dose received prior to the VTE diagnosis. As the analyses are restricted to vaccinated cases, immunization records will not be sought for VTE cases who do not appear to have Gardasil vaccination in the prior 1-77 days in the electronic claims data.

In order to identify the cases and obtain the medical charts, we will send programs for the Data Partners to run on their uniform-format patient-level files. These programs will produce a report of the number and characteristics (e.g. age) of the cases and, for each case, a report listing the health care encounters occurring within a specified number of days of VTE. The reports will include information on clinical setting, actual diagnosis, date of the diagnosis, and Gardasil doses. Clinical investigators will rank the VTE-related encounters of each case, based on which seem likely to produce the most definitive diagnostic information, and return the ranked lists to the Data Partners. The Data Partners will then attach patient name, insurance member number, and provider name and address to the visits for which records are being requested.

Each Data Partner will identify a preferred vendor to create chart extracts. These chart extracts will consist of specific items to be photocopied or scanned by the vendor. Examples for VTE chart extracts include the admission note, hospitalization progress notes, discharge summary, surgical reports where epidural or general anesthesia lasted for at least 30 minutes occurring within 3 months of the index date (defined as the date of the first eligible code for VTE), and all diagnostic procedures. The chart review vendor will notify the facilities, obtain the charts, photocopy or scan the appropriate pages, and redact the record of all personal identifiers. Data Partners will have the option of reviewing the redacted records to ensure that redaction is complete. Redacted records will be sent to the Mini-Sentinel Coordinating Center for abstraction and review.

Initially, PRISM clinical investigators will review the VTE chart abstractions and classify the cases. Two clinical investigators will independently review 20 charts, blinded to the timing of vaccination and to the other reviewer's decision. Investigators will complete a round of case classification to enable refinement of the classification rules. If there are zero discrepancies between reviewers, then the review will continue to use a single reviewer for the remainder of cases and only "probable" or "possible" cases will be double-adjudicated. If there are any discrepancies among the 20 test cases, double review of each subsequent case will be required. Adjudication by another clinician will be arranged if deemed appropriate by FDA.

The self-controlled analyses will use the chart-confirmed cases and timing according to symptom onset dates. A sensitivity analysis will be conducted using cases classified as probable or possible, if these amount to more than 5% of the total number of confirmed cases that could be used in the analysis in question.

The positive predictive value of the VTE identification algorithm will be determined by dividing the number of VTE cases classified as definite by the total number of potential cases identified electronically for which VTE charts were obtained. The PPV will be calculated overall and stratified by such covariates as Data Partner and setting.

IV. APPENDIX 1: CODES USED TO IDENTIFY SELECT VTE RISK FACTORS

Group	Category	Condition	Look back from VTE DX	Code type	Codes
1	**Primary hypercoagulable state**	Primary hypercoagulable state	Since enrolled	ICD9DX	289.81
		Sulfur bearing amino acid metabolism disturbances	Since enrolled	ICD9DX	270.4
	Coagulation defects	Congenital deficiency of clotting factors (dysfibrinogenemia)	Since enrolled	ICD9DX	286.3
	Secondary hypercoagulable state	Secondary hypercoagulable state	90 days	ICD9DX	289.82
2	**Cancer**	Malignancy (except skin)	183 days	ICD9DX	140.x–171.x, 174.x–208.x,
		Chemotherapy	183 days	ICD9PX	99.25
			183 days	ICD9DX	V58.1x
		Radiation therapy	183 days	ICD9DX	V58.0
				CPT4PX	20555
	Inflammatory conditions	Inflammatory bowel disease	Since enrolled	ICD9DX	555.x, 556.x
		Rheumatoid arthritis	Since enrolled	ICD9DX CPTP2	714.x 0540F, 3455F – 3476F, 4187F, 4192F – 4196F
		Systemic lupus erythematosis	Since enrolled	ICD9DX	695.4
	Infection	Sepsis	60 days	ICD9DX	003.1, 020.2, 022.3, 036.2, 038.x, 054.5, 449, 785.52, 995.91, 995.92
		Osteomyelitis	60 days	ICD9DX	003.24, 730.0x - 730.2x
3	**Cardiovascular conditions**	Metabolic syndrome	Since enrolled	ICD9DX	277.7
		Hyperlipidemia	Since enrolled	ICD9DX	272.0-272.4
		Diabetes mellitus	Since enrolled	ICD9DX	250.x
		Hypertension	Since enrolled	ICD9DX	401.x – 405.x
4	**Cardiac**	Congenital heart disease	Since enrolled	ICD9DX	745.x – 747.x
		Congestive heart failure	Since enrolled	ICD9DX	428.0
5	**Venous catheterization**	Central venous catheter	90 days	CPT4PX	36481, 36500, 36556, 36558, 36561, 36563, 36565, 36566,

Group	Category	Condition	Look back from VTE DX	Code type	Codes
					36569, 36571, 36575–36598
		Peripherally inserted central catheter	90 days	ICD9PX	38.93
		Central venous catheter placement with guidance	90 days	ICD9PX	38.97
	Transplant	Lung, heart, liver, bone marrow or hematopoietic stem cell, kidney, pancreas, intestine	90 days	ICD9PX ICD9DX	33.5, 33.6, 37.51, 41.0x, 50.5x, 52.8x, 55.6x V42.0, V42.1, V42.6, V42.7, V42.81-V42.83
			90 days	CPT4PX	32851 – 32854, 33935, 33945, 38340, 44133-44137, 47135, 48554, 50360, 50365, 50380
		Complications of transplanted organ	90 days	ICD9DX	996.81 – 996.86
	Immobility conditions	Fracture of skull, spine and trunk, lower limb	90 days	ICD9DX	800.x – 809.x, 820.x – 829.x, V54.13- V54.17, V54.23-V54.27
		Extracranial injury	90 days	ICD9DX	851.x-854.x, 861.x-869.x
		Crushing injury	90 days	ICD9DX	925.x – 929.x
		Burns (>10% body surface)	30 days	ICD9DX	948.1 – 948.9
		Spinal cord injury	90 days	ICD9DX	952.x
		Spina bifida	Since enrolled	ICD9DX	741.x
		Paralysis	Since enrolled	ICD9DX	342.x- 344.x
		Casting: halo, hip spica, long leg	90 days	CPT4PX	29000, 29305, 29325, 29345, 29365
	Open Urologic Surgery	Renal exploration or drainage	90 days	CPT4PX	50010–50045
		Repair of anomalous vessels of kidney			50100
		Procedures of renal pelvis			50100–50135
		Nephrectomy			50220-50240
		Open surgical procedures of the kidney			50400-50540
		Open repairs urinary system			51800–51980
		Nephrectomy	90 days	ICD9PX	55.4-55.5x
	Open Gynecologic Surgery	Myomectomy	90 days	CPT4PX	58140-58146
		Open procedures fallopian tubes with/without ovaries			58700-58770
		Open procedure ovary			58800-58925

Group	Category	Condition	Look back from VTE DX	Code type	Codes
		Removal ovary with/without multiple procedures for malignancy			58940-58960
		Tubal pregnancy, hysterotomy procedures			59100-59140
	Bariatric Surgery	Anesthesia for intraperitoneal procedures in upper abdomen including laparoscopy; gastric restrictive procedure for morbid obesity	90 days	CPT4PX	00797
		Laparoscopic gastric bypass with small bowel resection			43644, 43645
		Laparoscopic bariatric procedures			43770–43775
		Open bariatric procedure for morbid obesity			43842–43865
		Bariatric procedures: removal, replacement, revision port components			43886-43888
		Bariatric procedures	90 days	ICD9PX	43.7, 43.82, 43.89, 44.31, 44.38, 44.39, 44.5, 44.68, 44.69, 44.95-44.99, 45.51, 45.91
	Open Gastrointestinal surgery	Enterolysis, enterectomy	90 days	CPT4PX	44005, 44120-44128
		Colon resection			44139-44160
		Open repair procedures of intestine			44602-44680
		Open and transrectal procedures of rectum			45000-45190
		Resection of anal fistula			46270-46320
		Anal repairs			46700-46947
		Hepatectomy			47120-47130
		Open repair of liver			47300-47362
		Open procedures of the pancreas			48000-48548
		Exploratory and drainage procedures: abdomen and peritoneum			49000-49081
		Resection of presacreal/sacrrococcygeal tumor			49215

Group	Category	Condition	Look back from VTE DX	Code type	Codes
		Surgical repair abdominal wall			49900
		Open excision of large and small intestine, total abdominal colectomy, intestinal anastomosis	90 days	ICD9PX	45.6-45.9x
		Other repair of intestine			46.7x
		Resection or repair of rectum, repair of fistula			48.4-48.99
		Hepatectomy, repair of liver			50.22, 50.3, 50.4, 50.6x
		Exploratory laparotomy			54.11
	Intracranial neurosurgery	Craniectomy/craniotomy	90 days	CPT4PX	61304-61323, 61340-61530, 61566, 61567
		Lobectomy, hemispherectomy			61537-61543
		Craniotomy for hypophysectomy, pituitary tumor			61546
		Removal of foreign body from brain			61570, 61571
		Surgical treatment of arteriovenous malformation			61680-61692, 61705
		Surgical treatment brain aneurysm			61697, 61700
		Craniotomy, craniectomy	90 days	ICD9PX	01.2x
	Hip or lower extremity surgery	Incision, bone cortex, pelvis and/or hip (e.g. osteomyelitis or bone abscess)	90 days	CPT4PX	26992
		Procedures of bones and joints of hip and pelvis			27050-27071
		Radical resection of bone tumor of hip/pelvis			27075-27078
		Revision/reconstruction of hip and pelvis (e.g. slipped femoral epiphysis, hip arthroplasty)			01214, 01215, 27097-27187
		Open treatment of fracture/dislocation of hip/pelvis			27202, 27215, 27217, 27218, 27226-27228, 27236, 27248, 27253, 27254, 27258, 27269
		Knee arthroplasty			01402, 27437-27447, 27486,

Group	Category	Condition	Look back from VTE DX	Code type	Codes
					27487
		Open treatment of fracture/dislocation of femur/knee			27506, 27507, 27511, 27513, 27514, 27519, 27524, 27535, 27540, 27556, 27566
		Revision of hip and knee replacement	90 days	ICD9PX	00.7–00.87
		Application of external fixator device (pins/wires, screws into bone), internal fixation			78.15, 78.17, 78.55, 78.57, 79.15, 79.16, 79.26, 79.35, 79.36, 79.5, 84.7x
		Open reduction of dislocation of hip or knee			79.85, 79.86
		Joint replacement lower extremity			81.5x
	Spinal cord surgery	Partial resection vertebral component	90 days	CPT4PX	22100-22103
		Spinal fusion: lateral extracavitary approach			22532-22534
		Spinal fusion: anterior and posterior approach			22548-22632
		Procedures to correct anomalous spinal vertebrae			22800-22819
		Spinal instrumentation: segmental/non-segmental			22840-22855
		Vertebral corpectomy			63081-63091, 63101-63103, 63300-63308
		Exploration and decompression of spinal canal structures	90 days	ICD9PX	03.0x
		Meningocele and myelomeningocele repair			03.5x
		Spinal fusion			81.0x, 81.6 –81.64
6	**Pregnancy**	Pregnancy and postpartum	Variable		See Appendix 2
7	**Sickle cell anemia**	Sickle cell anemia	Since enrolled	ICD9DX	282.6, 282.41, 282.42
8	**Overweight**	Overweight and obesity	365 days	ICD9DX	278.0*, V85.3*, V85.4*, V85.54
			365 days	ICD9DX	278.02-278.09
9	**Renal**	Nephrotic syndrome	Since enrolled	ICD9DX	581.x
10	**Tobacco use**	Tobacco use	Since enrolled	ICD9DX	V15.82
				CPT2	4004F
			Since	ICD9DX	305.1, 649.0x, 989.84

Group	Category	Condition	Look back from VTE DX	Code type	Codes
			enrolled	CPT4PX	99406, 99407
				CPT2	1034F, 1035F, 4000F, 4001F
				HCPCS	D1320, G0436 – G0437, G8688, G8692, G9016, S4995, S9075, S9453

V. APPENDIX 2: CODES USED TO IDENTIFY PREGNANCY AND THE POST-PARTUM PERIOD AS A RISK FACTOR FOR VTE

Category	ICD9	Description	Period after VTE onset	First-in-X-days criterion
Stillborn	656.01	Papyraceous fetus, delivered, with or without antepartum condition	–42–280	280
Stillborn	656.4	Intrauterine death affecting management of mother	–42–280	280
Stillborn	656.40	Intrauterine death affecting management of mother unspecified as to episode of care	–42–280	280
Stillborn	656.41	Intrauterine death affecting management of mother delivered	–42–280	280
Stillborn	656.43	Intrauterine death affecting management of mother antepartum	–42–280	280
Stillborn	768.0	Fetal death from asphyxia or anoxia before onset of labor or at unspecified time	–42–280	280
Stillborn	768.1	Fetal death from asphyxia or anoxia during labor	–42–280	280
Prenatal care	V22*	Supervision of normal pregnancy	–266–56	280
Prenatal care	V23*	Supervision of high risk pregnancy	–266–56	280
Stillborn	V27.1	Mother with single stillborn	–42–280	280
Stillborn	V27.3	Mother with twins one liveborn and one stillborn	–42–280	280
Stillborn	V27.4	Mother with twins both stillborn	–42–280	280
Stillborn	V27.6	Mother with other multiple birth some liveborn	–42–280	280
Stillborn	V27.7	Mother with other multiple birth all stillborn	–42–280	280
Stillborn	V32*	Twin birth mate stillborn	–42–280	280
Stillborn	V35*	Other multiple birth (three or more) mates all stillborn	–42–280	280
Stillborn	V36*	Other multiple birth (three or more) mates liveborn and stillborn	–42–280	280
Preterm	644.2*	Early onset of delivery delivered with or without antepartum condition	–42–258	280
Delivery	650*	Normal delivery	–42–280	280
Delivery	669.5*	Forceps or vacuum extractor delivery without mention of indication	–42–280	280
Delivery	669.6*	Breech extraction without mention of indication	–42–280	280
Delivery	669.7*	Cesarean delivery without mention of indication	–42–280	280
Delivery	V24*	Postpartum care and examination	–42–280	280
Delivery	V27.0	Mother with single liveborn	–42–280	280
Delivery	V27.2	Mother with twins both liveborn	–42–280	280
Delivery	V27.5	Mother with other multiple birth all liveborn	–42–280	280
Delivery	V27.9	Mother with unspecified outcome of delivery	–42–280	280
Delivery	V30*	Single liveborn	–42–280	280
Delivery	V31*	Twin birth mate liveborn	–42–280	280
Delivery	V33*	Twin birth unspecified whether mate liveborn or stillborn	–42–280	280
Delivery	V34*	Other multiple birth (three or more) mates all liveborn	–42–280	280

Category	ICD9	Description	Period after VTE onset	First-in-X-days criterion
Delivery	V37*	Other multiple birth (three or more) unspecified whether mates liveborn or stillborn	–42–280	280
Delivery	V39*	Liveborn unspecified whether single twin or multiple	–42–280	280
SAB	632*	Missed abortion	0-105	105
SAB	634*	Spontaneous abortion	0-105	105
TAB	635*	Legally induced abortion	0-105	105
TAB	636*	Illegal abortion	0-105	105
TAB	637*	Unspecified abortion	0-105	105
TAB	640.01	Threatened abortion delivered	0-105	105
SAB	640.81	Other specified hemorrhage in early pregnancy delivered	0-105	105
SAB	640.91	Unspecified hemorrhage in early pregnancy delivered	0-105	105

TAB – therapeutic abortion, SAB – spontaneous abortion

Category	CPT4 / ICD9PX	Description	Period after VTE onset	First-in-X-days criterion
Delivery	01960	Anesthesia for vaginal delivery only	–42–280	280
Delivery	01961	Anesthesia for cesarean delivery only	–42–280	280
Delivery	01962	Anesthesia for urgent hysterectomy following delivery	–42–280	280
Delivery	01963	Anesthesia for cesarean hysterectomy without any labor analgesia/anesthesia care	–42–280	280
Delivery	01967	Neuraxial labor anesthesia/analgesia for planned vaginal delivery	–42–280	280
Delivery	01968	Anesthesia for cesarean delivery following neuraxial labor analgesia/anesthesia	–42–280	280
Delivery	01969	Anesthesia for cesarean hysterectomy following neuraxial labor analgesia/anesthesia	–42–280	280
Delivery	59400	Routine obstetric care including antepartum car, vaginal delivery, postpartum care	–42–280	280
Delivery	59409	Vaginal delivery only	–42–280	280
Delivery	59410	Vaginal delivery including postpartum care	–42–280	280
Delivery	59510	Routine obstetric care including antepartum car, cesarean delivery, postpartum care	–42–280	280
Delivery	59514	Cesarean delivery only	–42–280	280
Delivery	59515	Cesarean delivery, including postpartum care	–42–280	280
Delivery	59610	Routine obstetric care including antepartum care, vaginal delivery, postpartum care, after previous cesarean section	–42–280	280
Delivery	59612	Vaginal delivery only after previous cesarean section	–42–280	280
Delivery	59614	Vaginal delivery after previous cesarean section, including postpartum care	–42–280	280
Delivery	59618	Routine obstetric care including antepartum care, vaginal delivery, postpartum care, after previous cesarean section	–42–280	280

Category	CPT4 / ICD9PX	Description	Period after VTE onset	First-in-X-days criterion
Delivery	59620	Cesarean delivery only after previous cesarean section	–42–280	280
Delivery	59622	Cesarean delivery previous cesarean section, including postpartum care	–42–280	280
Delivery	72*	Forceps, vacuum, and breech delivery	–42–280	280
Delivery	73*	Other procedures including or assisting delivery	–42–280	280
Delivery	74.0-74.2, 74.4, 74.99	Cesarean section and removal of fetus	–42–280	280
SAB	01965	Anesthesia for incomplete or missed abortion procedures	0-105	105
SAB	59812	Treatment of incomplete abortion, any trimester, completed surgically	0-105	105
SAB	59820	Treatment of missed abortion, completed surgically; first trimester	0-105	105
SAB	59821	Treatment of missed abortion, completed surgically; second trimester	0-105	105
TAB	59840	Induced abortion, by dilation and curettage	0-105	105
TAB	59841	Induced abortion, by dilation and excavation	0-105	105
TAB	59850	Induced abortion, by 1 or more intra-amniotic injections	0-105	105
TAB	59851	Induced abortion, by 1 or more intra-amniotic injections with dilation and curettage and/or evacuation	0-105	105
TAB	59852	Induced abortion, by 1 or more intra-amniotic injections with hysterotomy	0-105	105
TAB	59855	Induced abortion, by 1 or more vaginal suppositories with or without cervical dilation	0-105	105
TAB	59856	Induced abortion, by 1 or more vaginal suppositories with or without cervical dilation with dilation and curettage and/or evacuation	0-105	105
TAB	59857	Induced abortion, by 1 or more vaginal suppositories with or without cervical dilation with hysterotomy	0-105	105

VI. APPENDIX 3: CODES USED TO IDENTIFY VTE

ICD9		Description
415.1*		
415.1		Pulmonary embolism and infarction
415.11		Iatrogenic pulmonary embolism and infarction
415.12		Septic pulmonary embolism
415.19		Other pulmonary embolism and infarction
451.*		
451		Phlebitis and thrombophlebitis
451.0		Phlebitis and thrombophlebitis of superficial vessels of lower extremities
451.1		Phlebitis and thrombophlebitis of deep veins of lower extremities
451.11		Phlebitis and thrombophlebitis of femoral vein (deep) (superficial)
451.19		Phlebitis and thrombophlebitis of other
451.2		Phlebitis and thrombophlebitis of lower extremities unspecified
451.8		Phlebitis and thrombophlebitis of other sites
451.81		Phlebitis and thrombophlebitis of iliac vein
451.82		Phlebitis and thrombophlebitis of superficial veins of upper extremities
451.83		Phlebitis and thrombophlebitis of deep veins of upper extremities
451.84		Phlebitis and thrombophlebitis of upper extremities unspecified
451.89		Phlebitis and thrombophlebitis of other sites
451.9		Phlebitis and thrombophlebitis of unspecified site
453.*		
453		Other venous embolism and thrombosis
453.0		Budd-Chiari syndrome
453.1		Thrombophlebitis migrans
453.2		Embolism and thrombosis of inferior vena cava
453.3		Embolism and thrombosis of renal vein
453.4		Acute venous embolism and thrombosis of deep vessels of lower extremity
453.40		Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.41		Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
453.42		Acute venous embolism and thrombosis of deep vessels of distal lower extremity
453.5		Chronic venous embolism and thrombosis of deep vessels of lower extremity
453.50		Chronic venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.51		Chronic venous embolism and thrombosis of deep vessels of proximal lower extremity
453.52		Chronic venous embolism and thrombosis of deep vessels of distal lower extremity
453.6		Venous embolism and thrombosis of superficial vessels of lower extremity
453.7		Chronic venous embolism and thrombosis of other specified vessels

ICD9		Description
453.71		Chronic venous embolism and thrombosis of superficial veins of upper extremity
453.72		Chronic venous embolism and thrombosis of deep veins of upper extremity
453.73		Chronic venous embolism and thrombosis of upper extremity, unspecified
453.74		Chronic venous embolism and thrombosis axillary veins
453.75		Chronic venous embolism and thrombosis of subclavian veins
453.76		Chronic venous embolism and thrombosis of internal jugular veins
453.77		Chronic venous embolism and thrombosis of other thoracic veins
453.79		Chronic venous embolism and thrombosis of other specified veins
453.8		Acute venous embolism and thrombosis of other specified veins
453.81		Acute venous embolism and thrombosis of superficial veins of upper extremity
453.82		Acute venous embolism and thrombosis of deep veins of upper extremity
453.83		Acute venous embolism and thrombosis of upper extremity, unspecified
453.84		Acute venous embolism and thrombosis of axillary veins
453.85		Acute venous embolism and thrombosis of subclavian veins
453.86		Acute venous embolism and thrombosis of internal jugular veins
453.87		Acute venous embolism and thrombosis of other thoracic veins
453.89		Acute venous embolism and thrombosis of other specified veins
453.9		Embolism and thrombosis of unspecified site

Acute venous thromboembolism (primary analysis)
Chronic venous thromboembolism (analyzed separately)

VII. REFERENCES

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