Assessment of GBS Risk Following Recombinant Zoster Vaccine (Shingrix)

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ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
CME	Common Medicare Enrollment
CMS	Centers for Medicare & Medicaid Services
CPT	Current Procedural Terminology
CWF	Common Working File
EDB	Enrollment Database
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
HCPCS	Healthcare Common Procedure Coding System
ICD-10	International Classification of Diseases, Tenth Revision, Clinical modification
IP	Inpatient
OP	Outpatient
PB	Physician Billing/Supplier Part B Claims file/Carrier file
SCCS	Self-controlled case series
SCRI	Self-controlled risk interval

OVERVIEW

EXECUTIVE SUMMARY

Increased GBS risk seen among Shingrix vaccinees

In near real-time sequential monitoring (Rapid Cycle Analysis [RCA]) of recombinant zoster vaccine (Shingrix), the Vaccine Safety Datalink (VSD) detected a statistical signal for an increased risk of GBS among members 50 years and older who received Shingrix compared to historical zoster vaccine live (Zostavax) recipients. At the time of the 4th RCA analysis, 106,121 Shingrix vaccines had been administered and four ICD-10 coded GBS cases had been observed in the 1-42 day risk window following vaccination. When the GBS rate in the 1-42 day risk windows following Shingrix vaccinations was compared with Zostavax vaccinations, an increased risk ratio of 5.06 was found.

Cohort & Self-Controlled Shingrix Analyses

We will conduct a cohort analysis to determine if the observed rates of GBS in the post-vaccination risk window (days 1-42) following Shingrix vaccination are significantly higher than the GBS rates in the post-vaccination risk window following Zostavax vaccination. Our cohorts will consist of Shingrix vaccinations observed between October 1, 2017 and December 31, 2018 and Zostavax vaccinations between October 1, 2012 and September 30, 2017.

We will conduct a vaccinated cases only self-controlled case series analysis to determine if there is increased risk of GBS in the 1-42 days following Shingrix vaccination. Our control period will be days 43-183 post-first dose (or until receipt of the second dose) and days 43-183 post-second dose (or until end of study period/disenrollment/death). Our cohort will consist of cases who received the Shingrix vaccine between October 1, 2017 and March 31, 2019.

1. BACKGROUND

On October 20, 2017, Recombinant Zoster Vaccine (Shingrix®, GlaxoSmithKline) was licensed as a two-dose series and approved for use in adults aged 50 years and older for the prevention of herpes zoster (shingles). Following licensure, the FDA initiated routine surveillance activities to complement information available from the pre-licensure randomized control trials, which evaluated the efficacy and safety of Shingrix. CDC also implemented post-licensure safety surveillance in its Vaccine Safety Datalink (VSD) program using near real-time sequential monitoring (Rapid Cycle Analysis [RCA]) to monitor 15 adverse events within acute post-vaccination risk windows. The VSD surveillance includes people who received the vaccine at seven VSD sites after March 2018. Recipients of Shingrix were compared to a historical population from 2013-2017 of Zostavax recipients.

Guillain–Barré syndrome (GBS) is a rare, immune-mediated polyneuropathy that causes an individual's immune system to damage nerve cells, which causes muscle weakness and occasionally paralysis. It affects approximately 3,000-6,000 people each year in the U.S. (approximately 1 to 2 cases per 100,000 person-years).[a] GBS is thought to result when immune response to an antecedent event cross-reacts with peripheral nerve components. Approximately two-thirds of cases are triggered by a preceding respiratory or gastrointestinal infection, but GBS has also been associated with vaccinations.[1]

The VSD RCA analysis used ICD codes for GBS diagnosed in three care settings: emergency department, inpatient, and outpatient. As a high-priority outcome, GBS monitoring included formal sequential testing with a signaling mechanism that triggered when the log likelihood ratio test of a 1-sided hypothesis exceeded a pre-defined threshold. This held the overall Type 1 error level at 0.05. The VSD RCA analysis using data through August 27, 2018 identified four potential GBS cases among 106,121 administered doses of Shingrix. This yielded a likelihood ratio statistic that exceeded the critical value and constituted a statistical signal for GBS. The corresponding incidence rate ratio was 5.06. Based on this finding in the VSD, and Acumen's experience with GBS monitoring across influenza seasons using Medicare data, this project seeks to conduct follow-up analysis of this VSD signal to determine if GBS is associated with Shingrix vaccination in the Medicare population. This project both replicates results identified by VSD within the Medicare population, and conducts further self-controlled analyses.

[a] https://www.cdc.gov/flu/protect/vaccine/guillainbarre.htm

2. OBJECTIVES

The objective is to assess the risk of GBS following Shingrix vaccination among Medicare beneficiaries ages 65 years and older. We conduct this assessment by (1) completing a cohort analysis of GBS risk following Shingrix administration (days 1-42 post-vaccination) in a manner similar to the VSD study and (2) completing a self-controlled analysis of GBS risk following Shingrix vaccination.

3. METHODS

3.1 DATA SOURCES

This study will rely primarily on two types of data, Medicare enrollment data and claims data. The monthly Enrollment Database provides information about Medicare enrollment eligibility and consists of data from the Medicare Enrollment Database (EDB) and Common Medicare Enrollment (CME). We will use the weekly Common Working File (CWF), which contains information about patient services and diagnoses, and Medicare Part D claims, which will be used to identify vaccination exposures. Part D claims are prescription drug claims that contain similar information that we observe on Inpatient (IP), Outpatient (OP), and Carrier (PB) claims.

We will use CWF and Part D claims to gather information on Shingrix/Zostavax vaccinations and GBS diagnoses. For this analysis, we will extract claims for the population enrolled in FFS (i.e., enrolled in Medicare Parts A, B, and D and not Part C), from the IP, OP, and PB files. We use Part D claims (NDC codes) to identify Shingrix and Zostavax vaccinations (Section 3.2.2). We use the IP claims setting to detect GBS.

The IP file contains claims submitted by inpatient hospital providers for reimbursement of facility costs. These claims include International Classification of Diseases, 9th revision, (ICD-9) diagnosis codes (until September 30, 2015) and ICD-10 diagnosis codes (October 1, 2015 onward), which we use to detect GBS claims following a Shingrix vaccination. The OP file contains claims submitted by institutional outpatient providers, such as hospital outpatient departments and rural health clinics; these claims include ICD, Current Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPCS) codes. Lastly, the PB file primarily consists of claims from non-institutional providers, such as physicians, physician assistants, and nurse practitioners; these claims include CPT/HCPCS codes. Shingrix and Zostavax vaccination status will be identified with the use of National Drug Codes (NDCs) in Medicare Part D claims.

3.2 COHORT ANALYSIS

3.2.1 Study Population

Our study population will be comprised of FFS Medicare beneficiaries ages 65 and older at the time of vaccination. Our treated population will be comprised of beneficiaries who received a Shingrix vaccine between October 1, 2017 and December 31, 2018. Our comparison cohort will be comprised of beneficiaries who received a Zostavax vaccine between October 1, 2012 and September 30, 2017.

For the primary analysis, the study population will consist of beneficiaries with a vaccination administration:

(i) who aged into Medicare;
(ii) with continuous enrollment in Parts A, B and D from 365 days prior to vaccination (i.e., the “clean period”); and

We will exclude vaccinations of beneficiaries

(i) who have had another Shingrix/Zostavax dose in the 42 days prior;

(ii) who have a non-standard administration of Shingrix/Zostavax (more than 1 administration of Zostavax and more than 2 administrations of Shingrix);[b]
(iii) with a GBS diagnosis in any position and any setting during the 365 days pre-vaccination or on the vaccination date; or
(iv) who are on chronic dialysis therapy, defined by receiving dialysis treatment in 7 days pre-vaccination or on the vaccination date, were in a nursing home, skilled nursing facility, or hospice on the vaccination date.

For the Shingrix population, a beneficiary's first observed dose being ineligible (e.g., due to insufficient enrollment prior to vaccination, prior GBS, etc.) does not automatically exclude that beneficiary's second observed dose. If the second observed dose meets all eligibility requirements, it will be included in the analysis regardless of the status of the first observed dose because we are treating GBS risk as constant following the first and second observed doses.

Because prior Zostavax vaccination may account for a large portion of our Shingrix cohort, we will not conduct any cleaning to ensure that our two cohorts are mutually exclusive.

3.2.2 Exposure (Shingrix & Zostavax Vaccination)

Vaccination status will be identified with the use of National Drug Codes (NDCs) for the Shingrix vaccine (Appendix A, Table 1) and for the Zostavax vaccine (Appendix A, Table 2) in Medicare Part D claims. Beneficiaries with a Part D claim for the Shingrix or Zostavax vaccine will be classified as vaccinated, with the index date defined as the date of eligible dose of vaccine administration, according to claims received.

The primary risk window will be days 1-42 post-vaccination.

3.2.3 Outcome (GBS) and Follow-up

For our cohort analyses, we define an incident GBS case as either (i) the first occurrence of a primary discharge diagnosis of GBS in the IP setting occurring during days 1-42 post-vaccination or (ii) a GBS diagnosis in any setting occurring during days 1-42 post-vaccination, followed by an IP GBS hospitalization within the subsequent 7 days.

We assign each case's "earliest onset date" as either the hospitalization date or, in the case of (ii), as the date of the earlier GBS claim in any position in the inpatient or outpatient claim in the seven days prior. For instance, if an OP GBS claim occurred on day 41 post-vaccination, followed by a primary IP GBS hospitalization on day 43, we would include that claim as a GBS case in our analysis with an onset date of day 41.

GBS claims are identified through the International Classification of Diseases, Ninth Revision, Clinical modification (ICD-9) code 357.0 (until September 30, 2015) and the ICD-10 code G61.0 as principal discharge diagnosis.

We will censor the eligible vaccination once we observe a GBS outcome, a non-specific GBS diagnosis, death, Part A/B or D disenrollment, receipt of the other herpes zoster vaccine, entrance into a nursing home, skilled nursing facility, or hospice care, the study end date, or the end of the 42-day risk window.

[b] Non-standard administrations account for less than 0.01% of Shingrix vaccinations and less than 0.3% of Zostavax vaccinations.

3.2.3.1 Medical Record Review

Medical record review will be conducted on all GBS cases identified following Shingrix or Zostavax vaccination. All inpatient GBS hospitalizations identified via claims in our cohort analysis will be included in the review.

3.2.4 Covariate Measures

Our cohort analysis will adjust for sex and age.

3.2.5 Statistical Analyses

3.2.5.1 Descriptive Statistics

We will produce descriptive statistics for each of the cohorts on each of the following:

(i) demographics (e.g., age, sex, race, region, original Medicare status);
(ii) the number of beneficiaries that are affected by the various eligibility criteria we use to construct our study population, including the number of beneficiaries who are included in both the Shingrix and Zostavax cohorts;
(iii) the number of GBS cases that are impacted by the "earliest onset date" algorithm (Section 3.2.3); and
(iv) the number of beneficiaries whose first observed dose is excluded but second observed dose is included (for Shingrix cohort).

3.2.5.2 Primary Analyses

In the cohort analysis, we will replicate the VSD analyses as closely as possible as a validation effort (*ShingrixProtocol 07_18_18.docx*).

We will compare the post-vaccination GBS rates between the treated Shingrix population and the Zostavax population, using a Poisson regression model with an offset equal to the natural logarithm of person-time (in days) as our primary analysis. Specifically, we will fit the following model

$$\log\big(E(Y|X)\big) = \beta_0 + \beta_1 * Vaccine + X\beta + \log(t)$$
$$Y = GBS\ outcome\ variable$$
$$Vaccine = Binary\ vaccine\ cohort\ term\ (Shingrix\ vs. Zostavax)$$
$$X = Covariates$$
$$t = exposure\ time$$

Given this model, e^{β_1} will be interpreted as the rate ratio for Shingrix vs. Zostavax. Cluster-robust standard errors will be estimated to adjust for correlation between beneficiaries who are included in both the Zostavax and Shingrix cohort, or received multiple doses of Shingrix. Clusters will be defined at the beneficiary level. Statistical significance will be determined using 95% confidence intervals of rate ratios and two-tailed p-values ($p \leq 0.05$). The use of a Poisson model would provide better comparability to the VSD study.

3.2.5.3 Sensitivity Analyses

The primary study group will be those beneficiaries 65 years and older at the time of vaccination for days 1-42 post-vaccination. Sensitivity analyses will include:

(i) Including beneficiaries who are in both the Shingrix and Zostavax cohorts in only the Zostavax cohort

(ii) Using a Cox proportional hazards model in place of a Poisson

3.3 SELF-CONTROLLED CASE SERIES ANALYSIS

Our study will employ a Self-Controlled Case Series (SCCS) methodology. In this methodology, only cases are sampled, with estimation of relative risk occurring within individuals rather than across cohorts. Designed to assess the risk of acute events in clearly defined risk periods, this design controls for time-invariant covariates by using individual observations as their own control. Comparing incidence within the risk period versus the control period provides an estimate of the relative incidence rate for the post-vaccination risk period. Unlike a Self-Controlled Risk Interval (SCRI) design, in the standard SCCS methodology, the observation period is independent of the vaccination date, with all time outside of the risk period counting as control time. In our study, we will only use a window of control time following vaccination to address the concern that our outcome of interest, GBS, may affect subsequent exposure.

While in the standard SCCS design, the study population includes all cases within the study period, with or without exposure. In our study, we will restrict to cases with Shingrix vaccination (i.e., we will be using a vaccinated cases only SCCS approach).[2]

3.3.1 Assumptions

As originally developed, the SCCS methodology rests on several key assumptions. They are listed below, along with any relevant accommodations we will make in our study, if they may not be met.

(i) Events must be independently recurrent and rare

The original SCCS model was developed to assess the risk of recurrent events.[3] However, due to the rare events assumption, this bias can be safely ignored if these non-recurrent events have a risk of occurrence <10%, as in the case of GBS.[4]

(ii) Occurrence of an event should not affect subsequent exposures or mortality

The standard implementation of SCCS requires that exposure must be exogenous. There is a concern in our study as our event (GBS) is likely to reduce the chance of subsequent exposure. We will not be including any control time from before the first dose; this will ensure that any cases recorded within our study will have occurred subsequent to initial exposure. To accommodate this concern for the second dose, we can again rely on the rare event assumption. The SCCS method may be applied to unique, non-recurrent outcomes only when the event is rare, like GBS.[4,5]

(iii) Events cannot happen at the exact same time or age.

We do not have concerns for this assumption in our study.

(iv) Event rates are constant within intervals

While there is some evidence suggesting that GBS risk is non-constant following exposure, we believe that this will introduce only limited bias to our results.

(v) Exposure is transient or intermittent

We do not have concerns for this assumption in our study.

3.3.2 Study Population

For our self-controlled analyses, the study population will include Shingrix-vaccinated beneficiaries with a GBS outcome and enrolled in FFS who:

(i) aged into Medicare;
(ii) were age 65 or older on October 1, 2017, when the Shingrix vaccine was first approved; and
(iii) were continuously enrolled in Medicare Parts A, B and D from October 1, 2017; and
(iv) were continuously enrolled in FFS (Parts A and B) for 183 days prior to vaccination, until day 183 post vaccination, their next Shingrix vaccination, the end of the study period, death, or disenrollment, whichever comes first.

We will exclude cases for beneficiaries

(i) who have more than two administrations of Shingrix;
(ii) who have a case following their second dose when the second dose is administered within six weeks of the first;
(iii) with a GBS diagnosis in any position and any setting during the 183 days pre-vaccination or on the vaccination date; or
(iv) who are on chronic dialysis therapy, defined by receiving dialysis treatment, or were in a nursing home, skilled nursing facility, or hospice at any point during the person time they would contribute to the study.

3.3.3 Exposure (Shingrix Vaccination)

We will identify vaccination status with the use of NDCs for the Shingrix vaccine in Medicare Part D claims. We will classify beneficiaries with a Part D claim for the Shingrix vaccine as vaccinated, with the index date defined as the date of the first observed dose of vaccine administration according to the claims received.

3.3.4 Outcome (GBS) and Follow-up

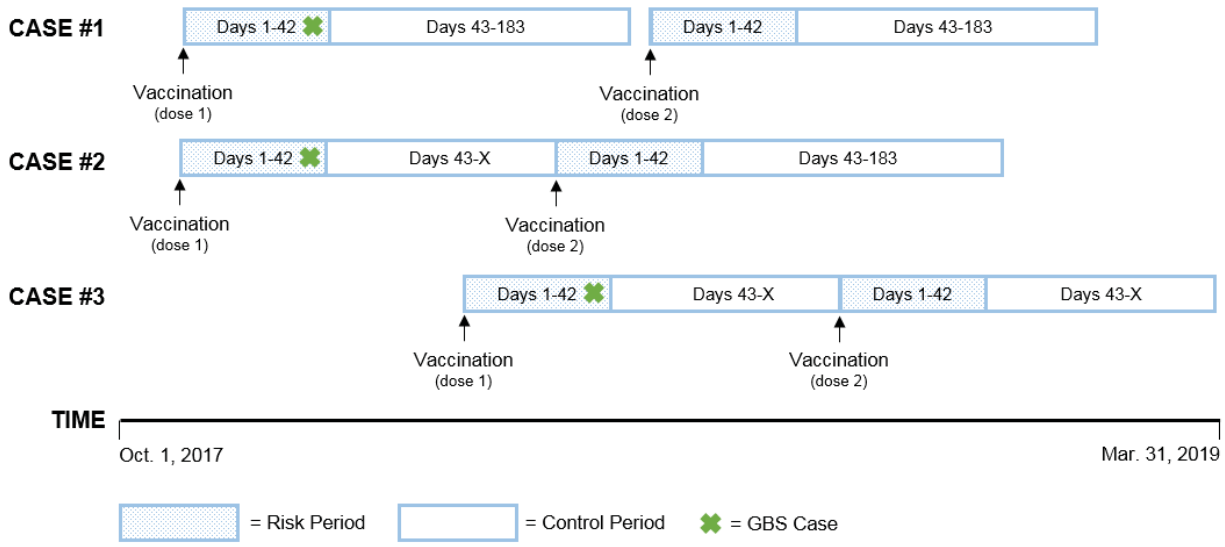
As in the cohort analyses, for the self-controlled analyses, we define an incident GBS case as the first occurrence of a primary discharge diagnosis of GBS in the IP setting occurring post vaccination, where GBS claims are identified through the ICD-10 code G61.0.

We assign each case's "earliest onset date" as either the hospitalization date or as the date of an earlier GBS claim in any position in the inpatient or outpatient claim in the seven days prior. If a beneficiary died or disenrolled prior to the end of the observation period, we include their person-time until this event.

The primary risk window is days 1-42 post-vaccination. As our primary analysis, we will assess "pooled" risk for the first and second dose combined. We will look at risk following the first dose, specifically, as a secondary analysis (Section 3.3.5.3). The control period for each beneficiary will be days 43-183 post-first dose (or until they receive their second dose) and days 43-183 post-second dose (or until end of study period/disenrollment/death). Figure 1 displays a selection of example cases that we may encounter using this design.

For those beneficiaries who do experience GBS in the 1-183 days, however, we will still include the whole follow up time period after the first GBS onset. That is, we are not censoring on the first GBS onset day even though the person is not "at risk" in the next 183 days by definition.

Figure 1. Example cases for SCCS design



3.3.4.1 *Medical Record Review*

Medical record review will be conducted on all GBS cases identified following Shingrix vaccination. All inpatient GBS hospitalizations identified via claims from the study period will be included in the review.

3.3.5 Statistical Analyses

3.3.5.1 *Descriptive Statistics*

We will produce descriptive statistics for GBS cases in each of the following population categories:

(i) by demographics (e.g., age, sex, race, region, original Medicare status);
(ii) the number of GBS cases with concomitant influenza vaccination or influenza vaccine administration in the risk or control periods for either dose (Appendix B, Table 3);
(iii) by the number of cases that are affected by the various eligibility criteria we use to construct our study population; and
(iv) by the number of GBS cases that are impacted by the "earliest onset date" algorithm (Section 1.1.3).

3.3.5.2 *Primary Analyses*

We will compare the GBS rates in the risk and control windows using a conditional Poisson regression model as our primary analysis. Specifically, we will fit the following model:

$$\log\big(E(Y|X)\big) = \beta_1(risk\_window) + \log(t) + strata(beneficiary\_id)$$

$$Y = GBS\ outcome\ variable$$
$$risk\_window = binary\ term\ indicating\ GBS\ occurrence\ in\ risk\ window$$
$$t = interval$$
$$beneficiary\_id = term\ identifying\ the\ beneficiary$$

Under this model, our null and alternative hypotheses can be written as:

$$\mathrm{H}_0: e^{\beta_1} = 1 \qquad \mathrm{H}_a: e^{\beta_1} \neq 1$$

where e^{β_1} will be interpreted as the rate ratio for GBS in the risk window compared to the control window. Thus, significance of the coefficient on the risk window variable at a pre-specified level will indicate a significant association between Shingrix vaccination and GBS. Statistical significance will be determined using 95% confidence intervals of rate ratios and two-tailed p-values ($p \leq 0.05$).

Attributable risk (per million vaccinations) will be calculated as well.

3.3.5.3 Secondary Analyses

As one secondary analysis, we will estimate the risk of GBS following Shingrix after only the first dose. Our risk window will be days 1-42 post-first dose, and our control time will be comprised of days 43-183 post-first dose (which can be truncated by the second dose or end of the study period). We will only include cases that occur after the first dose and before the second dose.

3.3.5.4 Sensitivity Analyses

We may complete a sensitivity analysis adjusting for seasonality using background influenza rates, as wild-type influenza has been seen to be associated with GBS. Seasonality adjustment may be done using weekly rates of confirmed influenza calculated as: the proportion of specimens testing positive for influenza among the total number of specimens submitted to the World Health Organization Collaborating Laboratories and the National Enteric Virus Surveillance System in the United States for influenza testing during the 2018-2019 influenza season, if the necessary influenza rates are available. See Appendix F for the detailed procedure. For the seasonality adjusted analysis, we will fit the following model, with a new offset term that is log of cumulative estimated risk for the interval instead of the log of length of interval in days.

$$\log\big(E(Y|X)\big) = \beta_1(risk\_window) + \log(t) + strata(beneficiary\_id)$$

$$Y = GBS\ outcome\ variable$$
$$risk\_window = binary\ term\ indicating\ GBS\ occurrence\ in\ risk\ window$$
$$t = cumulative\ estimated\ risk\ for\ the\ interval$$
$$beneficiary\_id = term\ identifying\ the\ beneficiary$$

Under this model, our null and alternative hypotheses can be written as:

$$\mathrm{H}_0: e^{\beta_1} = 1 \qquad \mathrm{H}_a: e^{\beta_1} \neq 1$$

As an additional sensitivity analysis, we may implement the adjusted SCCS approach proposed by Farrington that adapted the standard SCCS approach to allow exposures whose occurrence is influenced by the event (i.e., second doses of Shingrix).[6]

ETHICAL CONSIDERATIONS

This surveillance was approved by the FDA's Research Involving Human Subjects Committee. Medicare administrative data were used under a data use agreement with CMS and data use was approved by the Centers' privacy board.

4. REFERENCES

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5. ACKNOWLEDGEMENT AND CERTIFICATION

5.1 ELECTRONIC SIGNATURE

By submitting an electronic signature under this Acknowledgement and Certification of Understanding, you are acknowledging that you have read and agree to the contents of this protocol (version 1.4). By signing below, you submit your approval for the analyses outlined in this document.

X Richard A. Forshee -S

Digitally signed by Richard A. Forshee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000429529, cn=Richard A. Forshee -S
Date: 2019.08.05 16:33:05 -04'00'

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6. APPENDIX

A. HERPES ZOSTER VACCINE CODES

Table 1. NDC Codes Used to Identify Shingrix Vaccinations

NDC Code	Description
Supplied as an outer package of 1 dose	
58160-0828-01	Lyophilized gE Antigen Component (Vial 2 of 2)
58160-0829-01	Adjuvant Suspension Component (Vial 1 of 2)
58160-0819-12	Outer Package
Supplied as an outer package of 10 doses	
58160-0828-03	Lyophilized gE Antigen Component (10 vials)
58160-0829-03	Adjuvant Suspension Component (10 vials)
58160-0823-11	Outer Package

Table 2. NDC Codes Used to Identify Zostavax Vaccinations

NDC Code	Description
Merck	
00006-4963-00	1 Vial, Single-Dose in 1 Carton > .65 mL in 1 Vial, Merck
00006-4963-01	Zoster Vaccine Live for Injection, .65 mL, Merck
00006-4963-41	10 Vial, Single-Dose in 1 Carton > .65 mL in 1 Vial, Merck
Other Supplier	
54868-5703-00	Zoster Vaccine Live for Injection, .65 mL, Physicians Total Care
68258-8908-00	Zoster Vaccine Live for Injection, .65 mL, Dispensing Solutions, Inc
68258-8908-01	Zoster Vaccine Live for Injection, .65 mL, Dispensing Solutions, Inc

B. INFLUENZA VACCINE CODES

Table 3. List of influenza vaccine codes included in surveillance for the 2017-2018, 2018–2019 season

Code	SCRI Analyses (65+)	Description	Vaccine Categorization				
			Vaccine Classification		Strain	Abbreviation	Maps to Multiple Vaccine Types
90470	No (pandemic)	H1N1 Immunization administration (intramuscular, intranasal), including counseling when performed	Pandemic				
90630	Yes	Vaccine for influenza for injection into skin, quadrivalent, preservative free	Inactivated	Intradermal	Quadrivalent	IIV4-ID	No
90653	Yes	Vaccine for influenza for injection into muscle, inactivated, subunit, adjuvanted	Inactivated	Adjuvanted	Trivalent	aIIV3	No
90654	Yes	Vaccine for influenza injection into skin, trivalent, preservative free	Inactivated	Intradermal	Trivalent	IIV3-ID	No
90655	No (pediatric)	Vaccine for influenza for administration into muscle, 0.25 ml dosage, trivalent, split virus, preservative free (pediatric use)	Inactivated	Standard (split virus)	Trivalent	IIV3	No
90656	Yes	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, preservative free	Inactivated	Standard (split virus)	Trivalent	IIV3	No
90657	No (pediatric)	Vaccine for influenza for administration into muscle, 0.25 ml dosage, trivalent (pediatric use)	Inactivated	Standard (split virus)	Trivalent	IIV3	No
90658	Yes	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent	Inactivated	Standard (split virus)	Trivalent	IIV3	No
90659	No (code deleted)	Influenza virus vaccine, whole virus, for intramuscular or jet injection use	Inactivated	Standard (whole virus)	--	--	--
90660	No (not in 18-19 / ages 2-49	Vaccine for influenza for nasal administration, trivalent	Live	Attenuated	Trivalent	LAIV3	No
90661	Yes	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, cell culture-based	Inactivated	Cell-cultured	Trivalent	ccIIV3	No
90662	Yes	Vaccine for influenza for injection into muscle, split virus, enhanced immunogenicity via increased antigen content	Inactivated	High-dose	Trivalent	IIV3-HD	No
90663	No (pandemic)	Influenza virus vaccine, pandemic formulation, H1N1	Pandemic				
90664	No (pandemic)	Vaccine for influenza for nasal administration, pandemic formulation	Pandemic				
90666	No (pandemic)	Vaccine for influenza for injection into muscle, pandemic formulation	Pandemic				
90667	No (pandemic)	Vaccine for influenza for injection into muscle, pandemic formulation	Pandemic				
90668	No (pandemic)	Vaccine for influenza for injection into muscle, pandemic formulation	Pandemic				
90672	No (ages 2-49)	Vaccine for influenza for nasal administration, tetravalent	Live	Attenuated	Quadrivalent	LAIV4	No
90673	Yes	Vaccine for influenza administered into muscle, preservative and antibiotic free, trivalent, recombinant DNA-derived	Recombinant		Trivalent	RIV3	No
90674	Yes	Vaccine for influenza for administration into muscle, 0.5 ml dosage, tetravalent, cell-culture based	Inactivated	Cell-cultured	Quadrivalent	ccIIV4	No
90682	Yes	Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use)	Recombinant		Quadrivalent	RIV4	No

90685	No (pediatric)	Vaccine for influenza for administration into muscle, 0.25 ml dosage, quadrivalent, preservative free (pediatric use)	Inactivated	Standard (split virus)	Quadrivalent	IIV4	No
90686	Yes	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, preservative free	Inactivated	Standard (split virus)	Quadrivalent	IIV4	No
90688	Yes	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent	Inactivated	Standard (split virus)	Quadrivalent	IIV4	No
90756	Yes	Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, antibiotic free, 0.5mL dosage, for intramuscular use)	Inactivated	Cell-cultured	Quadrivalent	ccIIV4	No
G0008	Yes	Administration of influenza virus vaccine	General		--	--	Yes
Q2034	Yes	Influenza virus vaccine, split virus, for intramuscular use (agriflu)	Inactivated	Standard (split virus)	Trivalent	IIV3	No
Q2035	Yes	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (afluria)	Inactivated	Standard (split virus)	Trivalent and Quadrivalent	IIV3, IIV4	Yes
Q2036	Yes	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (flulaval)	Inactivated	Standard (split virus)	Trivalent and Quadrivalent	IIV3, IIV4	Yes
Q2037	Yes	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluvirin)	Inactivated	Standard (split virus)	Trivalent	IIV3	No
Q2038	Yes	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluzone)	Inactivated	Standard (split virus)	Trivalent and Quadrivalent	IIV3, IIV4	Yes
Q2039	Yes	Influenza virus vaccine, not otherwise specified	General		--	--	Yes

C. MEDICAL RECORD REVIEW

During the influenza season any GBS cases identified through Medicare claims may be sent through the medical record review process ("abstraction"). This abstraction process entails detailed review of the medical charts for all beneficiaries who were diagnosed with GBS to determine whether they truly have GBS. Once the count of true GBS cases and non-cases are returned, a chart-confirmed end-of-season SCRI analysis is completed using only the true GBS cases.

When conducted, the complete abstraction process entails (i) developing an abstraction tool that isolates the information from medical records needed to confirm a GBS diagnosis, (ii) testing the abstraction tool to ensure that it functions as intended, (iii) developing a user guide for abstractors, (iv) requesting records for claims-identified GBS cases, (v) abstracting records using the tool, (vi) calculating Brighton Scores using abstraction results, and (vii) resolving Brighton Score discrepancies. Steps (i), (ii), and (iii) have already been completed and do not need to be repeated for future iterations of abstraction. Moving forward, if the abstraction process is completed, there are four main steps:

1. **Requesting records**: After identifying the cases of interest (i.e., the beneficiaries with a GBS diagnosis claim), that list of beneficiaries is sent to a contractor, which then asks the associated medical facilities to share records corresponding to the hospitalization for GBS for each of the identified beneficiaries. It is noted if facilities do not respond to the contractor's record request.

2. **Abstracting records**: Upon receiving records, trained abstractors use the abstraction tool to complete a detailed review of the medical charts to determine whether the necessary clinical and diagnostic criteria required for a GBS diagnoses are met. Abstractors use the following Abstraction Manual:

GBS Abstraction Manual ICE 10-29-2(

3. **Calculating Brighton Scores**: The Brighton Collaboration's case definitions for GBS and Fisher Syndrome are used; classification criteria are detailed in Appendix D, Table 5. Each returned record is categorized as either Brighton level 1, 2, or 3, not a case, or as having insufficient evidence to determine a definitive GBS of Fisher Syndrome case. Brighton level 1 cases meet all necessary clinical criteria and further have both cerebrospinal fluid (CSF) and electrophysiological test findings consistent with GBS; level 2 cases meet all necessary clinical criteria and have evidence of GBS from only one of these tests; level 3 cases only meet the clinical criteria. Records classified as Brighton Level 1, 2, or 3 are deemed as "chart-confirmed" GBS cases, while "insufficient evidence" and "not a case" records are labeled as non-cases. We use a tool housed by The Brighton Collaboration to calculate Brighton Score.

4. **Resolving Discrepancies:** If there are multiple abstractors reviewing each record, and their conclusions differ (e.g., one abstractor indicates a medical record does show the presence of a condition and the other abstractor disagrees), then one additional person reviews the record to decide which abstractor is correct.

D. CLINICAL CASE DEFINITIONS FOR GBS AND FISHER SYNDROME

Table 5. Clinical case detailing the definitions used to classify medically reviewed cases of claims-identified GBS cases among the U.S. Medicare Population.

Syndrome	Diagnostic Criterion	Brighton Level 1 Diagnostic Certainty	Brighton Level 2 Diagnostic Certainty	Brighton Level 3 Diagnostic Certainty
Guillain-Barré Syndrome				
	Flaccidity	Bilateral and flaccid paresis of the limbs	Bilateral and flaccid paresis of the limbs	Bilateral and flaccid paresis of the limbs
	Reflexes	Decreased or absent deep tendon reflexes in affected limbs	Decreased or absent deep tendon reflexes in affected limbs	Decreased or absent deep tendon reflexes in affected limbs
	Monophasic illness	Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau	Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau	Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau
	Diagnostic studies	Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above the laboratory normal value and CSF total white blood cell count <50 cells/mm3) Electrophysiological findings consistent with GBS	CSF total white blood cell count <50 cells/mm3 (with or without CSF protein level above the laboratory normal value) or if CSF not collected or results not available, electrophysiological studies consistent with GBS	
	Alternative diagnoses	Absence of an identified alternative diagnosis for weakness	Absence of identified alternative diagnosis for weakness	Absence of identified alternative diagnosis for weakness
Fisher Syndrome				
	Ophthalmoparesis, hyporeflexia, and ataxia	Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia	Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia	Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia
	Limb weakness	Absence of limb weakness	Absence of limb weakness	Absence of limb weakness
	Monophasic illness	Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau	Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau	Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau
	Diagnostic studies	Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above the laboratory normal and total CSF white blood cell count <50 cells/mm3) Nerve conduction studies are normal or indicate involvement of sensory nerves only	CSF total white blood cell count <50 cells/mm3 (with or without CSF protein level above the laboratory normal value) or nerve conduction studies are normal or indicate involvement of sensory nerves only	
	Altered consciousness or corticospinal tract signs	No alterations in consciousness or corticospinal tract signs	No alterations in consciousness or corticospinal tract signs	No alterations in consciousness or corticospinal tract signs
	Alternative diagnoses	Absence of identified alternative diagnosis	Absence of identified alternative diagnosis	Absence of identified alternative diagnosis

E. MEDICAL RECORD REQUEST LETTER

Date: MM/DD/YYYY

Re: **REQUEST FOR MEDICAL RECORD(S)**

Dear Medical Records Director,

We are writing on behalf of Jonathan Gibbs, Research Director at Acumen, LLC. Information Collection Enterprises (ICE) is under contract with Acumen to request medical records under an Inter-Agency Agreement between the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS) to study the safety of medical products using Medicare data. The research study is being performed under a data use agreement with the Centers for Medicare and Medicaid Services (CMS).

Enclosed please find the patient and specific record information that is needed. Please submit a complete photocopy of the entire record related to the listed date(s) of service to ICE no later than the date indicated on the enclosed case listing. **Do not submit the medical record to Acumen**. Please ensure that all copies are complete, legible, and contain both sides of each page (including page edges), and that the cover sheet provided is placed on the top of the medical record prior to shipment.

ICE will reimburse your facility at a rate of $25 per inpatient facility record submitted.

As an organization, ICE is highly committed and sensitive to the need for protecting the security of protected health information (PHI) and has implemented reasonable electronic, physical, and technical safeguards to prevent unauthorized use or disclosure of PHI.

If you have any questions regarding the medical record(s) being requested or the shipping instructions, please contact ICE at (717) 650-6772. If you have questions about the nature of the research study, please contact the Acumen Research Director Jonathan Gibbs at (650) 558-8882 or jgibbs@acumenllc.com.

Your cooperation with this effort is greatly appreciated.

Enclosures: FDA cover letter
Acumen letter of authority
Instructions for submission of medical records
Case listing
Medical record cover sheets

Information Collection Enterprises LLC
INTEGRITY, CONFIDENTIALITY, EXCELLENCE

INSTRUCTIONS FOR SUBMISSION OF MEDICAL RECORDS

Photocopy the entire medical record for each of the cases on the case list. All documentation related to the specified date(s) of service should be copied.*

***ICE does accept imaged records on disk.** Please contact us for instructions for imaged record submission.

Please Do...

- **Submit the medical record to ICE**
- Copy on white paper
- Use blue coversheets provided
- Rubber band or staple each record separately if the record is more than 20 pages.
- Staple or paperclip if the record is 20 pages or less
- Use proper packaging such as free FedEx supplies and/or Tyvek material envelopes
- Use proper shipping tape

Please Do Not...

- **Submit the medical record to Acumen**
- Copy double sided
- Reduce and reproduce multiple pages on a single page
- Use manila or paper envelopes
- Use any tape other than heavy duty shipping tape
- Overpack boxes
- Ship for Saturday delivery
- Send records to Acumen

Ship Records To:
Information Collection Enterprises
1501 Mount Rose Ave,
Suite H-4
York, PA 17403

Should you have any questions regarding this request for medical records, please contact us at (717) 650-6772.

F. SEASONALITY ADJUSTMENT

Seasonality of influenza will be measured and introduced into the SCCS analysis in the following manner:

1) Choosing Seasonality Metric: the weekly rate of confirmed influenza, calculated as the total positive influenza count (the sum of positive tests for all sub-strains of influenza (A (H1N1), A (H3), A (unidentified), B, BVic, BYam, H3N2v)) divided by the total number of specimens submitted.
2) Defining "high" and "low" Seasons for Each Region: weeks with a influenza rate in the upper 25th percentile (i.e., 10 weeks) were deemed to be in the "high" influenza season while the remaining weeks (i.e., 30 weeks) were deemed to be in the "low" influenza season, for each HHS region.
3) Estimating Regional Baseline Risk: expected weekly number of GBS cases for each region was estimated using the fitted value from a Poisson regression model.
    a. Influenza season ("high" or "low"), as determined in (2), was the independent variable (dummy for "high" influenza season)
    b. Log of total FFS beneficiaries enrolled for each respective week and region was used as the offset
4) Calculating Weekly GBS Predicted Probability: the weekly number of GBS cases is predicted for each regional model and divided by the number of FFS beneficiaries from that region in that week to get a predicted GBS rate by region and week.
5) Calculating Weighted National GBS Predicted Probability for Each Week: the weekly predicted GBS probabilities from (4) are aggregated by region and weighted using the proportion of observed number of FFS beneficiaries in each region as the weight.
6) Calculating Cumulative Risk: Poisson regression model was used to estimate cumulative risk in risk interval and control interval for each beneficiary included in the SCCS analysis
    a. Cumulative risk calculated by summing weekly national baseline risk of GBS for risk and control period.
    b. Risk of getting GBS in a particular week was partially dependent on not having gotten it in previous weeks in the corresponding window period (risk or control)
        i. This dependence of risk among weeks was taken into account by multiplying each risk estimate for week q by $(1 - p_w)$ for each w, where p_w is the risk for week w and w runs from 1 to $(q - 1)$
        ii. Using the above-mentioned variables, the cumulative risk for a 6-week risk interval beginning in week 1 was calculated as such:
        Cumulative Risk = $p_1 + (1 - p_1)*p_2 + \ldots + (1 - p_1)* \ldots * (1 - p_5)*p_6$
7) Running New SCCS Model With Seasonality Measure: a conditional Poisson regression used for SCCS analysis conducted as before, with following difference: New offset term was log of cumulative estimated risk for the interval instead of the log of length of interval in days.

Assessment of GBS Risk Following Recombinant Zoster Vaccine (Shingrix)

Protocol Addendum February 10, 2020

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1. MEDICAL RECORD REVIEW

1.1 ABSTRACTION

To ensure the highest accuracy of the abstractions of medical records, redundancies are included in the abstraction process to confirm cross-abstractor compliance. These redundancies make certain that each abstractor accurately follows the abstraction process as prescribed by the abstraction tool and manual. For this study, all records are abstracted by two abstractors independent of each other to ensure the accuracy of the abstraction. Because the study has multiple abstractors, the abstraction data undergo an additional level of review to reconcile differences between the abstractions. A final reviewer looks at discrepancies between the two abstractions and then reviews the medical record themselves to determine the correct response.

1.2 CALCULATING BRIGHTON LEVELS

To classify cases of GBS based on the Brighton Collaboration's case definition for GBS, the team uses an independently developed and validated calculator. This calculator is based on the online tool created and hosted by the Brighton Collaboration. In previous studies, we used the online tool, however, the Brighton Collaboration has since been dissolved, and the online tool is no longer available.[1] Accordingly, we developed a calculator that replicates the original tool's functions and simultaneously produces descriptive statistics of the data. We validated our calculator by independently replicating the functions of the Brighton Collaboration's online tool programmatically in Excel and SAS. To additionally validate our calculator and programmatic tool, we input the data from the 2015-16 study into both of our internally developed tools. The output from both the Excel calculator and our SAS analytic tool matched the 2015-16 output produced from the Brighton Collaboration's online tool as well as the results described in the 2015-16 & 2016-17 influenza GBS manuscript.[2]

1.3 ADDITIONAL ADJUDICATION

To enhance the validity and accuracy of the adjudication process, two non-FDA specialist physicians will each carry out an additional independent adjudication of the abstracted data. The adjudicators will receive security training from Acumen so that they can receive clearance to gain access to the secure enclave. Once this is complete, the adjudicators will be oriented to the current abstraction and adjudication process. At this point, the adjudicators will be given access to the secure enclave within which they will review the abstracted data with the Brighton level annotated for each case and medical charts as needed. Both adjudicators will first review a training case from the 2015-2016 season to determine if any further clarification to the process is needed. Once we are confident that both adjudicators are appropriately reviewing all of the information provided, they will proceed with adjudicating the 2018-2019 GBS cases.

Adjudicators will, independent of each other, review all of the abstracted data for each case, understanding that they have the medical charts available to them as well. The adjudicators will not duplicate the abstraction process, but rather determine if there is any information observed in the abstracted data or charts that casts doubt on the automated Brighton classification for each case based

[1] Brighton Collaboration, Brighton Collaboration, www.brightoncollaboration.org/.
[2] Arya, Deepa P., Maria A. Said, Hector S. Izurieta, Silvia Perez-Vilar, Craig Zinderman, Michael Wernecke, Michael Alexander et al. "Surveillance for Guillain-Barré syndrome after 2015–2016 and 2016–2017 influenza vaccination of Medicare beneficiaries." *Vaccine* 37, no. 43 (2019): 6543-6549.

on the total circumstances of each individual. The adjudicators will note if they see any combinations of symptoms that seem questionable or that warrant further investigation, and, as needed, they will provide the relevant pages of the medical charts that lead to their interpretation. Looking at the entire picture, each adjudicator should respond with the following information:

- Do you agree with the assigned Brighton classification and level? If not, what Brighton classification and level should be assigned to this case?
- Do you agree with the onset date given in the abstracted data? If not, what do you believe to be the onset date?
- Do you have any comments regarding the reasons for your responses?

After the adjudicators have finished reviewing the abstraction data and relevant medical charts, Acumen will facilitate a process of reconciling any discordance between the adjudicators. Acumen will review whether they classified each case as (i) a confirmed case (i.e., level 1, 2, or 3), (ii) a case that does not meet levels 1, 2, or 3, according to the case definition using the abstracted data, but was diagnosed as GBS according to Medicare claims (i.e., level 4), or (iii) not a case according to the case definition using the abstracted data, but was billed as GBS according to Medicare claims (i.e., level 5). If the adjudicators reach the same classification, regardless of whether it matches the automated Brighton classification, we will use that as the final case classification. For any differences we observe between their output, we will bring the adjudicators together to discuss the discrepancies in hopes of reaching an agreed upon classification. If an agreement is reached, we will use it as the final case classification. If an agreement is not reached for at least one of the cases, we will conduct additional sensitivity analyses with the different classifications.

2. SELF-CONTROLLED CASE SERIES ANALYSES

2.1 PRIMARY ANALYSIS

Our primary analysis uses claims-identified GBS cases and claims-based onset dates (see original protocol document).

2.2 SENSITIVITY ANALYSES

2.2.1 Chart-Confirmation

Once the neurologist adjudication process described above is completed, the main self-controlled case series (SCCS) sensitivity analysis with chart-based GBS onset dates will use the resulting case classifications:

- Cases where both neurologists classify it as confirmed case (i.e., where the GBS classification falls under levels 1, 2 or 3); and
- Cases where the automated Brighton classification and only one of the neurologists classify it as a confirmed case.

A second SCCS sensitivity analysis will use the same case classifications as the main sensitivity analysis, but retain the claims-based onset date.

A third sensitivity analysis will use chart-based GBS onset dates, with slight variation in which case classifications from the neurologist adjudication will be treated as a confirmed GBS case:

- Cases where both neurologists classify it as confirmed case (i.e., where the GBS classification falls under levels 1, 2 or 3); and
- Cases where only one of the neurologists classifies it as confirmed case, regardless of whether or not the automated Brighton classification classifies it as a case.

2.2.2 Control Window

Based on preliminary investigations, chart-based onset date generally occurs prior to the claims-based onset date. Thus, using chart-based onset dates may cause cases to shift from the control window to the risk window or from after the end of the control to within the control window. As we requested cases with a claims-based onset date only up to day 183 post-vaccination for the medical record review,[3] our analyses may exclude GBS cases that would have otherwise shifted into the 43-183 day control window due to their chart-based onset dates.

To reduce the bias from missing potential cases with chart-based onset dates within our control window, we will complete a chart-confirmed SCCS sensitivity analysis where we use the chart-based GBS onset date and shorten the control window by 28 days (i.e., days 43-155 post-vaccination). Clinical GBS information estimates a 2-4 weeks period between the initial onset of neurological symptoms and nadir of weakness.[4] Shortening the control window ensures we have full claims and medical records information

[3] IP GBS claims within days 184-190 must have had an OP/PB GBS claim in the 7 days prior, which would result in a claims-based onset date within the 43-183 control window.

[4] Sejvar, James J., Katrin S. Kohl, Jane Gidudu, Anthony Amato, Nandini Bakshi, Roger Baxter, Dale R. Burwen et al. "Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data." Vaccine 29, no. 3 (2011): 599.

for cases whose chart-based onset date may occur between days 43-155 post-vaccination. The case definition will follow the main SCCS sensitivity analysis with chart-based onset dates.

Table 1. Inventory of SCCS Analyses

Analysis Type	GBS Status	Onset Date Assignment	Risk Window	Control Window
Primary	Claims-identified	Claims-based	1-42	43-183
Secondary	Claims-identified (only after first dose)	Claims-based	1-42	43-183
Sensitivity	Claims-identified (seasonality adjusted)	Claims-based	1-42	43-183
Sensitivity	Claims-identified (Farrington Method)	Claims-based	1-42	43-183
Sensitivity (NEW)	Chart-confirmed (both neurologists + one neurologist & Brighton algorithm agreement)	Chart-based	1-42	43-183
Sensitivity (NEW)	Chart-confirmed (both neurologists + one neurologist & Brighton algorithm agreement)	Claims-based	1-42	43-183
Sensitivity (NEW)	Chart-confirmed (neurologist agreement + one neurologist)	Chart-based	1-42	43-183
Sensitivity (NEW)	Chart-confirmed (both neurologists + one neurologist & Brighton algorithm agreement)	Chart-based	1-42	43-155

ACKNOWLEDGEMENT AND CERTIFICATION

ELECTRONIC SIGNATURE

By submitting an electronic signature under this Acknowledgement and Certification of Understanding, you are acknowledging that you have read and agree to the contents of this addendum to the August 2, 2019 version of the *Assessment of GBS Risk Following Recombinant Zoster Vaccine (Shingrix)* protocol. By signing below, you submit your approval for the analyses outlined in this document.

X Richard A. Forshee -S

Digitally signed by Richard A. Forshee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000429529, cn=Richard A. Forshee -S
Date: 2020.03.11 10:41:03 -04'00'

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Assessment of GBS Risk Following Recombinant Zoster Vaccine (Shingrix)

Protocol Addendum June 26, 2020

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1. EXTENDED STUDY PERIOD

On November 26, 2018, the Vaccine Safety Datalink (VSD) detected a statistical signal for an increased risk of GBS among individuals 50 years and older who received Shingrix compared to a historical cohort of Zostavax recipients. After the initial signal, VSD continued with GBS Shingrix surveillance and found that, while there was a signal for increased GBS risk early in surveillance, the estimated risk decreased over time. The ACIP HZ Working Group has hypothesized that there may be differences between early adopters of the vaccine and individuals who obtained the vaccine later in the study period that drove this change.

To ensure our Medicare analysis appropriately characterizes GBS risk after Shingrix vaccination, we will extend the study period for the claims-based SCCS analysis to include the latest available data, accounting for claims maturity. Further, we will conduct an additional time trend analysis to model change in GBS risk over time.

1.1 EXTENDED STUDY PERIOD SCCS ANALYSIS

The extended period SCCS analysis will replicate the original SCCS analysis framework outlined in the August 2, 2019 version of the study protocol; however, the study period will be extended to include the latest available data accounting for claims maturity (data through February 29, 2020). Our study population will be comprised of FFS Medicare beneficiaries ages 65 and older at the time of vaccination. Our analysis cohort will consist of all GBS cases who received the Shingrix vaccine between October 1, 2017 and February 29, 2020. We will determine (i) the pooled risk estimate among all beneficiaries across all doses, (ii) the risk estimate following the first dose only, and (iii) the risk estimate following the second dose only. We will further conduct influenza seasonality-adjusted analyses for each of these three groupings as well as use the Farrington Method, which adjusts for rare exposure post-outcome, for the pooled analysis.

1.2 SENSITIVITY ANALYSIS

Currently, death is treated as a censoring event, where follow-up after a GBS event is stopped at the time of death. In these cases, the observed person-time is included in the analysis, and the risk or control window would simply be truncated at the time of death. As a sensitivity analysis, we will no longer treat death as a censoring event and instead assume full observability of both the risk and control windows for any individuals who die before the end of the control window.

Table 1. Inventory of New SCCS Analyses

Analysis	GBS Status	Onset Date Assignment	Risk Window	Control Window
1	Claims-identified (pooled across both doses)	Claims-based	1-42	43-183
2	Claims-identified (only after first dose)	Claims-based	1-42	43-183
3	Claims-identified (only after second dose)	Claims-based	1-42	43-183
4	Claims-identified (seasonality adjusted; pooled across both doses)	Claims-based	1-42	43-183
5	Claims-identified (seasonality adjusted; only after first dose)	Claims-based	1-42	43-183

6	Claims-identified (seasonality adjusted; only after second dose)	Claims-based	1-42	43-183
7	Claims-identified (Farrington Method; pooled across both doses)	Claims-based	1-42	43-183
8	Claims-identified (assume full observability; pooled across both doses)	Claims-based	1-42	43-183
9	Claims-identified (assume full observability; only after first dose)	Claims-based	1-42	43-183
10	Claims-identified (assume full observability; only after second dose)	Claims-based	1-42	43-183

1.3 RISK TIME TREND ANALYSIS

In the VSD analysis, the observed GBS risk post-Shingrix vaccination decreased over time. To investigate the change in post-vaccination GBS risk over time in Medicare data, we will fit the following SCCS model:

$$\log\big(E(Y|X)\big) = \beta_1(risk\_window) + \beta_2(risk\_window * vaccination\_timing) + \log(window\_length) + strata(beneficiary\_id)$$

$$Y = GBS\ outcome\ variable$$
$$risk\_window = binary\ term\ indicating\ GBS\ occurrence\ in\ risk\ window$$
$$vaccination\_timing = days\ since\ Shingrix\ approval\ date$$
$$window\_length = interval\ (risk/control\ window\ length)$$
$$beneficiary\_id = term\ identifying\ the\ beneficiary$$

The model allows the risk of GBS in the risk window to change over calendar time, while assuming it remains constant in the control window over calendar time. Due to the low number of observations, we will assume linearity of change in GBS risk.

$Exp(\beta_2)$ will represent the change in risk per unit time since Shingrix approval date.

1.4 SEVERITY ANALYSIS

We will use two metrics to measure the severity of GBS cases occurring after Shingrix vaccination: (i) occurrence of respiratory failure or mechanical intubation, and (ii) length of hospital stay.

We will produce descriptive statistics determining the number of cases with a claim for respiratory failure or intubation during a hospitalization with a primary GBS diagnosis. We will use the codes in Table 2 to search for intubation and respiratory failure occurring during the same hospital stay as the primary GBS diagnosis.

Cases will additionally be assessed for severity based upon the length of stay during a hospitalization with a primary GBS diagnosis. We will define length of stay using the date of admission and the date of discharge. Additionally, we will determine which eligible GBS cases have death as the reason for discharge.

Table 2. Respiratory Failure and Intubation Codes

Code	Code Type	Description
31500	CPT	Emergent insertion of breathing tube into windpipe cartilage using an endoscope
J9600	ICD-10	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
J9601	ICD-10	Acute respiratory failure with hypoxia
J9602	ICD-10	Acute respiratory failure with hypercapnia
J9690	ICD-10	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia
J9691	ICD-10	Respiratory failure, unspecified with hypoxia
J9692	ICD-10	Respiratory failure, unspecified with hypercapnia

ACKNOWLEDGEMENT AND CERTIFICATION

ELECTRONIC SIGNATURE

By submitting an electronic signature under this Acknowledgement and Certification of Understanding, you are acknowledging that you have read and agree to the contents of this addendum to the August 2, 2019 version of the *Assessment of GBS Risk Following Recombinant Zoster Vaccine (Shingrix)* protocol. By signing below, you submit your approval for the analyses outlined in this document.

X Richard A. Forshee -S

Digitally signed by Richard A. Forshee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000429529, cn=Richard A. Forshee -S
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Jeffrey A Kelman
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