PASS INFORMATION

Title:	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States.
Protocol version identifier:	209696 (EPI-ZOSTER-032 VS US DB)
Date of last version of the protocol:	Final, 31 July 2020 Amendment 1 Final, 17 May 2021 Amendment 2 Final, 18 April 2022 Amendment 3 Final, 15 July 2022
EU PAS Register No:	EUPAS37133
Active substance:	VZV glycoprotein E (gE)
Medicinal product:	*Shingrix* (Recombinant Zoster Vaccine, RZV)
Product reference:	For EMA: EU/1/18/1272/001, EU/1/18/1272/002 For FDA: IND number 13857
Procedure number:	EMEA/H/C/004336/MEA/020.1
Marketing Authorization Holder (MAH):	GlaxoSmithKline Biologicals S.A. Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives:	To assess whether *Shingrix*, or RZV, is associated with an increased risk of new-onset Guillain-Barré syndrome, gout, polymyalgia rheumatica, giant cell arteritis, ischemic optic neuropathy (ION) or supraventricular tachycardia (SVT) within specified time periods after vaccination in people ≥ 65 years of age beginning January 2018 in CMS Medicare. SVT and ION will be investigated as secondary objectives.
Country of study:	United States
Authors:	PPD , University of Maryland, Baltimore

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Contributing authors *(Amended 15 July 2022):*	PPD , University of Maryland, Baltimore PPD , GSK PPD , GSK PPD , GSK PPD , GSK PPD , GSK PPD , GSK PPD GSK

MARKETING AUTHORIZATION HOLDER

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Based on GSK Biologicals' protocol template for post-authorization safety studies v17.0

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2. LIST OF ABBREVIATIONS

AE	Adverse Event
CBER	Center for Biologics Evaluation and Research
CCW	Chronic Condition Warehouse
CDC	Centers for Disease Control and Prevention
CITI	Collaborative Institutional Training Initiative
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
DME	Durable Medical Equipment
DMP	Data Management Plan
DUA	Data Use Agreement
ED	Emergency Department
EMA	European Medicines Agency
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration, United States
GBS	Guillain-Barre Syndrome
GCA	Giant Cell Arteritis
GSK	GlaxoSmithKline SA
HIPAA	Health Insurance Portability and Accountability Act
HOI	Health Outcome of Interest
HZ	Herpes Zoster
ICD	International Classification of Diseases
ID	Identification
ION	Ischemic Optic Neuropathy
MAH	Marketing Authorization Holder

MBSF	Medicare Beneficiary Summary File
NDC	National Drug Code
PASS	Post-Authorization Safety Study
PDE	Prescription Drug Event
PHN	Post-Herpetic Neuralgia
PHSR	Pharmaceutical Health Services Research
pIMD	potential Immune-Mediated Disorders
PMR	Polymyalgia Rheumatica
PPV	Positive Predictive Value
PRC	Pharmaceutical Research Computing
PVP	Pharmacovigilance Plan
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SCRI	Self-Controlled Risk Interval
SNF	Skilled Nursing Facility
SVT	Supraventricular Tachycardia
TSS	Targeted Safety Study
UMB	University of Maryland, Baltimore
US	United States
VZV	Varicella Zoster Virus
ZVL	Zoster Vaccine Live (*Zostavax*)

3. RESPONSIBLE PARTIES

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Study Teams *(Amended 15 July 2022)*:	Core UMB study team members: • PPD • PPD Core GSK study team members: • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD

4. ABSTRACT

Title:	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States.
Version and date of the protocol	Final: 31 July 2020 Amendment 1 Final, 17 May 2021 Amendment 2 Final, 18 April 2022 ***Amendment 3 Final: 15 July 2022***
Main author:	PPD, PhD, Principal Investigator, University of Maryland, Baltimore
Rationale and background:	*Shingrix*, or recombinant zoster vaccine (RZV), is a subunit, adjuvanted vaccine that was approved by the Food and Drug Administration in October 2017 and by the EMA in March 2018 for the prevention of herpes zoster (HZ) in adults ≥ 50 years of age. The Advisory Committee on Immunization Practices recommends RZV vaccination for the prevention of HZ in immunocompetent adults ≥ 50 years of age. In pre-licensure clinical trials, which are not designed to assess rare outcomes, numerical differences between the RZV and placebo groups were noted for certain conditions, including: 1) polymyalgia rheumatica (PMR); 2) giant cell arteritis (GCA); 3) gout; 4) ischemic optic neuropathy (ION); and 5) supraventricular tachycardia (SVT). The Centers for Disease Control and Prevention (CDC) detected a statistical signal for Guillain-Barré syndrome (GBS) during post-licensure safety surveillance of RZV using the Vaccine Safety Datalink. CDC applied an iterative algorithm that preferentially maximizes sensitivity over specificity that was designed for hypothesis (signal) generation. This targeted safety study will use the Centers for Medicare and Medicaid Services (CMS) Medicare data in the United States (US) to evaluate the real-world safety of RZV, focusing on the specific outcomes listed above.
Research question and objectives:	The study will address the question of whether RZV is associated with the risk of new-onset GBS, gout, PMR, GCA, SVT, or ION within specified time periods after vaccination in people aged 65 years and older enrolled in Medicare who were vaccinated in 2018 through 2020.

The primary objectives are to estimate the risk of new onset:

- GBS within 42 days,
- Gout within 30 days,
- PMR within 183 days and,
- GCA within 183 days following vaccination with RZV.

The secondary objective is to estimate the risk of new-onset:

- SVT within 30 days and,
- ION within 183 days following vaccination with RZV.

Study design:

- This is a Targeted Safety Study and a Post-Authorization Safety Study.
- A self-controlled risk interval design will be used to assess the risks of GBS, gout, and SVT (a secondary outcome).
- A cohort design with concurrent controls will be used to assess the risks of PMR, GCA and ION (a secondary outcome).

Population: The study population is a nationally representative sample of US Medicare beneficiaries aged 65 years and older, who are enrolled in Medicare Parts A, B, and D.

Variables: The exposure is receipt of at least one dose of RZV. The dependent variable is the occurrence of the health outcome of interest. Several covariates include age, sex, region of residence within US, calendar year-month, concomitant vaccination with other preventive immunizations, certain comorbidities, healthcare visits.

Data sources: The study will use the CMS Chronic Conditions Warehouse Medicare database that includes inpatient, outpatient, physician, and prescription claims for all health services and medications provided for Medicare enrollees with Parts A, B, and D. Data from January 2017 through December 2021 will be used in this study.

Study size: Sample size calculations suggest that the study will ultimately have at least 80% power to reject the null hypothesis of no association if the true relative risk is ≥ 4 for GBS, ≥ 2 for gout, ≥ 2 for PMR, and ≥ 3 for GCA.

The estimated number of individuals for each primary outcome (assuming all individuals receive 2 doses) is:

- GBS: 1 000 000 to detect a relative risk of 4.0 or more;

- Gout: 70 000 to detect a relative risk of 2.0 or more;
- PMR: 438 239 to detect a relative risk of 2.0 or more;
- GCA: 723 362 to detect a relative risk of 3.0 or more.

Data analysis: The analysis plan will include descriptive measures to characterize exposed and unexposed individuals, conditional Poisson regression models for the SCRI, and Cox proportional hazards regression models for the cohort design outcomes.

Milestones: The milestones are 11 September 2020 (Actual date) for start of data collection, Q4, 2024 (Tentative) for end of data collection and final report submitted to the Center for Biologics Evaluation and Research (CBER) and the European Medicines Agency (EMA) 30 June 2027.

Note: the above timelines are tentative and subject to change.

5. AMENDMENTS AND UPDATES

Protocol Amendment 2 dated 18 April 2022 was amended to address feedback received from regulatory authorities.

Amendment number	Date	Amendment or update	Section of study protocol	Reason
3	15 July 2022	Updated continuous enrollment requirement to clarify the allowable gap that defines continuous enrollment	9.2.2; 9.4.1; 9.7.3; 9.7.5; 9.7.6;	As requested by CBER to update sections of the protocol for consistency

6. MILESTONES

Milestone	Planned date
Start of data collection[1]	11 September 2020 (Actual date)
End of data collection	2024 (Tentative)
Final report submitted to the FDA's Center for Biologics Evaluation and Research (CBER) and to European Medicines Agency (EMA)	30 June 2027

Note: the above timelines are tentative and subject to change.
[1] Start of study activities

7. RATIONALE AND BACKGROUND

Herpes zoster (HZ), the result of reactivation of latent varicella zoster virus (VZV) in dorsal root ganglia, most commonly presents as a painful vesicular dermatomal rash. However, complications such as post-herpetic neuralgia (PHN), as well as disseminated disease in the immunocompromised population, can lead to significant disability and morbidity[1]. There are an estimated one million cases of HZ in the United States (US) annually, resulting in $5 billion in healthcare expenditures per year[2]. Risk factors for HZ include older age and immunocompromising conditions[3,4].

Shingrix, recombinant zoster vaccine (RZV), is a subunit, adjuvanted VZV vaccine. It is approved for the prevention of HZ in adults ≥ 50 years of age in several countries within Europe and the US. *Shingrix* is a two-dose vaccine, in Europe, Doses 1 and 2 should be given 2 months apart, with the possibility of extending the timing of Dose 2 to 6 months. In the US, RZV is given 2 to 6 months apart. Since this study is being conducted in the US, the recommended dosing schedule in the US will be considered. The Advisory Committee on Immunization Practices recommendations for RZV include the following: 1) RZV (as two doses 2 to 6 months apart) is recommended for immunocompetent adults aged 50 years and older; 2) RZV is recommended for immunocompetent adults previously vaccinated with the zoster vaccine live (ZVL, *Zostavax*); and 3) RZV is preferred over ZVL[5]. Vaccine efficacy against HZ in the two pivotal Phase III studies was 97.2% in adults ≥ 50 years of age (ZOE-50)[6] and 91.5% in adults ≥ 70 years of age[7]. Pooled safety analyses of clinical data from these two Phase III studies included a total of 14 645 RZV and 14 660 placebo recipients, with a median follow-up duration of 4.4 years[8]. The pooled analysis demonstrated a comparable incidence of unsolicited adverse

events (AE) in the Day 7 through Day 29 follow-up period (excluding Day 0 through Day 6 where reactogenicity was observed to be higher in RZV versus placebo recipients). Serious adverse events (SAE), and potential immune-mediated disorders (pIMDs) between the RZV and placebo groups, and specific SAEs and pIMDs were within the expected incidence for the study age group[8].

In descriptive analyses, there were numerical differences in AEs for some specific conditions, including 1) polymyalgia rheumatica (PMR); 2) giant cell arteritis (GCA); 3) gout; and 4) ischemic optic neuropathy (ION). During the entire post-vaccination follow-up period, PMR was reported by 32 (0.2% [95% confidence interval (CI): 0.1-0.3]) and 29 (0.2% [95% CI: 0.1-0.3]) ***participants*** in the RZV and placebo groups, respectively. GCA was reported by 6 (0.04% [95% CI: 0.0-0.1]) and 3 (0.02% [95% CI: 0.0-0.1]) ***participants*** in the RZV and placebo groups, respectively. For gout, there were 27 (0.18% [95% CI: 0.12-0.27]) and 8 (0.05% [95% CI: 0.02-0.11]) ***participants*** in the RZV and placebo groups, respectively, who reported an event of gout or gouty arthritis (relative risk = 3.38 [95% CI: 1.49- 8.60]. Among ***participants*** without a known history of gout at study entry, 19 ***participants*** in the RZV group versus 3 ***participants*** in the placebo group reported new-onset gout in the 30-day period following the last vaccination. For ION, at specific follow-up timepoints post-vaccination, 1 versus 0 cases at ≤ 30 days, and 2 versus 0 cases at ≤ 365 days, were reported in the RZV and placebo groups, respectively.

With respect to clinical trials, numerical differences were also noted between the RZV group and the placebo group on pooled analyses with respect to other clinical outcomes, including supraventricular tachycardia (SVT): 6 (0.04% [95% CI: 0.02-0.09]) and 0 (0.00% [95% CI: 0.00-0.03]) ***participants*** in the RZV and placebo groups, respectively, in the 365-day follow-up period post-last vaccination.

With respect to reports of GBS, there were 2 cases reported in the RZV group and 3 in the placebo group during the entire post-vaccination follow-up period. Recent RZV post-licensure safety surveillance by the Centers for Disease Control and Prevention detected a statistical signal using Vaccine Safety Datalink Rapid Cycle Analysis, using an algorithm that preferentially maximizes sensitivity over specificity. Specifically, at the time of the preliminary signal, there were 3 presumptive events compared to 0.57 expected events when comparing RZV to a historical cohort of ZVL users, with a relative risk of 5.25[9]. As of the most recent publicly available analysis, five presumptive events have been observed compared to 1.6 expected with a relative risk of 3.18. Of these 5, one case was confirmed as Brighton Criteria level 2, one case was confirmed as Brighton Criteria level 3 (with probable respiratory infection prior to GBS symptom onset), and three cases were ruled out as not being representative of true incident cases post-vaccination.

Robust data on the risk of these outcomes following administration of RZV are currently lacking. Furthermore, data on the use of RZV in complex patient populations are critical in assessing the safety of the vaccine in the real-world setting. An observational study utilizing the Centers for Medicare and Medicaid Services (CMS) Chronic Condition Warehouse (CCW) database, a large and comprehensive database representing US adults aged 65 and older, allows us to evaluate the real-world safety of RZV, including in

heterogeneous, complex populations, with a focus on the specific safety outcomes outlined above. A detailed description of this database is in Section 9.4.1 of the protocol.

8. RESEARCH QUESTION AND OBJECTIVES

This study will assess whether there is a risk of new onset GBS, gout, PMR, GCA, SVT and ION within specified time periods after RZV vaccination in people age 65 years and older enrolled in Medicare who were vaccinated in 2018 through 2020. A self-controlled risk interval (SCRI) design will be used to assess the risk of new onset GBS, gout, and SVT. A cohort design using a concurrent preventive care visit comparison group will be used to assess the risk of new onset PMR, GCA and ION.

8.1. Primary objectives

1. To assess the risk of new onset GBS within 42 days following RZV vaccination using a SCRI design.
2. To assess the risk of new onset gout within 30 days following RZV vaccination using a SCRI design.
3. To assess the risk of new onset PMR within 183 days following RZV vaccination using a cohort design.
4. To assess the risk of new onset GCA within 183 days following RZV vaccination using a cohort design.

8.2. Secondary objectives

1. To assess the risk of new onset SVT within 30 days following RZV vaccination using a SCRI design.
2. To assess the risk of new onset ION within 183 days following RZV vaccination using a cohort design.

9. RESEARCH METHODS

The University of Maryland, Baltimore (UMB) School of Pharmacy, Pharmaceutical Health Services Research (PHSR) department conducted a feasibility assessment to inform the methodological approaches to be implemented in this safety study. The feasibility assessment, conducted January through May of 2019, had two key objectives: (1) to provide a distribution of the primary and secondary outcomes of interest and (2) to provide a distribution of select covariates within the CMS Medicare population. The results informed the study methods and estimated timelines. The data source for the feasibility assessment was the CMS CCW Medicare claims data from 2007 through 2015 for a 5% random sample of US Medicare beneficiaries age 65 years and older, which was approximately three million individuals. Some of the study outcomes occurred in less than 1% of the individuals in the feasibility assessment. RZV exposure was not assessed in the feasibility because the vaccine was licensed in 2017. The distribution of primary and secondary outcomes of interest were identified using International Classification of

Diseases (ICD)-9 and 10 codes only, case definition algorithm had not been developed yet. The overall conclusion from the feasibility assessment was that it was feasible to conduct the safety study using CMS CCW Medicare claims data.

9.1. Study design

This study is a Targeted Safety Study (TSS) and a Post-Authorization Safety Study (PASS) that will assess the risk of new-onset GBS, gout, and SVT following RZV exposure using a SCRI design; and the risk of new-onset PMR, GCA, and ION following RZV exposure using a cohort design with a concurrent comparator.

The study population will comprise approximately 4 to 5 million CMS Medicare beneficiaries age 65 years and older who received at least one dose of RZV.

RZV exposure will be defined as receipt of at least one dose of vaccine; sensitivity analyses will be conducted to assess the risk of outcomes when Dose 2 is received per US dosing schedule, i.e. 2-6 months after Dose 1.

This study will be conducted using CMS CCW Medicare claims data (described in Section 9.4.1).

Table 1 provides an overview of the study designs for the primary health outcomes of interest (HOI).

Primary objectives 1 & 2: SCRI

To assess the risk of new-onset GBS and gout, a SCRI design will be used[10]. This design is a special (and simpler) case of both the case-crossover[11,12] and the self-controlled case series[12,13] designs, in which the cumulative number of cases in pre-specified risk and control intervals (or "window") are compared. Individuals serve as their own control. The analysis is conditioned on the interval (or "window"), and only RZV vaccinees who experience the HOI in the risk or the control interval contribute to the analysis. The SCRI design is ideal for acute outcomes and transient exposures[13]. The advantage of the SCRI design is the implicit control for time-fixed potential confounders such as sex, race/ethnicity and stable chronic medical conditions. However, potential time-varying confounders, such as age, seasonality, and possibly medication use, may introduce bias unless they are explicitly controlled for with in the analysis.

Primary objectives 3 & 4: Cohort design

A cohort design will be used to assess the risk of new onset PMR and GCA by comparing the hazard of these HOIs among individuals exposed to RZV relative to individuals with a preventive care visit who did not receive RZV. Given that the HOIs assessed using the cohort design are rare, the analyses will be unmatched so as not to arbitrarily reduce the size of the comparison group, which would reduce statistical power. Potential confounders between RZV recipients and comparators (e.g., age, sex, certain chronic conditions, calendar time, etc.) will be adjusted for in multivariable Cox proportional hazards regression models (details described in Sections 9.7.6 and 9.7.8 below).

The 183-day (6-month) follow-up period post-RZV exposure for new-onset PMR, GCA and ION makes the use of the SCRI design impractical, due to time-varying confounding and overlapping observation windows for Doses 1 and 2. The self-controlled designs, including the self-controlled case series are not ideal for outcomes that have an insidious onset or non-acute outcomes due to the difficulty of specifying an appropriate control and risk windows and the introduction of bias from time-varying confounding with long follow-up period post-exposure. The cohort design also maximizes statistical power because this approach leverages the large sample size of the exposed and comparator groups.

Details of the RZV unvaccinated comparator selection for the cohort design are described in Section 9.7.5 below.

Secondary objectives

The risk of new onset SVT following RZV exposure will be estimated using a SCRI design with a 30-day risk interval.

The risk of new onset ION following RZV exposure will be estimated using a cohort design with a 183-day risk period.

Index date

The vaccination date for RZV exposed individuals is the index date for both the SCRI and cohort design outcomes. The start of follow-up for the cohort design outcomes will commence at the index date, which is the vaccination date for the RZV exposed and the preventive care visit date for the RZV unvaccinated comparator.

Baseline period for the cohort design

The baseline period is specific to the HOIs assessed using a cohort design. This is defined as the 365 days prior to the index date during which prevalent cases of the HOI will be identified for exclusion from the analytical cohort and covariates will be assessed to control for confounding in statistical analyses. Individuals who experienced an HOI during the baseline period will be excluded from the cohort design analyses for that HOI. In addition, potential confounders such as demographics, receipt of age-recommended vaccinations, and health status/medical comorbidities will be identified in the baseline period for inclusion as covariates in statistical analyses.

Unlike EPI-ZOSTER-030 VS US DB, which uses a 730-day baseline period to exclude prevalent cases of gout, a 365 day baseline period will be used for all HOIs (including gout) in EPI-ZOSTER-032 VS US DB to retain as much sample size as possible, because the entry age into Medicare for this study, is age 65 years so those who received RZV close to their Medicare enrolment will not have enough medical history to be included in the study. (e.g., if a 730-day baseline period was required for gout, then this study would only be able to assess the risk of gout in patients 67 years and older).

Table 1 Features of the study design to be used for primary HOIs

Outcome	Study Design	Primary and Secondary Analyses	Post-RZV Risk Interval	Control Interval or Comparator Group	Comments	Sensitivity Analysis
GBS	SCRI	1°: At least 1 dose -Combined Doses 1 and 2 2°: At least 1 dose – Combined Dose 1 and Dose 2 – 3-week control window for both doses 2°: At least 1 dose- Combined Dose 1 and Dose 2 – 6-week control window for both doses	Days 1-42	Days 43-84	1^{o} : Dose 1 control window maximum of days 43-84 after Dose 1; if dose 2 occurs in the Dose 1 control window then censor at Dose 2 (i.e. use a shortened control window for Dose 1) and days 43-84 after Dose 2 as control window for Dose 2. 2^{o}: Dose 1 control window is days 43-63 (3-weeks) and days 43-84 (6-weeks) after Dose 1 Exclusions: 1^{o}: Dose 1 cases excluded if Dose 2 received in Dose 1 risk window – no Dose 1 control window exists; 2^{o}: Dose 1 control window cases if also in Dose 2 risk window	Dose 1 and 2 compliant – dose spacing 2-6 months apart (subset of 1^{o} analysis) Separate analysis for Dose 1 with control window days 43-84 after Dose 1 (subset of second 2^{o} analysis) Separate analysis for Dose 2 with control window days 43-84 after Dose 2 (subset of second 2^{o} analysis)
Gout	SCRI	1°: At least 1 dose -Combined Doses 1 and 2 2°: At least 1 dose – Combined Dose 1 and Dose 2 – 30-day control window for both doses	Days 1-30	Days 31-60	1^{o} : Dose 1 control window maximum of days 31-60 after Dose 1; if dose 2 occurs in the Dose 1 control window then censored at Dose 2, (i.e. use a shortened control window for Dose 1) and days 31-60 after Dose 2 as control window for Dose 2. Exclusions: 1^{o}: Dose 1 cases excluded if Dose 2 received in Dose 1 risk window – no Dose 1 control window exists; 2^{o}: Dose 1 control window cases if also in Dose 2 risk window	Dose 1 and 2 compliant – dose spacing 2-6 months apart (subset of 1^{o} analysis) Separate analysis for Dose 1 with control window days 31-60 after Dose 1 (subset of 2^{o} analysis) Separate analysis for Dose 2 with control interval days 31-60 after Dose 2 (subset of 2^{o} analysis)

Outcome	Study Design	Primary and Secondary Analyses	Post-RZV Risk Interval	Control Interval or Comparator Group	Comments	Sensitivity Analysis
PMR	Cohort	1°: Dose 1 and Dose 2 - separate analyses for Doses 1 and 2 separate risk estimates 2°: Combined Dose 1 and Dose 2 in one analysis for a single risk estimate 2°: Combined Dose 1 and Dose 2 in one analysis with 2 separate risk estimates	Days 1-183	Days 1-183 (from index date)		Analysis with a sub-sample that received Dose 1 and Dose 2 per US dosing schedule, i.e., 2-6 months apart for both combined secondary analyses – yielding a single and separate risk estimates.
GCA	As for PMR	As for PMR	As for PMR	As for PMR	As for PMR	As for PMR

9.2. Setting

9.2.1. Source population

The source population includes US adults age 65 and older who are enrolled in Medicare any time from 2017 through 2021. Medicare is fully funded by the US government to subsidize healthcare services for individuals aged 65 and older or who are entitled because of a qualifying condition other than age. CMS is the US federal agency responsible for oversight and management of the Medicare program. As defined by CMS, Medicare is a health insurance program for:

1. People age 65 and older
2. People under age 65 years old with certain disabilities
3. People of all ages with End-Stage Renal Disease (ESRD)

Most US adults in the Medicare program (80%) qualify based on age 65 years and older and about 20% are younger than 65 years old and qualify due to a disabling condition. Approximately 55%-67% of the Medicare population is covered fully or partly through a fee-for-service arrangement as opposed to a supplemental Medicare Advantage plan (see below).

Individuals enrolled in Medicare receive benefits from different 'parts' of Medicare insurance that pay for all or a portion of specific healthcare services. These parts are referred to as Parts A, B, C and D. Each is described below.

- Medicare Part A: Also referred to as Hospital Insurance, Part A pays for healthcare services provided in inpatient settings including hospitals, critical access hospitals, skilled nursing facilities (SNFs) (not custodial or long-term care), hospice care and some home health care.
- Medicare Part B: Also referred to as Medical Insurance, Part B pays for doctors' services and outpatient care as well as services not covered by Part A, such as physical and occupational therapists and some home health care. Certain vaccines are covered under Part B: influenza, pneumococcal, and Hepatitis B.
- Medicare Part C: Also referred to as supplemental coverage, Part C was first established in 1997 under the name Medicare + Choice but was renamed in 2003 to the Medicare Advantage program. Under Part C, CMS contracts with public or private organizations to offer a variety of health plan options for Medicare beneficiaries, such as health maintenance organizations, provider sponsored associations, and preferred provider organizations. These health plans must provide all Medicare Parts A and B benefits, and most offer additional benefits beyond those covered under the original Medicare program. Individuals pay a monthly premium for Part C. Services provided under Part C are not available in the CMS CCW Medicare database, and so all data will be missing for individuals who are only enrolled in Part C during the study period.
- Medicare Part D: Also referred to as Prescription Drug Coverage, Part D first became available in January 2006. It is available to everyone with Medicare, but

individuals must enroll in a Medicare-approved plan that offers Medicare drug coverage. Individuals must pay a monthly premium to receive Part D benefits.

9.2.2. Study population *(Amended 15 July 2022)*

The study population will be comprised of all US Medicare beneficiaries who received the RZV vaccine (i.e., exposed) in 2018 through 2020 as well as a random sample of Medicare beneficiaries who did not receive the RZV vaccine but who had at least one preventive care visit ***(i.e., comparator group)***, as defined in Section 9.7.5. The study population is a longitudinal cohort that is followed over time until they are no longer in Medicare. This means there will be continuity of their data over time, i.e., there is not a new random sample selected each study year.

Study inclusion / exclusion criteria

US Medicare beneficiaries who meet the following criteria will be included in the study:

1. Age 65 and older at the date of the RZV vaccination or preventive care visit for the RZV unvaccinated comparator, **AND**
2. Enrolled in Medicare due to age or ESRD as the original and current qualifying reason, **AND**
3. Continuously enrolled in Medicare Parts A, B, and D fee-for-service for at least 365 days preceding the date of RZV vaccination or preventive care visit for the RZV unvaccinated comparator. Continuous ***enrollment*** is determined by Medicare enrollment in the month of the RZV vaccination or preventative care visit and ***enrollment*** in at least 11 of the 12 preceding months.

Beneficiaries enrolled due to ESRD or receiving dialysis are included in the study population as this condition is prevalent among US Medicare beneficiaries aged 65 and older, and this is a subgroup in which RZV use may be common. The requirement for continuous enrollment in Medicare Parts A, B, and D in the 365 days***, allowing one calendar month gap,*** before the RZV vaccination or preventive care visit will ensure complete data on all services covered by Medicare on a fee-for-service basis in the baseline study period for the cohort design. Parts A and B provide information on the HOI and Part D provides information on RZV exposure.

Beneficiaries who satisfy the following criteria will be excluded:

1. Continuously enrolled only in Medicare Part C in the baseline period, OR
2. Enrolled in Medicare due to disability as the original qualifying reason for enrollment.

Individuals who qualify for Medicare due to a disability are likely not comparable to the population of adults age 65 and older within the Medicare health insurance program in many important aspects, such as medical comorbidities, illness severity, and health seeking behavior.

It will be possible to obtain sufficient sample sizes for all HOIs with a study population accrual from 2018 through 2020. Conservative estimates are that 1.5 million Medicare beneficiaries with Parts A, B, and D will receive RZV in each year from 2018 through 2020, for a total RZV exposed of 4.5 million across all three years. If 50% are enrolled in Parts A, B, and D for at least 365 days, there will be a little more than 2 million individuals exposed to RZV who meet the study criteria. It will be possible to accrue 8 million unvaccinated individuals with a preventive care visit in 2018 through 2020 to achieve a 1:4 ratio of exposed to comparators for the cohort design.

All CMS CCW Medicare claims data from January 2017 through December 2021 will be obtained for the RZV exposed and the unvaccinated comparators accrued from 2018 through 2020. Data spanning five years are needed to cover a) the 365 days prior to the HOI for the SCRI design; b) the 365 days prior to the index date for the cohort design; c) the 60- and 84-day risk and control intervals for the SCRI design; and d) the 183-day risk window for the cohort design.

9.3. Variables

9.3.1. Exposure measure

RZV exposure will be defined as receipt of at least one dose of RZV for the primary analyses; per-dose analyses will be performed in secondary analyses. RZV vaccination will be identified by means of the national drug code (NDC) and by the Current Procedural Terminology (CPT) code. Part D generally pays for commercially available vaccines. The NDCs from the prescription drug events (PDE) file that will be used to identify RZV exposure as a prescription dispensing in an outpatient pharmacy setting are: 58 160-0828-01; 58 160-0829-01; 58 160 082 311; 58 160-0828-03; 58 160-0829-03; 58 160 082 311; and 58 160-0823-11. The CPT code 90750 for RZV will identify vaccine administration in a Part B (physician office setting) claim. It is anticipated that most will be identified from the PDE file and should only occur in one of the claims files since Medicare will not pay for the same vaccine administration twice, i.e., exposure will not be counted twice.

RZV vaccination records occurring within 27 days after a previous RZV vaccination record (i.e., on days 1-27, where the day of the previous RZV record is day 0) will be considered a duplicate record and will be deleted. The ***participant*** will be retained for the analytic cohort. For ***participants*** who receive more than two doses of RZV, even after removal of possible duplicates, we will exclude from analysis RZV doses beyond two per study ***participant***.

Preventive care visits for comparison with RZV vaccinations will be identified by means of CPT, ICD-10, and Healthcare Common Procedure Coding System (HCPCS) codes, as shown in Table 2. The presence of any of the below codes qualifies as an eligible "preventive care visit."

Table 2 Preventive care visit description for the comparators in the cohort analyses

ICD10	HCPS	CPT	Code Description
			Routine Adult Annual Exam
		99386	Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 40-64 years
		99387	Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 65 years and older
		99396	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years
		99397	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 65 years and older
	G0438		Annual wellness visit; includes a personalized prevention plan of service (pps), initial visit
	G0439		Annual wellness visit, includes a personalized prevention plan of service (pps), subsequent visit
	G0468		Federally qualified health center (fqhc) visit, ippe or awv; a fqhc visit that includes an initial preventive physical examination (ippe) or annual wellness visit (awv) and includes a typical bundle of medicare-covered services that would be furnished per diem to a patient receiving an ippe or awv
	S5190		Wellness assessment, performed by non-physician
	G0402		Initial preventive physical examination; face-to-face visit, services limited to new beneficiary during the first 12 months of medicare enrollment
Z00.00			Encounter for general adult medical exam without abnormal findings
Z00.01			Encounter for general adult medical examination with abnormal findings
			Colonoscopy Screening
		45378	Colonoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	G0105		Colorectal cancer screening; colonoscopy on individual at high risk
	G0121		Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk
	G9661		Patients greater than 85 years of age who received a routine colonoscopy for a reason other than the following: an assessment of signs/symptoms of gi tract illness, and/or the patient is considered high risk, and/or to follow-up on previously diagnosed advance lesions
	G9659		Patients greater than 85 years of age who did not have a history of colorectal cancer or valid medical reason for the colonoscopy, including: iron deficiency anemia, lower gastrointestinal bleeding, crohn's disease (i.e., regional enteritis), familial adenomatous polyposis, lynch syndrome (i.e., hereditary non-polyposis colorectal cancer), inflammatory bowel disease, ulcerative colitis, abnormal finding of gastrointestinal tract, or changes in bowel habits
	G0104		Ca screen;flexi sigmoidscope

ICD10	HCPS	CPT	Code Description
	G0106		colorecteral screeningn ca screen;barium enema
	G0107		colorecteral screening / rectal cancer screening; fecal-occult blood test
	G0120		colorecteral screeningn ca scrn; barium enema
	G0122		colorecteral screeningn ca scrn; barium enema
	G0328		colorecteral screeningrectal cancer screening, fecal occult blood test
Z12.11			Encounter for screening for malignant neoplasm of colon
			Mammography Screening
		77067	Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (CAD) when performed
		77057	Screening mammography, bilateral (2-view film study of each breast) Office/Freestanding (Global)
		76092	Screening mammography, bilateral (two view film study of each breast).
	G0202		Screening mammography, bilateral (2-view study of each breast), including computer- aided detection (CAD) when performed.
	G0203		Diagnostic mammography, including computer-aided detection (CAD) when performed; bilateral.
	V7611		Screening mammogram for high-risk patient
	V7612		Encounter for screening mammogram for malignant neoplasm of breast
	G0204		Diagnostic mammography, including computer-aided detection (CAD) when performed; bilateral.
	G0206		Diagnostic mammography, including computer-aided detection (CAD) when performed; unilateral.
Z12.3			Encounter for screening for malignant neoplasm of breast
Z12.31			Encounter for screening mammogram for malignant neoplasm of breast
Z12.39			Encounter for other screening for malignant neoplasm of breast
			Osteoporosis Screening
		77080	Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; axial skeleton (eg, hips, pelvis, spine)
		77081	Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; appendicular skeleton (peripheral) (eg, radius, wrist, heel)
	G0062		PERIPHERAL SKELETAL BONE MINERAL DENSITYN20030626
	G0063		CENTRAL SKELETAL BONE MINERAL DENSITY STN20030626
	G0130		SINGLE ENERGY X-RAY ABSORPTIOMETRY (SEXAN20110101: Single energy x-ray absorptiometry (sexa) bone density study, one or more sites; appendicular skeleton (peripheral) (e.g., radius, wrist, heel) (Single energy x-ray study)
	G0131		COMPUTERIZED TOMOGRAPHY BONE MINERAL DENN20060101
	G0132		ULTRA-SOUND BONE MINERAL STUDY, ONE OR MORE SITES, APPENDICULAR SKELETON
	G0133		Bone mineral density
Z13.820			Encounter screening for osteoporosis

9.3.2. Outcome identification algorithms

The primary HOIs are GBS, gout, PMR, and GCA. Secondary HOIs are SVT and ION. Table 3 describes the case definition algorithm for the primary and secondary HOIs, which also details the sensitivity analyses where validated outcome identification algorithms are not available in the literature for reference.

- All algorithms use medical claims from the inpatient, outpatient or carrier claim files and are based on the ICD-10 codes.
- An inpatient claim is defined as a claim generated from an admission to a hospital.
- An ED (Emergency Department) visit is defined as a claim generated from a visit to an urgent care unit within a hospital, but it is not a hospital admission.
- An outpatient claim is defined as a claim generated by a visit to a provider in an ambulatory practice setting, e.g., physician office, health clinic.
- For algorithms that require ≥ 2 claims, the date of the first claim will define the first occurrence of the HOI. The two claims must occur within the designated follow-up interval.
- For the SCRI design, new onset of the HOI, i.e., incident case, is determined based on the first occurrence and no record of the HOI in the preceding 365 days.
- For the cohort design, new onset of the HOI, i.e., incident case, is determined based on the first occurrence after the index date (i.e., RZV vaccination or the preventive care visit date for RZV unvaccinated comparators) and no record of the HOI in the 365 days preceding the index date (i.e., baseline period).
- For GBS, the earliest onset date is the hospitalization date for claims in the inpatient setting or the earlier GBS claim when the diagnosis occurs in any setting followed by an inpatient claim within 7 days.

Table 3 HOI case identification algorithms

1	2	3	4	5	6	7	8	9	10
Study Outcome (Study design)	**ICD-10 code(s) for case ascertainment**	**Validation Statistics**	**Other requirements[c]**	**Setting for case ascertainment**	**Risk Interval**	**Look-back period & settings to determine incidence**	**What to look back for**	**What to look back from**	**Sensitivity Analysis**
GBS (SCRI)	G61.0	PPV: 50% (Inpatient visit)[14]	None	Inpatient primary position OR Diagnosis in any setting followed by an inpatient claim within 7 days	Days 1-42	1 year; inpatient; primary position only	Same as in Col.2	HOI	N/A
Gout (SCRI)	M10.x, M1A.x (chronic gout)	PPV: 61% (≥ 2 visits associated with the diagnosis)[15]	At least one gout-specific oral medication (allopurinol, colchicine, probenecid, febuxostat) prescribed within 3 months after the first date of the diagnosis.	≥2 outpatient claims within the follow-up window[a] OR ≥1 inpatient claim	Days 1-30	1 year; diagnosis code –all settings[b] OR At least one gout-specific oral medication (allopurinol, colchicine, probenecid, febuxostat);	Same as in Col. 2 OR Col. 4	HOI	-Exclude chronic and secondary gout codes. -Examine frequency distribution of ICD-10 codes and consider low-frequency codes such as codes for chronic gout (M1A*), lead-induced gout (M10.1*, drug-induced gout (M10.2*), and gout due to renal impairment (M10.3*) (note: this exclusion of gout codes does not apply in assessing prevalent gout)[d]

1	2	3	4	5	6	7	8	9	10
Study Outcome (Study design)	**ICD-10 code(s) for case ascertainment**	**Validation Statistics**	**Other requirements[c]**	**Setting for case ascertainment**	**Risk Interval**	**Look-back period & settings to determine incidence**	**What to look back for**	**What to look back from**	**Sensitivity Analysis**
PMR (Cohort)	M35.3 – PMR M31.5 – GCA w/ PMR	Sensitivity: 99.5% Specificity: 92.2%[16] (based on the 3 methods used by Bernatsky: diagnosis in inpatient or outpatient, or a visit by a rheumatologist/ internist)	2 oral glucocorticoids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone) prescriptions; The first dispensing within 6 months of PMR diagnosis and the second dispensing date within 6 months after the first dispensing.	≥2 outpatient claims within the follow up window a OR ≥1 inpatient claim	Days 1-183	1 year; all settings[b]	Same as in Col. 2	Exposure	N/A
GCA (Cohort)	M31.6 (GCA), M31.5 (GCA with PMR), M31.9 (necrotizing vasculopathy unspecified)	Not available	2 oral glucocorticoids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone). The first dispensing within 6 months of GCA diagnosis and the second dispensing date within 6 months after the first dispensing.	≥2 outpatient claims within the follow up window[a] OR ≥1 inpatient claim	Days 1-183	1 year; all settings[b]	Same as in Col. 2	Exposure	-Use the primary algorithm based on the GCA diagnosis code and steroid prescription but ADD a requirement for a temporal artery biopsy at the time of diagnosis, as determined by a CPT code=37609

1	2	3	4	5	6	7	8	9	10
Study Outcome (Study design)	**ICD-10 code(s) for case ascertainment**	**Validation Statistics**	**Other requirements[c]**	**Setting for case ascertainment**	**Risk Interval**	**Look-back period & settings to determine incidence**	**What to look back for**	**What to look back from**	**Sensitivity Analysis**
ION (Cohort)	H47.01	Not available	Exclude patients who had coronary artery bypass graft (CABG) surgery[17] or lumbar or lumbosacral spinal fusion and/or laminectomy surgery within 30 days before ION diagnosis date	≥1 claim in all settings	Days 1-183	1 year; all settings[b] ICD code only	Same as in Col. 2	Exposure	Additional criteria for arteritic: ≥ 40 mg/day of prednisone prescription ± 4 weeks of the diagnosis plus an ophthalmologist/neuro-ophthalmologist consult (if possible) and GCA diagnosis within 3 months; lookback to rule out prevalent cases will use ICD code only; all settings
SVT (SCRI)	I47.1	Sensitivity-91.7% [18]	None	≥1 ED or inpatient claim any position	Days 1-30	1 year; all settings[b] any position	Same as in Col. 2	HOI	N/A

Definitions: ALS - Amyotrophic Lateral Sclerosis; CVA - Cerebrovascular Accident; GCA - Giant Cell Arteritis; GSB - Guillain-Barré Syndrome; ION - Ischemic Optic Neuropathy; PMR - Polymyalgia Rheumatica; SCRI - Self-controlled Risk Interval; SVT - Supraventricular Tachycardia;

[a] Outpatient visits are defined using ≥2 claims for consistency with methods used by CMS algorithms using the CMS CCW Medicare data to define chronic conditions, and to avoid misclassification of the outcome due to the potential for 1 visit to reflect rule-out diagnosis.

[b] Includes inpatient, emergency department, and outpatient settings.

[c] Based on external expert opinion.

[d] Consistent with the study EPI-ZOSTER-030 VS US DB, no analysis will be conducted for the gout sensitivity HOI definitions. These definitions are for administrative purposes only .

9.3.3. Covariates

Covariates to be evaluated include the following, some of which will be used to adjust or stratify the cohort during the analytic modeling:

- Region of residence within US [as defined by either Department of Health and Human Services (11 regions) or Census Bureau (4 regions)]
- Calendar year-month of vaccination or preventive care visit
- Age in years at vaccination or preventive care visit (aggregated into age groups: 65-69, 70-74, 75-79, 80-84, 85+)
- Sex (binary as male/female)
- Race and ethnicity (e.g., white, black, Asian, Hispanic, North American Native, other)
- Concomitant vaccination (e.g., influenza, pneumococcal, etc.)
- Certain immunocompromising conditions (e.g., transplant, cancer, autoimmune/inflammatory condition, etc.)
- Certain other co-morbidities (e.g., diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, etc.)

9.3.4. Potential confounding variables and effect modifiers

A confounder is defined as any variable that is associated with both the exposure and the study HOI. Since a confounder cannot be on the causal pathway from exposure to the outcome, all confounders will be captured in the 365 days preceding the index date, i.e., RZV Dose 1 and Dose 2 vaccination date and the RZV unvaccinated comparator preventive care visit for the cohort design. All confounders identified using Medicare enrollment and medical or prescription claims data will be used for covariate adjustment in multivariable models. Propensity score methods will be considered for confounding adjustment, depending on identified imbalances in the observed covariates between the exposed and comparator groups. Confounding variables defined by health care services and comorbidities will be identified using a combination of ICD-10, CPT and HCPCS codes.

- **Demographic variables** will include age, sex, and race and ethnicity (i.e., white, black, Asian, Hispanic, North American Native, and other/unknown based on the US government categories)
- **Healthcare service variables** will include admissions to skilled nursing facilities (SNFs), number of hospitalizations, number of ED visits and Durable Medical Equipment (DME) use. These will be considered to control for potential imbalances between RZV vaccinees and RZV unvaccinated comparators in health impairment requiring more intensive services. The place of service and revenue code on the claim are used to designate the type of service setting.
- **Preventive care services** will include receipt of age-recommended vaccine (e.g., influenza, pneumococcal, and tetanus, diphtheria, pertussis). These will be

considered to control for potential healthy adherer bias that could result in imbalances in healthcare services and prior health seeking behavior patterns between RZV vaccinees and RZV unvaccinated comparators. Table 2 lists the preventive care services. Since mammography, bone mineral density, and colorectal screening are criteria for the unvaccinated comparator selection, these are not included as confounders in the analysis.

- **Medical comorbidities specific to PMR/GCA**. Potential risk factors specific to these conditions may include:
  - Age, which is found to be the strongest risk factor;[19]
  - Female sex is found to be a risk factor;[19]
  - Race/ethnicity as a significantly lower incidence is reported in African, Asian, Latinos;[19]
  - Gout has been associated in a few studies (from same group using CMS data);[20,21]
  - Prior hematologic malignancy has conflicting results on the association, but has been shown in some studies;[22]
  - Case reports/series with use of checkpoint inhibitors show development of PMR or PMR-like syndrome;[23]
  - Immunocompromising conditions, given that PMR is an immune-mediated disorder, potentially imbalance in T-regulatory lymphocytes and proinflammatory T-helper 17 cells.
- **Medical comorbidities specific to ION**. Risk factors specific to ION include:[24-28]
  - Arteritic ION is significantly less common than non-arteritic and is strongly associated with GCA, thus we will consider similar risk factors/potential confounders.
  - Non-arteritic ION Anterior Ischemic Optic Neuropathy has reported associations with obstructive sleep apnea, vasculopathic/ prothrombotic conditions (e.g., diabetes, hypertension, spinal and cardiac surgery, some medications (amiodarone, phosphodiesterase type 5 inhibitors).
- **General medical comorbidities**. Other comorbidities or chronic conditions may be important to address confounding by indication, e.g., relatively common conditions that are indicative of functional status or illness severity.
  - Diabetes mellitus
  - Chronic kidney disease
  - Chronic lung disease - chronic obstructive pulmonary disease and chronic bronchiectasis
  - Congestive heart failure
  - Ischemic heart disease
  - Dementia - Alzheimer’s Disease and Related Disorders or Senile Dementia

  - Chronic liver disease - cirrhosis and other liver conditions except hepatitis
  - Stroke/Transient Ischemic Attack

- **Immunocompromised conditions**. This includes solid organ transplant, hematopoietic cell transplant, hematologic or solid malignancy with recent receipt of chemotherapy, autoimmune/inflammatory condition ***or*** on an immunosuppressive regimen, and human immunodeficiency virus infection.

9.4. Data sources

9.4.1. Description of the databases (*Amended 15 July 2022*)

CMS CCW Medicare data is a secondary administrative database of all paid claims for fee-for-service billable healthcare services in inpatient and outpatient settings, SNF, hospice, home health services, and for the provision of DME and prescription drugs for older and disabled US citizens. The claims data are available in six different datasets and a unique identification (ID) is used to link an individual across all data sets. Annex 1 provides a detailed description of the data sets and the variables within each dataset.

Master Beneficiary Summary File (MBSF): The information in this dataset relevant to this study includes beneficiary enrollment ***each calendar month*** in Medicare Parts A, B, and D. This file will be used to obtain information on the baseline study variables, including original and current enrollment reason, eligibility, and demographic characteristics.

Inpatient Claim File: This dataset contains fee-for-service claims submitted by inpatient hospital providers for reimbursement of facility costs, including hospitalizations and ED visits. Up to 25 diagnosis fields, including the admission diagnosis as well as a principal diagnosis, are available on each claim. CPT codes for services rendered are available on each claim.

Outpatient Claim File: This dataset contains fee-for-service claims submitted by *institutional outpatient providers*. Institutional outpatient providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, Federally Qualified Health Centers and community mental health centers. The outpatient files contain up to 25 diagnosis fields as well as CPT codes.

Carrier File: This dataset includes fee-for-service claims submitted by *professional providers*, including physicians, physician assistants, clinical social workers, nurse practitioners and by *organizational providers*, including freestanding facilities (i.e., independent clinical laboratories), ambulance providers, freestanding ambulatory surgical centers and freestanding radiology centers. The Carrier files contain up to 12 diagnosis fields as well as CPT codes.

SNF Claim File: This dataset includes fee-for-service claims for paid services that are submitted by SNF *institutional facility providers*.

PDE File: This dataset includes all medications filled at an *outpatient pharmacy* that have been submitted by the prescription drug plan. The NDC variable will be used in this study to identify all medications dispensed during the baseline and follow-up period.

The MBSF will be used primarily to select the study population and determine eligibility for this study. The inpatient, outpatient, carrier and SNF files will be used to ascertain the HOIs and the confounding variables. The PDE file will be used to ascertain RZV exposure.

9.4.2. Quality of the data

Quality of the ICD Codes for Identifying HOIs: The chronic medical condition variables were developed using algorithms based on ICD-9-CM diagnoses codes, Medicare Severity Diagnosis Related Group codes, or procedure codes. CMS has confirmed the consistency of the prevalence of the chronic conditions between the ICD-9 and ICD-10 codes. The link to the document is found here: https://www2.ccwdata.org/web/guest/ccw-medicare-datra-white-papers. All of the algorithms used to identify CCW chronic conditions from the claims data were updated for the conversion from ICD-9 to ICD-10. However, the validation statistics for these algorithms are not reported in the CCW white paper. Specifications for the algorithms are located under the 'Conditions Categories' tab at www.ccwdata.org. With regards to the HOIs in this study, gout (see Sentinel report) has demonstrated consistent prevalence during the period of transition from ICD-9 to ICD-10.

Completeness of the CMS CCW Medicare Claims for Assessment of Study Outcomes: The claims from each of the databases are over 99% complete by 12 months post-service date. This will reduce the likelihood of missing information as all data measured for this study will have a minimum of a one-year lag period.

This study uses de-identified Medicare data curated for research; investigators cannot access medical charts for case adjudication. Case identification will be limited to use of an algorithm that combines medical billing diagnosis code, procedure and/or drug codes.

9.4.3. Number of years and duration of data availability

For this study, five years of CCW Medicare data will be purchased: 2017 through 2021. This is necessary to ensure an adequate sample size for the primary HOIs (see Section 9.5 for a detailed description of the sample size). The span of five years (2017 through 2021) will ensure claims data are available for 365 days preceding the HOI (in the SCRI design) and the index date (in the cohort design) and throughout the duration of the study follow up for all of the Dose 1 and Dose 2 analyses. All individuals will be followed longitudinally throughout the study.

CCW Medicare data are available for request in December for the prior year's claims (e.g., the 2018 data should be available for request in December 2019).

9.4.4. Rationale for selecting the database and advantages

Rationale for Selecting the Database: Several factors support the rationale for using the CMS CCW Medicare data.

- It is the largest comprehensive dataset of healthcare service utilization of US adults age 65 and older.
- Data linkage across different data sets permits evaluation across the continuum of healthcare settings and services.

Advantages of the CMS CCW Medicare Data: The CMS CCW Medicare data offers many strengths for a vaccine safety study using observational data. The relevant strengths of CCW Medicare for this study include:

1. There is continuity of medical and prescription claims data. Once enrolled, most beneficiaries remain enrolled in Medicare for the rest of their lives because Medicare is the only entitlement health insurance coverage for older adults in the US. The exception is adults who enroll in Part C, and all of their data are missing because it is not captured in the CMS CCW fee-for-service data. The feasibility assessment revealed that, 54% of the Medicare beneficiaries had continuous enrollment in Parts A, B, and D for at least one-year preceding the first occurrence of a claim with a diagnosis corresponding the one of the HOIs in this study. Most Medicare beneficiaries (56%) were continuously enrolled in Parts A, B, and D for at least one-year after the first occurrence of a claim with a diagnosis corresponding to one of the HOIs in this study. Approximately 20% were continuously enrolled in Parts A, B, and D for five or more years. This will ensure sufficient data for the baseline and follow up assessments in this study with minimal loss to follow-up.
2. Comprehensive data that are linkable across service settings. The data will include medical and prescription encounter data from inpatient, institutional, outpatient physician, outpatient hospital, and outpatient pharmacies that are linked via a beneficiary identification number. This permits assessment of the study outcomes in relation to the timing of a medication exposure, including vaccines. Key variables include those related to diagnoses, procedures, and place of service.
3. Large population. The Medicare population is large and will permit detection of rare outcomes, as some HOI in this study like GBS, GCA and ION are rare.
4. Representation of geographic diversity of the US, since the data represent all Medicare enrollees across all states. The data provide geographic diversity within the context of the US.

9.5. Study size

9.5.1. Projected study size

CMS CCW Medicare claims data will be obtained for up to 20 million Medicare beneficiaries. This will include all RZV vaccinees in 2018 through 2020 in addition to a random sample of Medicare beneficiaries who did not receive RZV and had a preventive care visit. The estimated sample size for the SCRI design with vaccinees (Table 4) and the cohort design with vaccinees and the unvaccinated comparators (Table 4) needed to detect the specified relative risk with 80% power is attainable.

9.5.2. Sample size considerations

SCRI design sample size estimates

For the SCRI design, the required number of events was calculated based on the method for self-controlled case series studies[29]. The sample size estimates shown in Table 4 indicate that 1 000 000 individuals are needed to detect a relative risk of at least 4.0 for GBS and 70 000 individuals are needed to detect a relative risk of 2.0 for gout. The sample size calculation only takes into consideration the control window because the risk of GBS or gout in the control window would reflect the background risk. Due to the dose spacing and the possibility of Dose 1 control window overlapping the risk window for Dose 2, the full 42-day control window for Dose 1 may not be observed, we expect this to occur in about 50% of 2 dose vaccine recipients (based on internal GSK data from 2018-2019 regarding timing of Dose 2 receipt in the US). Hence the average length of the control window observed would be about 36 days.

Table 4 SCRI design sample size estimates for GBS and gout with 80% statistical power under a two-sided type 1 error (alpha) of 0.05

Outcome	IR	CW (days)	Scalar of Risk Window	No. of cases expected per 100 000 CWs [a]	RR	Total events needed	*No. of cases expected in CW	No. of CWs (aka vaccinations) needed/100 000 [b]	**No. vaccinations needed	***No. of vaccinated people needed
GBS	2/100 000 PY	36	0.098563	0.197125	3	30	8	41	4,100,000	2,050,000
					4	20	4	20	2,000,000	1,000,000
Gout	200/100 000 PY	30	0.082136	8.706365503	2	68	23	140	140,000	70,000
					2.5	40	11	67	67,000	33,500

IR: Incidence rate; RR: Relative risk; CW: Control window
[a] Assuming no risk from vaccination exists in CW
[b] vaccinations are synonymous with post-vaccination control windows
*Total events needed were calculated using the method described by Musonda et al [29].
** Expected vaccinations were obtained assuming the control window was truly not a period od=f increased risk
*** Approximate numbers, assuming that individuals receive 2 doses

In order to use the control window (assumed to be free of risk due to vaccination) to project the number of vaccinations needed, we scaled the background risk to the length of the control window, i.e., multiplied the respective background rate by 36/365.25 for GBS and by 30/365.25 for gout.

We then calculated the number of cases we would need in the control window for each relative risk scenario, given the minimum total number of events needed in risk and control windows combined.

For example, for a true relative risk of 2, a total of 71 cases are needed to achieve 80% power to see an association. We would expect about 47 of the 71 cases to be in the risk window and 24 to be in the control window.

To generalize to other relative risk scenarios, the number of cases in the control window out of the total events needed is [total events needed/(RR+1)]. The expected numbers in the control window (vaccinations) needed is simply the ratio of the number of cases in the control window (i.e., the number expected on the basis of the true relative risk and the total number of events needed in risk and control windows combined) and the background rate scaled to the control window length.

Cohort design sample size estimates:

For the cohort design, the sample size was estimated using Poisson Regression in the Power Analysis and Sample Size software (NCCS Statistical Software, 2013, version 12.0.2). The analysis performed for the PMR and GCA sample size estimates was based on a 183-day risk period with a cohort ratio of 1:4 exposed to unvaccinated preventive care visit comparator.

The sample size estimates shown in Table 5 indicate that a total sample of 438 239 individuals is needed to detect a relative risk of 2.0 for PMR and a total sample of 723 362 individuals are needed to detect a relative risk of 3.0 for GCA. The study is powered for the primary outcomes of PMR and GCA.

Table 5 Sample sizes with cohort design for PMR and GCA with 80% statistical power under a two-sided type I error (alpha) of 0.05, Cohort 1:4 ratio, and 6 months follow up

Outcome	RR	Baseline Response	Total Cohort Sample Size, N	Vaccinated Population, N	Control Population, N
PMR	2	0.000405	438,239	87,648	350,591
	2.5		242,212	48,442	193,770
	3		164,320	32,864	131,456
	3.5		123,991	24,799	99,192
GCA	2	0.000092	1,929,204	385,841	1,543,363
	2.5		1,066,257	213,252	853,005
	3		723,362	144,673	578,689
	3.5		545,828	109,166	436,682
	4		439,133	87,827	351,306

The estimated sample sizes for the SCRI design with vaccinees (Table 4) and the cohort design with vaccinees and the unvaccinated comparators (Table 5) needed to detect the specified relative risks (≥ 4 for GBS, ≥ 2 for gout, ≥ 2 for PMR, and ≥ 3 for GCA) with 80% power is attainable.

9.6. Data management

Full details of the data management will be described in the Data Management Plan (DMP). The DMP is bound by the provisions of CMS. Included in the DMP are (1) description of data acquisition procedures (2) physical possession and storage of data files and (3) data sharing, electronic transmission and distribution.

9.6.1. Data collection

Data collection. Through a Data Use Agreement (DUA) with CMS, University of Maryland, Baltimore (UMB) acquires adjudicated administrative claims data for the US Medicare population. There is no data collection occurring at the UMB site. The data acquired through CMS are deemed research identifiable files, which means dates of service visits, dates of birth, and zip code information are available in the data.

Physical possession and storage of data files. All original media containing sensitive data files are kept onsite by the Pharmaceutical Research Computing (PRC) Center at UMB in an access-controlled room in a fireproof locked safe. The PRC System Administrator is responsible for the upload of data onto the secure servers, which are accessible only to study personnel. Database management at PRC is built with multiple layers of security and follows best practices for securing sensitive data.

Projects requiring special handling of backups especially at the termination of the project are stored in a specific directory on the PRC system. Files are backed-up and encrypted as a whole and saved on their own non-removable backup drive.

Data access. Only study personnel approved by the Project Officer/Principal Investigator are allowed access to the assigned secure private workspace. PRC employs the principle of least privilege, allowing only authorized access for users which are necessary to accomplish assigned tasks. Study personnel must have current Health Insurance Portability and Accountability Act (HIPAA), Collaborative Institutional Training Initiative (CITI) and security training records on file with PRC before an account or access is finalized. To increase security, external access to PRC's secure environment is blocked by a UMB campus firewall, as well as a local software-based server firewall. All study personnel access is monitored on an ongoing basis using a digital footprint.

Data inventory. The staff at PRC maintain custodianship over the data files contained on the PRC server and PRC staff maintain compliance with DUA expirations.

Data Breach. In order to comply with the Privacy Act of 1974, HIPAA, federal security requirements outlined by National Institute of Standards and Technology, and DUA-required standards, PRC has adopted measures to prevent or minimize potential system security breaches.

Data sharing, electronic transmission, and distribution. Data analysis is conducted with SAS 9.4. Users are unable to upload or download data from the PRC. Files may only be outputted to directories with write access permissions. All users must abide by the project specific DUAs when sharing or distributing data.

9.7. Data analysis

- All the statistical analyses will be done in SAS 9.4.
- All the statistical tests will be two-sided at alpha level of 0.05.
- All 95% CIs will be estimated as the point estimate ± 1.96*standard error.

9.7.1. Hypothesis testing

9.7.1.1. Hypothesis for the SCRI analysis

Hypothesis (HA1): The incidences of new onset GBS and gout in the RZV exposed person will differ in the risk window compared to the control window, as determined by an incident rate ratio not equal to 1.

These hypotheses will be tested separately for each of the two primary HOIs using the specific risk periods provided that at least 68 cases be recorded for gout (with a total cohort size of 70 000 we will have 80% power to detect relative risk of ≥ 2); and at least 20 cases recorded for GBS (with a total cohort size of 1 000 000 we will have 80% power to detect relative risk of ≥ 4).

9.7.1.2. Hypothesis for cohort analysis

Hypothesis (HA2): The incidence of new onset PMR and GCA in the RZV exposed cohort will differ from the incidence in the RZV unvaccinated comparator, as determined by a hazard ratio not equal to 1.

These hypotheses will be tested separately for each of the two primary HOIs during a 183-day risk period. With a cohort ratio of 1:4 RZV vaccinated to RZV unvaccinated comparator, a total sample size of 438 239 for PMR has 80% power to detect a relative risk of ≥ 2.0 and a total sample size of 723 362 for GCA has 80% power to detect a relative risk of ≥ 3.0.

9.7.1.3. Statistical analysis sequence

Since the sample sizes needed are HOI dependent, the statistical analysis will be staggered in phases. The proposed sequence is: gout; PMR and GBS; GCA, SVT, and ION as noted in Table 6. A comprehensive final report will be prepared upon completion of all primary and secondary analyses. This final comprehensive report will be submitted to the FDA Center for Biologics Evaluation and Research (CBER) and the EMA.

Table 6 Sequence of analyses to be conducted

Outcome	Target risk to detect	Analysis Sequence
Gout	RR of ≥2	Phase 1
GBS	RR of ≥4	Phase 2
PMR	RR of ≥2	
GCA	RR of ≥3	Phase 3
SVT	N.a.	
ION	N.a.	

N.a.:Not Applicable

9.7.2. Handling of missing data

Based on the feasibility assessment study, we do not anticipate any missing data on age and sex. Approximately 0.01% of the population has missing information on the state of residence and 1.42% report "unknown" race. Individuals may be lost to follow-up if they lose eligibility or switch to Part C and all their data will be missing, at which point they will be censored in the analysis. Under the assumption that data are missing at random, multiple imputation will be used to impute missing values.

9.7.3. *Participant* disposition (*Amended 15 July 2022*)

Participant disposition will be summarized for the overall study population and for the RZV vaccinated and RZV unvaccinated comparators with a preventive health visit by computing:

- Number of individuals screened overall to determine eligibility for the study.
- Number and percent of individuals who do not satisfy criteria for inclusion in the study, overall and by cohort, for each of the following reasons:
  - Age < 65 at the index date
  - Not continuously enrolled in Medicare Parts A, B, and D for 365 days***, allowing one calendar month gap,*** preceding the index date
  - Only enrolled in Medicare Part C
  - Qualify for Medicare due to a disabling condition
- Number of eligible ***participants*** in each cohort.

9.7.4. Descriptive analyses

Baseline characteristics of the RZV vaccinees and the RZV unvaccinated comparators will be compared using chi-square tests for categorical data and t-tests and simple linear regression for continuous data. According to the central limit theorem, with large sample sizes, as will be the case with the CMS CCW Medicare data, a two-sample t-test is robust to data that are not normally distributed. The Wilcoxon two-sample test is an alternative to the t-test because it makes no assumption about the underlying distribution of the data. It is best when the distribution of the two groups is similar, but it performs less optimally when the groups' distribution differs due to extreme outliers[30]. Data will be inspected

using graphical plots to first test that statistical assumptions are met before implementing an approach.

- Comparisons on key baseline characteristics (i.e., before the index date) will include (see Section 9.3.4 for list of confounders):
  - Demographic characteristics: age at the index date, gender, race, ethnicity, region of residence, and the duration of Medicare Parts A, B, and D enrollment preceding cohort entry.
  - Medical comorbidities: common chronic conditions being considered that may confound the exposure-outcome association.
  - Health service use: number of all cause inpatient and ED visits, use of DME, hospice, home health, and SNF.
  - Preventive health services: Receipt of vaccine (age-recommended vaccine: influenza, pneumococcal, and tetanus, diphtheria, pertussis).
- Evaluation of the characteristics by patterns of RZV dosing will include:
  - Comparison of the baseline characteristics of individuals who receive only one dose with individuals who receive both doses of RZV.
  - Characterize RZV dosing patterns such as the mean and median time between Dose 1 and Dose 2.
  - The EMA wishes to see whether a meaningful number of study ***participants*** receive Dose 2 within 2 months after Dose 1 in order to determine the applicability of the study results to the European context. In accordance with this request, we will report the proportion of all 2-dose recipients receiving the second dose on days 28-60 after the first dose.
  - Report on the number of GBS cases with evidence in the inpatient or outpatient claims of respiratory or gastrointestinal infection (including COVID-19) in the 60 days prior to the GBS diagnosis, noting in which post-RZV windows (risk versus control) these GBS cases occurred.

9.7.5. Analysis population (*Amended 15 July 2022*)

Population for the SCRI design analyses

Only the cases of new-onset gout, GBS and SVT recorded in the RZV exposed cohort during either the risk or the control windows will be included in the respective HOI SCRI analysis.

Population for the cohort design analyses

The study population for the cohort design will comprise all RZV exposed and RZV unvaccinated comparators with a preventive care visit who satisfy the inclusion criteria. With the cohort design, to exclude prevalent cases of the HOI prior to the index date, all ***participants*** who had the HOI at any point in the 365-day pre-vaccination baseline period will be excluded.

Generating an index date for unexposed comparators. In an attempt to control healthy user bias among individuals who receive the RZV vaccine, the unvaccinated comparators will be selected from individuals who have at least one preventive care visit. The steps described below will be performed separately for Dose 1 and Dose 2.

1. Create a pool of eligible comparators with at least one preventive care visit.
   - The pool of eligible comparators are unvaccinated individuals who had at least one preventive care visit, which is defined as having at least one visit for a routine adult annual exam OR at least one preventive screening intervention performed (Table 2).
   - To ensure complete data for the baseline period preceding cohort follow-up, individuals must be continuously enrolled in Medicare Parts A, B, and D for a minimum of 365 days preceding the preventive care visit***. Continuous enrollment is determined by Medicare enrollment in the month of the preventative care visit and enrollment in at least 11 of the 12 preceding months.*** Visits that do not satisfy this criterion will be excluded. For individuals with multiple preventive care visits, only visits that do not meet the eligibility criterion will be excluded. For individuals with only one preventive care visit, the entire person will be excluded if the visit does not meet eligibility criterion.
2. Randomly select one preventive care visit from eligible comparators. For an individual to be eligible as a comparator, the individual must not have had RZV at any time in available history prior to or on the day of the preventive care visit.
3. The preventive care visit is the index date for the unexposed comparator.

9.7.6. Inferential analyses for the primary outcomes (*Amended 15 July 2022*)

An overview of the planned primary, secondary, and sensitivity analyses were presented earlier in Table 1. Details of the analysis are described here.

- GBS and gout will be analyzed using a SCRI design
- PMR and GCA will be analyzed using a cohort design

Analysis of the SCRI Design

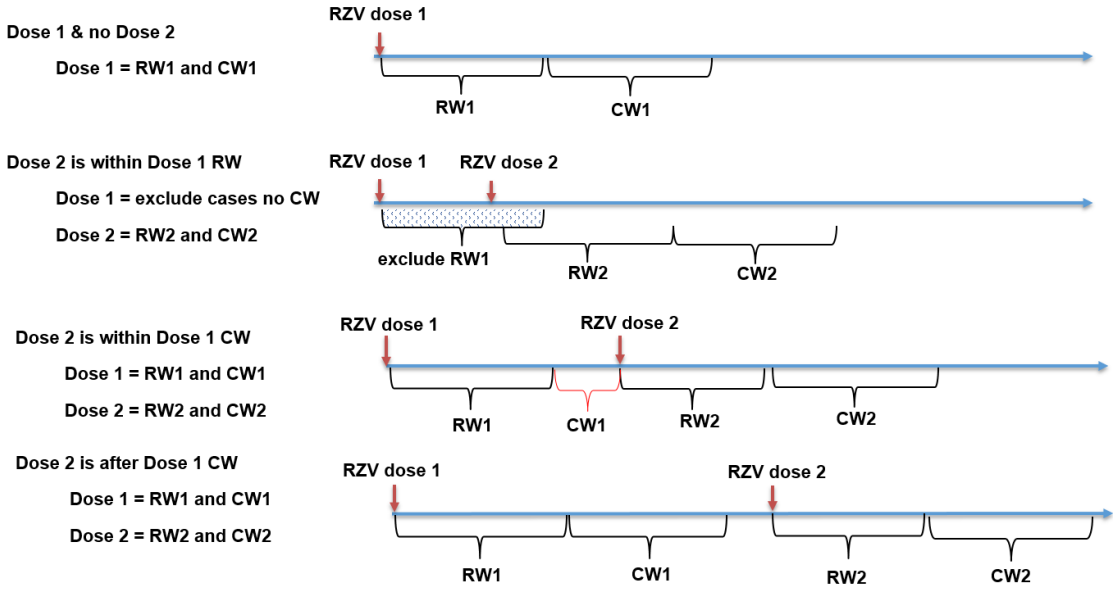
Additional inclusion requirements for the SCRI design analyses for new onset (i.e., incidence) primary HOIs GBS and gout include:

1. Receipt of RZV vaccination;
2. First occurrence in a 365-day look-back from the HOI in the risk or control interval;
3. ***Continuously enrolled in Medicare Parts A, B, and D fee-for-service for at least 365 days preceding the date of RZV vaccination. Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination and enrollment in at least 11 of the 12 preceding months.***
4. ***Continuous*** enrollment in Parts A and B (and in the case of gout Part D to capture gout-specific medication) through the end of the respective control interval.

The use of a first-in-365-days definition of HOI incidence is important and customary with the SCRI design to establish an equal opportunity for a case to be ascertained regardless of where in the follow-up (risk and control) period it might appear. The enrollment requirement for the defined amount of follow-up time, i.e., through the end of the control interval, will exclude people who die or lose eligibility before that time. However, because the HOIs addressed in this study are usually not fatal, we do not expect this requirement to produce any appreciable bias in our analyses. Moreover, the follow-up time (risk and control) is relatively short (84 and 60 days for GBS and gout, respectively), and we do not expect exclusion due to death would impact many individuals. In the relatively short follow-up time, we also do not anticipate loss of eligibility will produce appreciable bias in the analyses.

Per US schedule, RZV is indicated as a two-dose schedule, 2 to 6 months apart, thus it is not possible to define a consistent control interval for Dose 1. The control interval following Dose 1 may overlap with the risk interval following Dose 2. Therefore, the control interval following Dose 1 will depend upon the time between doses. The potential scenarios are illustrated in Figure 1.

Figure 1 SCRI design with variable spacing between Dose 1 and Dose 2



RW1: Risk window for dose 1; RW2: Risk window for dose 2; CW1: Control window for dose 1; CW2: Control window for dose 2;
Risk window: GBS days 1-42 following vaccination; Gout days 1-30 following vaccination
Control window (may be shorted in some scenarios): GBS days 43-84 following vaccination; Gout days 31-60 following vaccination.

Primary SCRI design analysis of combined doses.

The primary analysis for the SCRI design will combine both doses (i.e. the number of events in risk windows and number of events in the control windows, regardless of dose), yielding one risk estimate. Although RZV dose spacing is 2 to 6 months according to the US product label, there might be variations in schedule in real-world settings resulting in overlapping risk and control window. This presents some challenges with the two-dose analysis. GBS is used as an example to illustrate this (also depicted in Figure 1).

- Risk interval: Days 1-42 following vaccination with Dose 1 and days 1-42 following vaccination with Dose 2.
- Control interval: This will depend upon the spacing between doses (see Figure 1).
  - If Dose 2 is 1-43 days after Dose 1 (i.e. within Dose 1 risk window): Dose 1 cases excluded since no control window exists; Day 43-84 following vaccination with Dose 2 is the control window for Dose 2 (second scenario of Figure 1; anticipate that this scenario will rarely happen).
  - Dose 2 is 43-60 days after Dose 1 (i.e., within Dose 1 risk window and before the 2-month US product label indication): Day 43 up to Dose 2 following vaccination with Dose 1 is the control window for Dose 1 (i.e., shortened control window in third scenario of Figure 1.)
  - Dose 2 is 43-84 days after Dose 1 (i.e. within Dose 1 control window): Day 43 up to the receipt of Dose 2 following vaccination with Dose 1 is the control window for Dose 1 (i.e., shortened control window in third scenario of Figure 1). Days 43-84 following vaccination with Dose 2 is the control window for Dose 2.
  - Dose 2 is > 84 days after Dose 1 (i.e. after Dose 1 control window): Days 43-83 following vaccination with Dose 1 is the control window for Dose 1 and days 43-84 following vaccination with Dose 2 is the control window for Dose 2 (i.e., fourth scenario of Figure 1).

Secondary SCRI design analyses. The secondary analyses will vary the length of the control windows for Dose 1 and 2.

- Shortened control window for both doses: This will yield a single risk estimate but will use a 3-week (days 43-63) control window for both doses. Dose 1 control window cases will be excluded if also in the Dose 2 risk window.
- Allow a 6-week control window for both doses: This will yield a single risk estimate and will use days 43-84 after Dose 1. The Dose 1 control window cases will be excluded if also in the Dose 2 risk window.

Sensitivity analyses for SCRI design

- Separate dose analysis for Dose 1 and Dose 2: This will yield separate risk estimates for Dose 1 and Dose 2. This risk and control windows for each dose will be defined according to the primary analysis.
- Subgroup analysis of dose compliant individuals who receive both doses according to the US schedule, i.e. within 2 to 6 months: The analysis will be similar to the primary combined dose analysis yielding one risk estimate, but in a subset of the vaccines who receive the vaccine as indicated.

Potential seasonality adjusted SCRI analyses for GBS and gout We will assess any seasonal pattern of RZV vaccination graphically, and will adjust for seasonality in secondary SCRI analyses for GBS and gout, as both of these outcomes are known to have a seasonal pattern.

Analysis of the Cohort Design

Additional inclusion requirements for the cohort design analyses for new onset (i.e., incidence) primary HOIs PMR and GCA include:

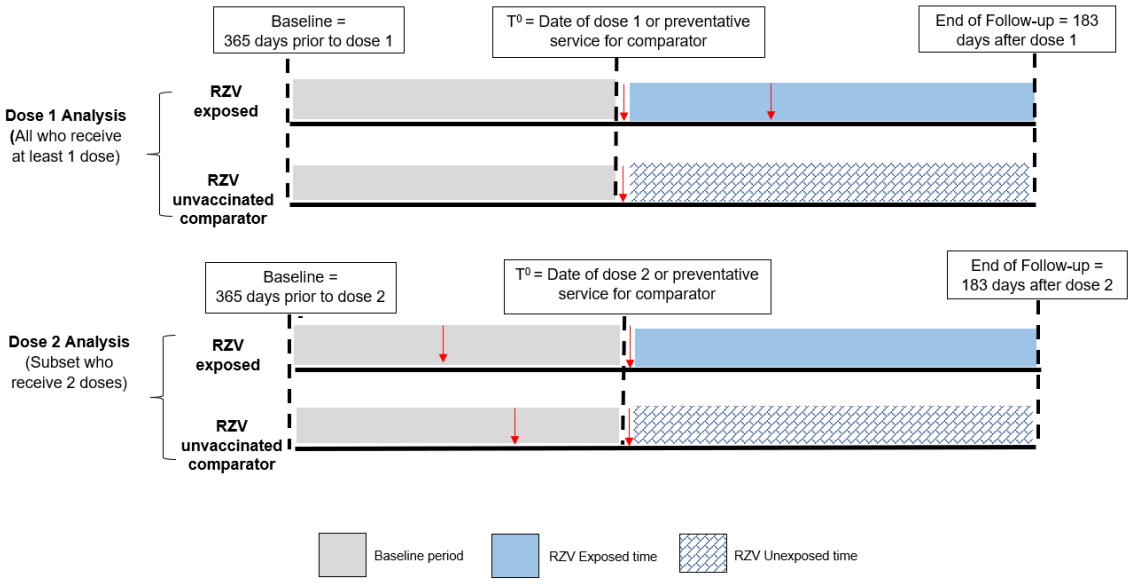
1. RZV vaccine exposed and a preventive care visit comparator;
2. A 365-day look-back from the index date (i.e., vaccination or preventive care visit date) to rule out prevalent cases;
3. At least 365 days (1 year) of Parts A, B, and D ***continuous*** enrollment prior to the index date. ***Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination or preventative care visit and enrollment in at least 11 of the 12 preceding months.***

Primary analysis of separate doses.

The analysis accounts for the variation in the interval between Dose 1 and Dose 2. The risk period after Dose 1 may overlap in part with the risk period after Dose 2 and/or the baseline period before Dose 2. To mitigate time-window bias, there is similar risk period after each dose.

The primary analysis will assess each dose separately and will yield two separate risk estimates for Dose 1 and Dose 2. Exposure is defined as at least one dose of the RZV vaccine. The risk period for the cohort analysis is 183 days from index date. The index dates are Doses 1 and 2 is the vaccination date for the RZV cohort and preventive care visit date for the RZV unvaccinated cohort. The scenarios for the primary analysis are illustrated in Figure 2.

Figure 2 Cohort Design: Primary analysis with separate Dose 1 and Dose 2 analysis



Secondary analyses of the cohort design.

The secondary analyses will combine Dose 1 and Dose 2.

- One risk estimate: This secondary analysis of combined doses does not distinguish between doses to yield one risk estimate.
- Two separate risk estimates: An additional secondary analysis combines Dose 1 and Dose 2 in the same analytic model but yields two separate risk estimates.

All individuals will be followed up for 183 days from the Dose 1. The maximum allowable spacing between doses will be 365 days. This means that Dose 2 is not included in the analysis if it is received more than 365 days after Dose 1. We anticipate the majority of individuals will receive Dose 2 within 365 days. RZV vaccinated individuals may have up to two measures (i.e., one for Dose 1 and one for Dose 2). The RZV unvaccinated comparators similarly will have up to two measures for the index dates for preventive care visits. Robust variance estimators will be used to account for repeated measures on the same individual.

Sensitivity analysis of the cohort design.

- Dose compliant analysis: The sensitivity analysis is restricted to the sub-sample that received Dose 1 and Dose 2 per US dosing schedule, i.e., 2-6 months apart. Analysis will be conducted similar to the secondary analysis (i.e combined doses yielding a single risk estimate and separate doses yielding two risk estimates).

Sensitivity analysis of alternative definition of GCA

- The number of cases and the incidence rate (or cumulative incidence) among vaccinated and preventative care comparators who are identifed using the sensitivity analysis HOI definition of GCA (Table 3 Column 10) will be reported. Futher analysis consistent with the primary (1^{o}) analysis for the cohort design (i.e. analysis of separate doses) will be conducted, if an appropriate number of cases are identified to allow meaningful inference.

Censoring events. Exposed person-time will be defined as the period between the index date and the earliest of the following events:

- End of study period (defined as the lesser of 183 days after the index date or Dec 31. 2021)
- Date of disenrollment from Medicare Parts A, B, and D
- Date of death
- Date of *Shingrix* vaccination among comparators
- Date of *Zostavax* vaccination
- Date of first diagnosis of the outcome of interest.

9.7.7. Inferential analyses of the secondary outcomes

The analysis of SVT will be similar to the SCRI design analyses for gout. The analysis of ION will be similar to the cohort design analysis for PMR and GCA.

Sensitivity analysis of alternative definition of ION

- The number of cases and the incidence rate (or cumulative incidence) among vaccinated and preventative care comparators who are identified using the sensitivity analysis HOI definition of ION (Table 3 Column 10) will be reported.Further analyses consistent with the primary (1^{o}) analysis for the cohort design (i.e.analysis of separate doses) will be conducted if an appropriate number of cases are identified to allow meaningful inference.

9.7.8. Sensitivity analysis to evaluate the impact of the COVID-19 pandemic

Sensitivity analyses will exclude exposures from the analytical cohort for which follow-up ended after February 1, 2020. These sensitivity analyses will be conducted for each HOI and will be aligned with the primary (1°) SCRI and cohort analysis as described in Table 1 and sections 9.7.6 and 9.7.7. These sensitivity analyses will allow for an evaluation of the robustness of the primary findings after excluding cases and vaccinations during the COVID-19 pandemic. The sensitivity analyses will be descriptive if the exclusion of ***participants*** after February 1, 2020 compromises the sample size such that there is insufficient power to generate meaningful estimates. Such descriptive analysis will report the number of cases in the risk and control windows (for the SCRI design) or the incidence rate (or cumulative incidence) for the cohort design.

9.7.9. Statistical models

Statistical models for the SCRI design

The primary, secondary and sensitivity analyses of the SCRI design will use a conditional Poisson regression model. This will estimate the incidence rates generated in risk and control windows of the same individual accounting for the within ***participant*** dependence using generalized estimating equations for robust variance estimation. The conditional Poisson regression model is a multinomial model, where time-fixed confounders within each stratum are controlled by conditioning on the sum of events in this stratum[31]. The general form of a conditional Poisson regression model can be written as:

$$n_{ik} \sim \text{Poisson}(\lambda_{ik} e_{ik})$$

$$\log(\lambda_{ijk}) = \phi_i + \theta_k$$

The response variable is n_{ik}, the number of events for the *i*th individual in the k (risk or control) interval. The log of the time spent in the interval ($ln e_{ik}$) is the offset term.

In the model, λ_{ik} denotes the incidence within each interval, ϕ_i is the effect for individual i (log of baseline incidence of HOI for individual i), and β_k is the effect for risk group k[32]. The model generates incidence rate ratio with a 95% CI.

PROC GENMOD with the Poisson distribution, a log link function, and the EXACT statement will be employed using SAS 9.4 to perform a conditional Poisson regression model. The main model will include the dependent variable (*Y*) as the number of events, a binary independent variable as the interval (risk or control), and the log of person days in the interval as the offset term.

The Deviance goodness of fit test will be used to evaluate the Poisson model fit. When using PROC GENMOD to fit a Poisson regression model, the "Criteria For Assessing Goodness Of Fit" output provides the Value/DF ratio. The ratio should be close to 1 to denote a good fit of the model to the data. If the Value/DF ratio is ≥ 2, there is over-dispersion, which can result in underestimation of standard error and thus overestimate statistical significance. The "DSCALE" or "PSCALE" options in the GENMOD procedure use "deviance chi-square" and "Pearson chi-square" to make the adjustment for over-dispersion. A negative binomial link function will be used should there be over-dispersion.

Temporal scan statistics

Temporal scan statistics will be used as a supplemental method for assessing the possibility of an association between RZV vaccination and an HOI during the respective follow-up period. This method evaluates whether there is any statistically significant temporal clustering of cases, the existence of which may suggest, although not confirm, an association.

Statistical models for the cohort design

Separate analysis for Dose 1 and Dose 2. The primary analysis for the cohort design will be conducted using a Cox proportional hazards regression model. This is a semi-parametric model in that it assumes a parametric form for the effects of the explanatory variables and an unspecified form for the underlying survival function. The general form of a Cox proportional hazards regression model can be written as:

$$h_i(t,x) = \lambda_0(t)\ \exp[\beta_1 x_{i1} + \ldots. \beta_k x_{ik}]$$

where, $h(t)$ is the expected hazard at time t; $\lambda_0(t)$ is the baseline hazard function and represents the hazard when all predictors are equal to 0.

PROC PHREG will be employed using SAS 9.4 to estimate the Cox proportional hazards regression model. The effect estimate generated from Cox proportional hazards model is hazard ratio, expressed as:

$$HR(t,1,0,\beta) = \frac{h(t \mid x=1,\beta)}{h(t \mid x=0,\beta)} = \exp(\beta)$$

where x (1,0) denotes to exposure status, and β is the estimated parameter from the regression model. Violations of the proportional hazard assumption will be evaluated

using a graphical approach by plotting the log[-logS(t)] versus log(t) and the Schoenfeld residuals by time, by testing the interaction between the covariates and log(t), and by using the assess statement available in the PROC PHREG procedure. Non-parallel lines or none-zero slope in the graphical approach, a significant interaction term, and a significant supremum test would indicate a violation of the proportional hazards assumption. If the proportional hazard assumption is violated, an interaction term of time and the variable of interest will be included in the model.

Combined analysis of Dose 1 and Dose 2 yielding one risk estimate. A partly conditional survival model will be used in the secondary analysis of combined doses. Since an individual may contribute more than one observation in the analysis (i.e., Dose 1 and Dose 2), this model is appropriate as it estimates the effect of longitudinal measures, in this case dose, on survival allowing for repeated measures for each individual[33,34].

Whereas typically survival is modeled as the time from study entry to the event, i.e., event time, D_i, in partly conditional survival analysis, regression parameters depend upon the time of measurement, S_i, for the predictor (i.e., dose receipt) and the time of measurement for the event to measure the follow up time since the measurement, $D_i - S_i$. This is considered partly conditional since the hazard function that is being modeled conditions on the covariate history through S_i. As a result, there are multiple event times for each individual which corresponds with the repeated measures for each dose.

A general form of the regression model for the hazard is shown below,

$$\lambda_{ik}(t* \,/\mathbf{Z}_{ik},\, 0 \le s_{ik} \le T_i) = g[\lambda_0(t*, s), \boldsymbol{\beta}(t*, s)^{\top} \mathbf{Z}_{ik}]$$

where T_i is the time to event (or censor) for ***participant*** i, s_{ik} denotes measurement times for each dose, $t^* = t - s_{ik}$ measures the follow-up time since dose, $g(\lambda, \eta)$ is a link function, $\lambda_0(t^*, s)$, is the baseline hazard, $\beta(t^*, s)$ is the regression coefficient, and Z_{ik} is a vector of covariates associated with ***participant*** i, at time s_{ik}.

The analysis will be conducted using SAS 9.4, and standard errors will be calculated using a robust sandwich estimator for repeated measures survival data.

Combined analysis of Dose 1 and Dose 2 yielding separate risk estimates. To generate a separate risk estimate for each dose in a combined analysis, where a binary indicator defines the Dose 1 and Dose 2 risk windows, a time-varying Cox proportional hazards regression models will be used. In the time-dependent model, we allow the risk window to vary for each dose. The time after dose 1 until dose 2 or end of follow-up if no dose 2 occurs defines the dose 1 risk window, and the time from dose 2 until end of follow-up defines the dose 2 risk window. Thus, a ***participant*** who receives two doses will contribute time to the dose 1 risk window and the dose 2 risk window. In the unvaccinated comparators the time from index date to end of follow-up is considered unexposed time. A general form of time-dependent Cox models can be written as:

$$h_i(t,x) = \lambda_0(t)\, \exp[\beta_1 x_{i1} + \ldots. \beta_2 x_{i2}(t)]$$

where x_{i1} represents a time-independent variable, and x_{i2} represents the time-dependent variable. This analysis will use the full cohort and obtain estimates for both doses

whereas the primary separate dose analysis either ignores dose 2 or includes only the subset of the sample who received 2 doses.

This analysis allows us to use the full cohort to compare the findings to the primary separate dose analysis. The primary Dose 1 analysis ignores Dose 2, and as such the events after Dose 2 may be attributed to Dose 1, thereby increasing the HR for Dose 1 (and its unknown which dose carries the highest risk). The primary Dose 2 analysis only includes individuals who did not experience the event after Dose 1, which could reflect potentially the more robust individuals. This could bias the estimate towards the null, and it is difficult to determine whether the estimate is a function of the vaccine or the characteristics of the Dose 2 subgroup. The time-varying model for this analysis uses the entire cohort, and attributes events to the respective dose risk window yielding a HR for each dose. Therefore, the full cohort sensitivity analysis allows us to estimate the hazard for each individual dose risk and to compare the results with the primary analysis estimates.

The effect estimates generated from the time-dependent Cox proportional hazards model will be a hazard ratio for Dose 1 relative to unexposed and a hazard ratio for Dose 2 relative to unexposed. Both hazards are generated in the same model with the full cohort, using time since the Dose 1 index date or the preventive care visit.

Sensitivity analysis for receipt of the Dose 1 and Dose 2 on schedule. The sensitivity analysis will be restricted to the sub-sample of individuals who receive both RZV doses on schedule per US label. This will test the sensitivity of the primary and secondary analyses, which examine the HOI incidence regardless of the dose spacing. This will follow the primary separate dose analysis and the secondary combined dose analysis.

Supplemental analysis

Some individuals in the analysis may contribute person-time both to the comparison group and (subsequently) to the RZV-vaccinated group. At CBER's request, a supplemental analysis will be conducted for the primary analysis, excluding from the control arm those ***participants*** who received RZV at any point, so that each ***participant*** contributes person-time to only one arm.

9.7.10. Methods to control for confounding

Covariate-adjusted analysis. A multivariable model adjusted for baseline covariates will be the primary method to control for confounding. These include the demographic (age, sex, race, US region), vaccination or preventive care visit (calendar year/month, care setting), comorbidities and immunocompromising conditions. The list of covariates to be evaluated are detailed in Section 9.3.4. Variables between the RZV exposed and the RZV unvaccinated comparators that differ by a standardized mean difference greater than 0.10 will be adjusted for in the statistical models. The standardized mean difference is preferred over a p-value metric that can be influenced by large sample sizes when in fact there is little meaningful difference between groups.

Propensity score methods for the cohort design analysis. We may consider using propensity score methods to correct for imbalance in confounders between RZV exposed and RZV unvaccinated comparators. A logistic regression model will be used to estimate the conditional probability of receiving the RZV vaccine predicted by the baseline covariates observed in the 365 days preceding the start of follow-up (i.e., index date) and that were listed in Section 9.3.4. Variables are selected empirically based on a statistically significant association, as determined from bivariate analyses, between the confounder and the exposure and the confounder and the outcome of interest.

We will select the propensity score implementation method, such as inverse probability of treatment weighting, that yields the best covariate balance between the groups[35]. To determine whether the propensity score method adequately addressed imbalances in covariates, we will evaluate the standardized mean differences between RZV vaccinated and RZV unvaccinated comparators less than 0.10, i.e., indicative of good confounder balance.

Bias analysis to test for unmeasured confounders for the cohort design analysis. One assumption underlying the cohort analyses is that there are no unobserved confounders related to RZV exposure and the study outcomes of interest, given the observed covariates. Unobservable factors, related to illness severity and health status, could influence RZV receipt and the outcomes of interest. The goal of the bias analysis is to estimate the magnitude of effect an unobserved confounder needed to change the statistical inference[36-38].

9.8. Quality control

Outline of data extraction procedures. The study team will request CMS CCW claims data for all beneficiaries who received the RZV vaccine and a random sample of beneficiaries who did not receive the RZV vaccine that will enable a 1:4 ratio of exposed to unexposed. CMS provides research identifiable data that contain dates of service, date of birth, and zip code. However, to preserve anonymity and confidentiality, the data do not contain personal identifying information, such as name, address, Medicare identification number, or social security numbers. A de-identifiable beneficiary ID is used to link data files; however, CMS does not provide the key that links the de-identified beneficiary ID to personal identifying information.

The data extraction procedures to ensure the quality and integrity of the data are:

- **CMS data acquisition-retrospective data collection/analysis**. All claims data acquired will include year's 2017 (baseline pre-period for 2018), 2018, 2019, 2020, and 2021 (follow-up period for 2019) for beneficiaries identified for the study.
- **Extraction of individual data**. All data extracted for individual level analyses will undergo reviewed by a second programmer to ensure accuracy of the programming code. Programming code includes those used to identify exposed and unexposed individuals eligible for the study, to apply the inclusion and exclusion criteria to identify the study cohort and to identify individuals eligible for the planned analyses.

- **Dataset check**. All programs and outputted datasets will undergo a 3-person review-initial programmer, second programmer and project coordinator. The initial programmer is responsible for the first review of his/her programs and output. A second programmer, whose sole responsibility is quality control, will be responsible for secondary review of the task list and all programs. The project coordinator who oversees the task order for each programming serves as the third reviewer who will be responsible for review of all output to ensure that it adheres to the protocol.
- **Perform consistency checks**. Files will be inspected for correct application of inclusion criteria as outlined in this document and stored in a manner consistent with DUA specifications. Once the list of inconsistencies is reviewed, discrepancies can either be confirmed or corrected, as applicable. Once completed, the data files will again be re-transferred in a secure manner, in the required format for a final check, database freeze/archival, and lock of the dataset.

9.9. Limitations of the research methods

The section describes the potential limitations that impact the inferences that can be drawn from this study along with the likely success of efforts taken to reduce bias.

Study design. Despite the careful selection of appropriate study designs to address the study objectives, there are some limitations. The SCRI design mitigates bias through implicit control for time-fixed confounders. A limitation is that it does not control for time-varying confounders. With the short risk windows for this study, there may be minimal change in confounders, and thus minimal bias would be introduced.

A limitation of the cohort analysis is dis-enrollment from Medicare Parts A, B, and D, which could impact the 365-day baseline period. The feasibility assessment showed that requiring more than 365 days would reduce the sample size because individuals lose Parts A, B, or D coverages. Further, individuals who receive RZV close to age 65, the age at which individuals qualify for Medicare, may not have a full year of enrollment prior to the vaccination date. Consultation with clinical experts confirmed that the 365-day baseline would be adequate to exclude prevalent cases of the HOIs. According to the sample size estimates, the large sample size in the CMS Medicare population should be sufficient, even if the sample is reduced due to less than 365 days of enrollment in Parts A, B, and D prior to the vaccination or preventive care visit date.

Data sources: limitations of the CCW Medicare data.

Services covered by Medicare Advantage (Part C) plans are not included in the CCW Medicare data. Older adults who opt to purchase supplemental insurance are covered under the Medicare Advantage plans, or Part C. All medical encounters and services are paid for by the supplemental insurance, and thus data on these individuals are missing.

Data on clinical metrics, such as laboratory values and illness severity, that could have been used for case identification are not available in the claims data.

Analytic methods. The analytic models selected for the analyses have minimal assumptions, and most of which can be verified through analytic tests and graphical display of the data. However, they could still have some unverifiable assumptions.

Methods to Control for Confounding and Bias. A primary source of confounding in this study are healthy user bias, which refers to the fact that individuals who seek preventive care service may also participate in other healthy behaviors, thus are less likely to experience an outcome. In the cohort analyses, our proposed use of a concurrent preventive care visit as the comparison group will mitigate the effects of healthy user bias on the risk estimate as both RZV vaccinated and unvaccinated will be users of preventive care services.

While other measurable confounding variables that differ between the two groups will be adjusted for in multivariable regression models and possible by using propensity score methods, the risk estimates could still be biased by confounders that were not measured (unmeasured confounders) or not properly measured (residual confounding). A bias analysis is planned to identify how strong an unmeasured confounder must be to explain away the observed effect estimate.

The Dose 2 analysis is conditioned on the subset of individuals who self-select to receive 2 doses within the study period. This may introduce selection bias if there are characteristic differences in measured and unmeasured factors that influence why some individuals receive two doses whereas some only receive one dose. This can underestimate the risk relative to the unvaccinated.

Generalizability. Medicare is the most comprehensive data on older adults, and so the findings will generalize to US adults aged 65 and older. We do not expect appreciable differences between those in the study and those age 65 and older who are not enrolled in Medicare Parts A, B, and D that would affect the HOI risk estimate post-vaccination with RZV.

Sources of random error. The goal is to mitigate bias due to random error. However, it is possible that random sources of error will occur since this is an observational study using secondary claims data. All attempts have been made to ensure appropriate study designs, well-thought out case identification algorithms, appropriate confounder adjustment methods, and planned sensitivity analyses are implemented in the conduct of the study.

Temporal variation. There may be temporal variation due to availability of the vaccine. To address variability in the timing of the vaccine and the preventive care visit, the calendar month-year will be a covariate in the analytic models.

Case ascertainment. It will not be possible to conduct a chart review to validate HOIs. Case-finding algorithms using administrative data are rarely sensitive and specific. The algorithms used in this study are found to have high positive predictive value in published case validation studies and we consulted with experts.

9.10. Other aspects

To comply with regulatory requirements and GSK standards, administrative obligations relating to protocol amendments, protocol administrative changes and termination of the study must be fulfilled.

Record retention

Data files and programs will be retained on PRC secure servers for the duration of the study as stipulated in the DUA. However, a DUA may be renewed for an indefinite duration of time, depending upon the study needs.

During project closeout, project specific programs, output, data sets and documentation are archived unless stipulated otherwise. A custodial server assessment determines what, if any, resources remain after this process.

Upon completion of research activities or expiration of the DUA, data resources covered by the DUA must be destroyed to prevent breach of confidentiality. This data destruction is then certified and reported to CMS within 30 days. Additional project files may be preserved on the PRC server archive for up to 3 years following the closure of the DUA; however, the DUA may remain active for as long as needed for the study purpose and requirement to maintain the data for a specified period of time. In this study, the project files will be preserved for 15 years, per contractual agreement.

Quality assurance

The PHSR department and PRC are guided the management concept of Total Quality Management. PHSR and PRC highly value quality assurance measures utilizing standardized project management procedures managing projects and project files. Best practices have been established to assist in assuring outputs are as accurate as possible.

Posting of information on publicly available clinical trial registers and publication policy.

<u>Observational studies evaluating a product:</u>

- The key design elements of this protocol and results summaries will be posted on the GSK Clinical Study register in compliance with GSK policy according to the timelines described below.
  - Protocol summaries will be registered prior to study start.
  - Results summaries along with redacted protocol and SAP will be posted within 12 months of analysis completion date.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical trial registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK Biologicals will also provide the investigator with the full summary of the study results.

- GSK also aims to publish the results of these studies in the searchable, peer-reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis. Any publications will follow guidelines, including those for authorship (e.g., guidelines established by the International Committee of Medical Journal Editors 2018) and for reporting of observational studies in epidemiology (e.g. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE,) 2007)[39].

PASS studies:

- Protocol summaries for non-interventional post-authorization safety studies will be registered along with redacted protocol in the EU PAS register prior to study start.
- Redacted Clinical Study Report (CSR) will be submitted in the EU PAS register within 12 months of end of data collection.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK Biologicals will also provide the investigator with the full summary of the study results.

Provision of study reports to regulatory authorities

The final study report will provide an overview of the study background, objectives, methods, and findings and will be submitted to regulatory agency authorities by the vaccine manufacturer. Final study results, as well as the main methodological components developed as part of this study, will be disseminated as oral or poster presentations at scientific meetings and as peer-reviewed publications

10. PROTECTION OF HUMAN SUBJECTS

Adequate protections include mandatory training in human subjects research for all study team members, including HIPAA and CITI training. The study will be reviewed and approved by the UMB Institutional Review Board. Annual study reports are required for continuing review and approval for ongoing study conduct. Any concerns during the study conduct will be reported to the Institutional Review Board as soon as it is identified.

Source files and derived data resources will be maintained in project specific directories with restricted permissions. Neither source files nor derived products may be placed on personal storage or removable media, as affirmed by the PRC data access agreement for CMS CCW Medicare data. Violations of this policy may result in criminal penalty or corrective action. Investigators and staff are required to sign the PRC data access agreement and review data security policies for the PHSR department. Policy requirements include restricted data access, secure storage and strict maintenance of privacy as required by HIPAA. To maintain confidentiality and anonymity of the ***participants***, data are de-identified and cannot be linked back to the individual. As required by the CMS DUA, and this project's DMP, cells of tables will be suppressed when size less than 11.

Ethical conduct of the study

The study will be conducted in accordance with all legal and regulatory requirements. Additionally, we will adhere to commonly accepted research practices, including those described in the following guidance documents:

- The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology. Available at: [http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideonMethStandardsinPE_Rev7.pdf]
- International Society of Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices. Pharmacoepidemiology and drug safety. 2008;17(2):200-208. doi: 10.1002/pds.1471 [published Online First: 2007/09/18] [https://www.pharmacoepi.org/resources/policies/guidelines-08027/]
- FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment [https://www.fda.gov/media/71546/download]
- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data. Rockville, MD. May 2013. [https://www.fda.gov/media/79922/download]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is an observational, retrospective, post-authorization safety study, based on data extracted from the US CMS CCW Medicare databases. Individual medical records will not be directly examined, and ***participant*** reports linked between databases will be de-identified prior to analysis. Therefore, individual case adverse event/adverse reaction reports will not be generated from this study.

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Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	209696	31-Jul-2020	List of stand-alone documents
2	209696	31-Jul-2020	Glossary of terms
3	*209696*	*17 May 2021*	*List of principal and coordinating investigators*
4	209696	31-Jul-2020	Sponsor Information
5	*209696*	***15 July 2022***	*Amendments to the protocol*
6	*209696*	***15 July 2022***	*Protocol Amendment **3** Sponsor Signatory Approval*
7	*209696*	***15 July 2022***	*Protocol Amendment **3** Investigator Agreement*
8	209696	31-Jul-2020	ENCePP checklist for study protocols

Annex 2 Glossary of terms

Adverse event:	Any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Anonymized data:	Information about an individual that GSK or a third party cannot reasonably attribute to the individual or could only attribute to the individual by expending a disproportionate amount of time, effort or expense (e.g. de-identified or aggregated information). For the purpose of this policy, Key-Coded personally identifiable information shall not be considered Anonymized Information
Cohort study:	A form of epidemiological study where participants in a study population are classified according to their exposure status/disease and followed over time (prospective/ retrospective) to ascertain the outcome(s).
Commitment:	Agreement made with Regulatory Authorities as specific condition of regulatory approval and authorization, either made at the time of product approval or during the lifecycle of the approved product.
Database:	A database is a set of pre-existing tables and views containing data. The term “pre-existing” implies that the analysis will be done on retrospective data and the term “views” implies that the data can be made readily available in an electronic format through a straightforward extract, without re-encoding and manual manipulation (like a transpose, a translation, split of a field into several fields, etc.).
Database study:	A study involving the use of pre-existing data maintained in an electronic format; this will not include collection of new data that requires (re-)encoding via CRF/eCRF and retesting of human biological samples.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
eTrack:	GSK's tracking tool for clinical/ epidemiological trials.
Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Post-Authorization Safety Study:	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorization and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorization' means that the product is used according to the European label (e.g., within the recommended dose range, the approved formulation, indication etc.).
Prospective study:	A study in which the participants/cases are identified and then followed forward in time in order to address one or more study objectives. A prospective study usually involves primary data collection.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. Note: Any change that falls under the definition of a protocol amendment (e.g., a change that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Protocol amendment:	The International Council on Harmonization defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.

Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.
Retrospective study:	A study that looks backward in time (e.g., at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Self-controlled risk interval (SCRI):	Statistical method for assessing the association between a transient exposure and an adverse event. The method was developed to study adverse reactions to vaccines. The method uses only cases; no controls are required as the cases act as their own controls. Each cas''s given observation time is divided into control and risk periods. Risk periods are defined during or after the exposure. The method estimates a relative incidence rate, that is, the incidence in the risk period relative to the incidence in the control period. An advantage of the method is that confounding factors that do not vary with time, such as genetics, location, socio-economic status, are controlled for implicitly.
Study population:	Sample of population of interest.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.

Annex 3 List of principal and coordinating investigators

The list of all investigators and their contact details are available upon request.

Annex 4 Sponsor Information

Sponsor:

GlaxoSmithKline Biologicals (GSK)
Rue de l'Institut, 89
1330 Rixensart, Belgium

Annex 5 Amendments to the protocol

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

GlaxoSmithKline Biologicals SA **Vaccines R & D** **Protocol Amendment *3***	
eTrack study number and Abbreviated Title:	209696 (EPI-ZOSTER-032 VS US DB)
Amendment number:	Amendment 3 Final
Amendment date:	15 July 2022
	Amendment 2 Final: 18 April 2022
	Amendment 1 Final: 17 May 2021
Protocol Approved	Final: 31 July 2020

Previous Amendments Summary of Changes table:

Amendment or update no	Date	Amendment or update	Section of study protocol	Reason
2	18 April 2022	Modified end of data collection from Q1 2024 to Q4 2024. Added clarification regarding continuous enrollment gap allowance Footnote for gout added to Outcome identification algorithms *Table 3* (column 10) Added clarification to evaluate graphical distribution of RZV and conduct seasonality adjusted analysis Added sensitivity analysis of alternative definition of GCA Updated inferential analyses for the primary outcomes - Censoring events	Refer to Section 6 Section 9.2.2 Section 9.3.2 Section 9.7.6 Section 9.7.6 Section 9.7.6 Section 9.7.7 Section 9.7.8 Section 9.10 Section 9.2.2 Section 9.7.6	Section 6: Data collection updated as Q4 2024 to align with revised timelines for obtaining the report for GCA/SVT/ION. Section 9.2.2: Study inclusion / exclusion criteria updated to clarify the operational definition of continuous enrollment Sections 9.3.2, 9.7.6, 9.7.7: To clarify the analytical approach for the sensitivity HOI definitions for gout, GCA and ION as defined in Table 3 (column 10). Section 9.7.6: To clarify the seasonality adjusted SCRI analysis for gout and GBS

Amendment or update no	Date	Amendment or update	Section of study protocol	Reason
		Added sensitivity analysis of alternative definition of ION Added sensitivity analysis to evaluate the impact of COVID-19 Updated Other aspects Posting of information on publicly available clinical trial registers and publication policy		Section 9.7.6: To clarify the end of study period censoring event Section 9.7.8: Amended in response to CBER's request to evaluate the impact of the COVID-19 pandemic due to the concern that people may change their health seeking behavior due to COVID-19 and associated pandemic lock-down measures. Section 9.10: To align with policies and regulations regarding disclosure activities.
1	17 May 2021	Exposure measure Covariates Potential confounding variables and effect modifiers Descriptive analyses Inferential analyses for the primary outcomes Statistical models	Refer to Section 9.3.1 Section 9.3.3 Section 9.3.4 Section 9.7.4 Section 9.7.6 Section 9.7.8	Regulatory feedback

Detailed description of the current Protocol Amendment 3:

PASS Information

Contributing authors:	PPD

Section 3 Responsible Parties

Study Teams:	Core UMB study team members: PPD

Section 9.2.2 Study population

The study population will be comprised of all US Medicare beneficiaries who received the RZV vaccine (i.e., exposed) in 2018 through 2020 as well as a random sample of Medicare beneficiaries who did not receive the RZV vaccine but who had at least one preventive care visit ***(i.e., comparator group)***, as defined in Section 9.7.5.

Study inclusion / exclusion criteria

3. Continuous ***enrollment*** ~~eligibility~~ is determined by Medicare enrollment in the month of the RZV vaccination or preventative care visit and ***enrollment*** in at least 11 of the 12 preceding months.

The requirement for continuous enrollment in Medicare Parts A, B, and D in the 365 days***, allowing one calendar month gap,*** before the RZV vaccination or preventive care visit will ensure complete data on all services covered by Medicare

9.4.1 Description of the database

Master Beneficiary Summary File (MBSF): The information in this dataset relevant to this study includes beneficiary enrollment ***each calendar month*** in Medicare Parts A, B, and D. This file will be used to obtain information on the baseline study variables, including original and current enrollment reason, eligibility, and demographic characteristics.

Section 9.7.3 ~~Subject~~ *Participant* Disposition

~~Subject~~ ***Participant*** disposition will be summarized for the overall study population and for the RZV vaccinated and RZV unvaccinated comparators with a preventive health visit by computing:

- Not continuously enrolled in Medicare Parts A, B, and D for 365 days***, allowing one calendar month gap,*** preceding the index date

Section 9.7.5 Analysis Population

Population for the Cohort Design Analysis

To ensure complete data for the baseline period preceding cohort follow-up, individuals must be continuously enrolled in Medicare Parts A, B, and D for a minimum of 365 days preceding the preventive care visit***. Continuous enrollment is determined by Medicare enrollment in the month of the preventative care visit and enrollment in at least 11 of the 12 preceding months.***

Section 9.7.6 Inferential analyses for the primary outcomes

Analysis of the SCRI Design

Additional inclusion requirements for the SCRI design analyses for new onset (i.e., incidence) primary HOIs GBS and gout include:

3. ~~Parts A, B, and D enrollment 365 days prior to the HOI;~~ ***Continuously enrolled in Medicare Parts A, B, and D fee-for-service for at least 365 days preceding the date of RZV vaccination. Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination and enrollment in at least 11 of the 12 preceding months.***

4. ***Continuous*** enrollment in Parts A and B (and in the case of gout Part D to capture gout-specific medication) through the end of the respective control interval.

Analysis of the Cohort Design

Additional inclusion requirements for the cohort design analyses for new onset (i.e., incidence) primary HOIs PMR and GCA include:

3. At least 365 days (1 year) of Parts A, B, and D ***continuous*** enrollment prior to the index date. ***Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination or preventative care visit and enrollment in at least 11 of the 12 preceding months.***

Annex 6 Protocol Amendment 3 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	209696 (EPI-ZOSTER-032 VS US DB)
Date of protocol amendment	Amendment 3 Final, 15 July 2022
Title	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States.
Sponsor signatory	Agnes Mwakingwe-Omari, Clinical and Epidemiology Project Lead, GSK Vaccines
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

Annex 7 Protocol Amendment 3 Pharmacovigilance Signatory Approval

eTrack study number and Abbreviated Title	209696 (EPI-ZOSTER-032 VS US DB)
Date of protocol	Amendment 3 Final: 15 July 2022
Title	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States.
QPPV signatory	PPD PPD Clinical Safety and Pharmacovigilance, GSK
Signature	_____
Date	_____

Note: In order to comply with the pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) must be involved in the review, content approval and sign off (in addition to sponsor signatory) of Post-Authorization Safety studies (PASS) protocols (GVP Module 1). This also applies to Targeted Safety Study (TSS) protocols.

Annex 8 Protocol Amendment 3 Investigator Agreement

I agree:

- **To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.**
- **To assume responsibility for the proper conduct of the study at this site.**
- **That I am aware of, and will comply with, ENCePP guide for methodological standards in pharmacoepidemiology, the International Society of Pharmacoepidemiology guidelines for good pharmacoepidemiology practices, and all applicable regulatory requirements.**
- **To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.**
- **To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.**
- **To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions and to implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.**
- **To have control of all essential documents and records generated under my responsibility before, during, and after the study**
- **That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.**

Hence I:

- **Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).**
- **Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.**
- **Agree that GSK may disclose any information it has about such ownership interests and financial ties to regulatory authorities.**
- **Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.**

eTrack study number and Abbreviated Title	209696 (EPI-ZOSTER-032 VS US DB)
Date of protocol amendment	Amendment 3 Final, 15 July 2022
Title	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States.
Investigator name	Susan dos Reis, University of Maryland, Baltimore
Signature	
Date	

Annex 9 ENCePP Checklist for study protocols

Section 1: Milestones			Yes	No	N/A	Section Number
1.1	Does the protocol specify timelines for					
	1.1.1	Start of data collection[1]	☒	☐	☐	6
	1.1.2	End of data collection[2]	☒	☐	☐	6
	1.1.3	Progress report(s)	☐	☐	☒	
	1.1.4	Interim report(s)	☐	☐	☒	
	1.1.5	Registration in the EU PAS Register®	☒	☐	☐	
	1.1.6	Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question			Yes	No	N/A	Section Number
2.1	Does the formulation of the research question and objectives clearly explain:					
	2.1.1	Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
	2.1.2	The objective(s) of the study?	☒	☐	☐	8
	2.1.3	The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	9.2
	2.1.4	Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	9.7.1
	2.1.5	If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.8
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.8
3.5	Does the protocol describe the approach for the collection and reporting of AEs/adverse reactions? (e.g. AEs that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations			**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?		☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:					
	4.2.1	Study time period	☒	☐	☐	9.4.3
	4.2.2	Age and sex	☒	☐	☐	9.2.2
	4.2.3	Country of origin	☒	☐	☐	9.2.2
	4.2.4	Disease/indication	☒	☐	☐	9.2.2
	4.2.5	Duration of follow-up	☒	☐	☐	9.4.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)		☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorized according to time windows?	☐	☒	☐	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.7.5

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3.4 9.7.10
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.7.5
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.4.2 9.3.1 9.3.2 9.7.6

Comments:

Section 8: Effect measure modification		Yes	No	N/A	Section Number
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources			Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:					
	9.1.1	Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3
	9.1.2	Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
	9.1.3	Covariates and other characteristics?	☒	☐	☐	9.3
9.2	Does the protocol describe the information available from the data source(s) on:					
	9.2.1	Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4.1
	9.2.2	Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4.1

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.2.3	Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4.1
9.3	Is a coding system described for:				
9.3.1	Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
9.3.2	Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3	Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4.1

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.8
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7.4
10.4	Are stratified analyses included?	☐	☐	☒	
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.10
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	9.7.6

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2	Are methods of quality assurance described?	☒	☐	☐	9.8 9.10
11.3	Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☒	☐	☐	9.9
	12.1.2 Information bias?	☒	☐	☐	
	12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2	Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9

Comments:

Section 13: Ethical/data protection issues		**Yes**	**No**	**N/A**	**Section Number**
13.1	Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2	Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3	Have data protection requirements been described?	☒	☐	☐	9.6 10

Comments:

Section 14: Amendments and deviations		**Yes**	**No**	**N/A**	**Section Number**
14.1	Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Section Number**
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	9.4
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	9.4

Comments:

Name of the main author of the protocol: PPD PhD, Professor, University of Maryland, Baltimore

Date: / /

Signature: _____

Note: The Sponsor confirms his/her agreement with the completed ENCePP checklist by signing the Protocol Sponsor Signatory Approval page.

Signature Page for 209696 TMF-14833531 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 20-Jul-2022 18:26:57 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 22-Jul-2022 20:38:05 GMT+0000

Signature Page for TMF-14833531 v1.0