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TITLE PAGE

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Title: Effectiveness of Adjuvanted Recombinant Zoster Vaccine (RZV) against Postherpetic Neuralgia (PHN) and against Cardiovascular Disease (CVD) events after Herpes Zoster (HZ) in United States adults in Medicare Fee-for-Service (FFS) + Inovalon's MORE² Registry®

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STUDY INFORMATION

Title	Effectiveness of Adjuvanted Recombinant Zoster Vaccine (RZV) against Postherpetic Neuralgia (PHN) and against Cardiovascular Disease (CVD) events after Herpes Zoster (HZ) in United States adults in Medicare Fee-for-Service (FFS) + Inovalon's MORE ² Registry
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Procedure number	Not yet assigned
Marketing authorisation holder(s)	GlaxoSmithKline Biologicals SA. Rue de l'Institut, 89 1330 Rixensart, Belgium
Research question and objectives	The study will evaluate the effectiveness of 2 dose RZV against PHN and CVD events following HZ among adults ≥ 50 years using the 100% Medicare FFS and MORE ² Registry® databases. Vaccinated participants will be compared with RZV unvaccinated comparators.
Country(-ies) of study	United States
Author	PPD Global Epidemiology, GSK

MARKETING AUTHORISATION HOLDER(S)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
aHR	Adjusted hazard ratio
AMI	Acute myocardial infarction
AID	Autoimmune disease
aRR	Adjusted relative risk
CI	Confidence interval
CIF	Cumulative incidence function
CKD	Chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary disease
CPT	Current Procedural Terminology
CVD	Cardiovascular disease
DCI	Deyo-Charlson comorbidity index
DME	Durable medical equipment
DUA	Data use agreement
ED	Emergency department
FDA	Food and Drug Administration
FFS	Fee-for-Service
GSK	GlaxoSmithKline
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome

Abbreviation	Definition
HR	Hazard ratio
HZ	Herpes zoster
HZO	Herpes zoster ophthalmicus
IC	Immunocompromised
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICMJE	International Committee of Medical Journal Editors
IHD	Individual human data
IPCW	Inverse probability of censor weighting
IPTW	Inverse probability of treatment weighting
IRB	Institutional Review Board
KPSC	Kaiser Permanente Southern California
MACE	Major adverse cardiovascular events
MBSF	Master Beneficiary Summary File
NDC	National drug code
PDE	Prescription drug event
PHN	Postherpetic neuralgia
PPV	Positive predictive value
PY	Person-years
RCT	Randomized controlled trial
RZV	Recombinant zoster vaccine
SMD	Standardized mean differences
SNF	Skilled nursing facility
TIA	Transient ischemic attack

Abbreviation	Definition
U.S.	United States
VE	Vaccine effectiveness
VSD	Vaccine Safety Datalink
VZV	Varicella zoster virus
YOA	Years of age
ZVL	Live-attenuated zoster vaccine

TRADEMARK INFORMATION

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Shingrix	SAS
	Windows
	Zostavax

1. RESPONSIBLE PARTIES

This study will be operationalized by Inovalon on behalf of GSK.

1.1. Sponsor Signatory

Title: Effectiveness of Adjuvanted Recombinant Zoster Vaccine (RZV) against Postherpetic Neuralgia (PHN) and against Cardiovascular Disease (CVD) events after Herpes Zoster (HZ) in United States adults in Medicare Fee-for-Service (FFS) + Inovalon's MORE² Registry®

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Note: Not applicable if an eSignature process is used to get the sponsor approval.

2. SYNOPSIS

Title

Effectiveness of Adjuvanted Recombinant Zoster Vaccine (RZV) against Postherpetic Neuralgia (PHN) and against Cardiovascular Disease (CVD) events after Herpes Zoster (HZ) in United States adults in Medicare Fee-for-Service (FFS) + Inovalon's MORE² Registry®

Rationale and background

Herpes zoster (HZ) results from reactivation of latent varicella zoster virus and is common among older adults, leading to complications such as postherpetic neuralgia (PHN) and increased risk of cardiovascular (CVD) events. Pre-licensure trials of adjuvanted recombinant zoster vaccine (RZV) showed high efficacy against PHN, but existing post-licensure evidence on durability by year since vaccination is limited, and few studies have evaluated CVD event outcomes using standardized major adverse cardiovascular event (MACE) definitions. Additional real-world evidence is needed to assess long-term RZV effectiveness against PHN and CVD complications in adults ≥ 50 years using large, nationally representative U.S. data sources. Due to the high efficacy of RZV and relatively rare incidence of HZ complications such as PHN and CVD events after HZ, a retrospective observational study is the best opportunity to generate this data, with 100% of the Medicare FFS and MORE² Registry® databases being particularly fit for purpose.

Research question and Objective(s)

The study will evaluate the effectiveness of RZV against PHN and CVD events following HZ among adults ≥ 50 years using 100% of the Medicare FFS and MORE² Registry® databases. Vaccinated participants will be compared with RZV-unvaccinated comparators. Primary objectives focus on adults ≥ 50 years, while secondary objectives will include adults ≥ 18 years with immunocompromising or autoimmune conditions (IC/AID).

Primary Objectives:

- To estimate the VE of 2 doses of RZV (2-6 months apart) in preventing PHN in adults aged ≥ 50 years, overall and by follow-up year since vaccination.
- To estimate the VE of 2 doses of RZV (2-6 months apart) in preventing 3-point MACE (composite of hospitalized acute myocardial infarction [AMI], hospitalized stroke, or cardiovascular death) occurring within 3 months after HZ diagnosis in adults aged ≥ 50 years, overall.

Secondary Objectives: The study will estimate the effectiveness of 2-dose RZV in preventing PHN, other HZ complications (HZO), and HZ hospitalizations in adults ≥ 50 years, and in adults ≥ 18 years with IC/AID. It will also assess 2-dose RZV effectiveness in preventing 3-point MACE and its components across multiple post-HZ diagnosis time windows and all-cause, in adults ≥ 50 years, and in adults ≥ 18 years with IC/AID.

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Study Design

The study will be a retrospective, matched cohort study among adults using 100% of the Medicare FFS data plus the MORE² Registry® of closed claims database at Inovalon from 01 October 2015 to 31 December 2024. The MORE² Registry® database includes individuals with managed Medicaid, Medicare Advantage, or commercial insurance. The results from this study will reflect the entire population of Medicare FFS who meet study criteria, and be representative of all major U.S. healthcare payers.

Population

This is a retrospective matched cohort study based on the 100% Medicare FFS and Inovalon MORE² closed claims databases. The study population will consist of the following cohorts:

- Cohort #1: ≥ 50 years, RZV 2-dose 2-6 months cohort
- Cohort #2: ≥ 18 years IC/AID, RZV 2-dose 1-6 months cohort

Variables

RZV exposure for Cohort #1 will be defined as 2 doses given 2–6 months apart; Cohort #2 will define RZV exposure as 2 doses given 1-6 months apart. Unvaccinated comparators will be patients with a preventive care visit and no prior RZV; individuals may be reclassified as exposed if later vaccinated.

The primary endpoints are PHN and 3-point MACE within 3 months after HZ, defined as the first occurrence of hospitalized AMI, hospitalized stroke, or cardiovascular death after HZ.

Data sources

This study will leverage 100% Medicare FFS data and the MORE² Registry® database at Inovalon.

Study size

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Data analysis

A series of matched, multivariable, and weighted analyses will be conducted to address the research objectives focused on assessing the vaccine effectiveness in preventing new diagnosis of PHN and 3-point MACE after HZ among individuals included in the MORE² Registry® or individuals aged ≥ 65 receiving Medicare FFS benefits.

Milestones

Estimated delivery dates for this study are presented below:

- Start of data analysis: 30 September 2026
- End of data analysis: 31 January 2027
- Final report of study results: 30 June 2027

3. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	14 Aug 2026	Section 4	Updated timelines	Addressing comments following consultation
		Section 5.2, 6, 7.1, 7.4, 7.7	Added possibility results will be aggregated via meta-analysis	
		Section 7.1, 7.3, 7.7	Matching on IC/AID group	
		Section 7.3	Clarified handling of duplicate vaccination records	
		Section 7.3	Clarified HZ event algorithm	
		Section 7.3, 7.4	Change in outcome definition for cardiovascular death, with linkage to Veritas cause of death data	
		Section 7.8	Addition of a pre-specified data quality assessment	

4. MILESTONES

Milestone	Planned date
Start of data analysis	30 September 2026
End of data analysis	31 January 2027
Final report of study results	30 June 2027

5. BACKGROUND AND RATIONALE

5.1. Background

Herpes zoster (HZ), also known as shingles, is caused by reactivation of varicella zoster virus (VZV). Primary infection with VZV usually occurs in childhood resulting in varicella (chicken pox). The virus then remains latent in the dorsal-root or cranial-nerve ganglia until reactivation [Nagel, 2017]. Due to a decline in cell-mediated immunity with age or immunocompromised status, the virus reactivates, causing HZ. HZ starts with a prodromal phase with severe, sharp radicular pain in the affected dermatomes. It then progresses to appear as a painful, pruritic rash along one or more dermatomes. HZ affects at least 1 million people in the United States (U.S.) each year and the lifetime prevalence is approximately 25-33% [Bowsher, 1999; Centers for Disease Control and Prevention (CDC), 2024a; CDC, 2025]. In the U.S., the incidence of HZ overall is 4.5 per 1,000 person-years (PY) and increases with age, with incidence rates ranging from 0.9 per 1,000 PYs in individuals aged <19 years to 12.8 per 1,000 PYs in individuals aged ≥80 years, increasing rapidly after age 50 years [Chen, 2014; Johnson, 2015; Yun, 2016]. Other risk factors for HZ include female sex, geographic ancestry, a family history of HZ, autoimmune and immunocompromising conditions, chronic diseases and comorbidities, and receipt of immunosuppressive therapies [Kawai, 2014; Kawai, 2017; Chen, 2014; Marra, 2020; Steinmann, 2024]. Individuals with immunocompromising conditions (IC) have an increased risk of HZ, with incidence rates ranging from 31 to 96 per 1,000 PYs, depending on the specific IC [Zhang, 2017; Chen, 2014; Sahoo, 2017; Winston, 2018; Bastidas, 2019; Koo, 2014; Pergam, 2011; Habel, 2013; Dagnew, 2019; Arness, 2008]. Similarly, individuals with autoimmune disease (AID) have an increased risk of HZ, with incidence rates ranging from roughly 8-16 per 1,000 PYs, depending on the specific AID [Chen, 2014; Baumrin, 2019].

Among those who develop HZ, the most common HZ complication is postherpetic neuralgia (PHN), a chronic neuropathic pain that persists for more than 90 days after the initial HZ rash onset and on the site where the rash once was. PHN can last for months or years [Harpaz, 2008]. Before the introduction of adjuvanted recombinant zoster vaccine (RZV) vaccination, it was estimated that 5%-20% of those with HZ went on to develop PHN [Klompas, 2011; Fashner, 2011]. The frequency and severity of PHN also increase with age, with PHN occurring in ~11% of people 50 years of age (YOA) who had acute HZ, increasing to ~25% of people aged >80 YOA in recent U.S. estimates (2007-2018) [Thompson, 2021]. Key risk factors for PHN include older age, immunosuppression, smoking, and comorbidities including diabetes mellitus, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) [Forbes, 2016; Wang, 2025].

Other complications of HZ, aside from PHN, include subsequent risk of cardiovascular and cerebrovascular disease. Specific major adverse cardiovascular events (MACE), including myocardial infarction and stroke, are becoming widely recognized as complications of HZ [Gabutti, 2025]. During reactivation of VZV, the virus travels peripherally along the axons to the skin causing HZ. However, the virus can also travel centrally resulting in complications associated with VZV vasculopathy occurring due to direct VZV infection of arteries resulting in arterial inflammation and remodeling [Yawn, 2023; Nagel, 2017]. Beyond clinically overt HZ, VZV-associated vascular involvement has been documented in the absence of preceding clinically diagnosed HZ, indicating that clinically apparent HZ is not required for vascular activity. For example, in one study HZ rash was absent in 37% of VZV-vasculopathy cases (11/30) [Nagel, 2018]. VZV vasculopathy can lead to MACE, specifically cerebrovascular events including stroke (ischemic or hemorrhagic), transient ischemic attacks (TIA), and aneurysms when there is productive VZV infection in cerebral arteries [Nagel, 2014; Yawn, 2023], as well as ischemia and coronary heart disease [Curhan, 2022].

In the U.S., recent estimates of stroke incidence rates are approximately 2 per 1,000 PYs in adults aged 45-64 years and 5-6 per 1,000 PYs in adults aged 65 and older [Madsen, 2020; Koton, 2020]. Recent estimates of myocardial infarction incidence rates from 2019 are approximately 2-3 per 1,000 PYs in adults aged 46-64 years across data sources and 13 per 1,000 PYs in adults aged 65 and older in Medicare Fee-for-Service (FFS) [Moll, 2023]. There is robust epidemiological evidence demonstrating increased risk of MACE events following HZ, including stroke, myocardial infarction and TIA [Kawai, 2025; Curhan, 2022; Patterson, 2019; Wu, 2019; Marra, 2017; Yawn, 2023]. The most recent meta-analysis that investigated the risk of cardiovascular disease (CVD) and stroke following HZ reported relative risks of 1.31 for CVD, 1.12 for coronary heart disease (CHD; includes MI), and 1.18 for stroke; this analysis included 18 studies (12 cohort, 3 self-controlled case series, and 3 case-control studies) [Kawai, 2025]. There is also a differential risk of MACE events depending on the time since HZ and age at the HZ infection. The elevated risk of stroke or myocardial infarction following HZ is highest in the periods immediately following HZ onset but diminishes with time [Patterson, 2019; Lian, 2017; Marra, 2017; Zhang, 2017; Liu, 2016; Erskine, 2017; Yang, 2017]. One meta-analysis investigating the risk of stroke following HZ reported a relative risk of 1.45, 1.32, 1.08, 1.18 and 1.05 within 1 month, 3 months, 6 months, 1 year and more than 1 year after HZ [Lian, 2017]. Additionally, the risk is highest among younger age groups (<40 years) [Wu, 2019; Patterson, 2019; Zhang, 2017; Marra, 2017]. Meta-analyses demonstrate that the relative risk of stroke after HZ is higher in adults <40 YOA compared to adults ≥40 YOA, with relative risk ranging from 2.03 to 2.96 vs. 1.19 to 1.78, respectively among ≥40 YOA [Marra, 2017; Zhang, 2017]. There is also some evidence suggesting a lower risk of stroke in treated (with antivirals) versus untreated HZ [Zhang, 2017; Langan, 2014].

Some studies have shown that herpes zoster ophthalmicus (HZO), which occurs in approximately 10% to 20% of HZ cases, is of particular interest. HZO occurs due to VZV reactivation in the ophthalmic branch of the trigeminal nerve which lies close to the cerebral arteries (affecting the eyes and forehead) and is associated with an increased risk of stroke [Wu, 2019; Zhang, 2017; Langan, 2014].

RZV, a 2-dose subunit zoster vaccine, is indicated in the U.S. for the prevention of HZ in (1) adults ≥ 50 YOA [Food and Drug Administration (FDA), 2017] and (2) adults ≥ 18 YOA who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy [FDA, 2021]. RZV is currently recommended by the Advisory Committee on Immunization Practices (ACIP) for use in adults ≥ 50 YOA [Dooling, 2018] and in immunodeficient or immunosuppressed adults ≥ 19 YOA [Anderson, 2022]. Additionally, live-attenuated zoster vaccine (ZVL; Zostavax, Merck), a 1-dose live attenuated strain of VZV, was FDA approved in 2006 for prevention of HZ in people ≥ 60 YOA [FDA, 2006] and in 2011 for prevention of HZ in people ≥ 50 YOA [FDA, 2011]. Zostavax is no longer available for use in the U.S., as of November 18, 2020 [CDC, 2024b].

Pre-licensure randomized trials showed high RZV efficacy against HZ and against PHN [Cunningham, 2016; Lal, 2015]. RZV demonstrated 97.2% efficacy against HZ in adults aged ≥ 50 years (ZOE-50), as well as 91.3% efficacy against HZ and 88.8% efficacy against PHN in adults aged ≥ 70 years (ZOE-70). One prior vaccine effectiveness (VE) study evaluated RZV in an observational cohort study of Medicare FFS beneficiaries aged >65 years and not in a nursing home, skilled nursing facility, or hospice [Izurieta, 2021]. The study started with the population who met eligibility criteria on 1 November 2017 (shortly after FDA approval of RZV) and included up to 2 years of follow-up (until 20 October 2019). They found RZV 2-dose VE against PHN was 76.0% (95% confidence interval [CI]: 68.4–81.8%). Another study conducted among Kaiser Permanente Southern California (KPSC) adult members ≥ 50 YOA with ≥ 2 years of follow-up found 2-dose RZV VE against PHN was 83.7% (95% CI: 75.1–89.3%) [Tseng, 2025]. The effectiveness was similar across sex and age groups. In analysis by year since vaccination, effectiveness against PHN was durable; VE was 80.8% (95% CI: 50.4–92.6%) at year 1 and 87.2% (95% CI: 67.5–95.0%) at year 4 of follow-up. A third observational cohort study of data from 4 health plans in the Vaccine Safety Datalink (VSD) of adult members ≥ 50 YOA with up to 4 years of follow-up showed overall 2-dose RZV VE against PHN was 87% (95% CI: 83–90%), with a small amount of waning in analyses by year since vaccination [year 1: 91% (95% CI: 86–94%); year 2: 90% (95% CI: 82–94%); years 3 and 4: 77% (95% CI: 66–84%)] [Zerbo, 2025]. While randomized trial data demonstrate high RZV efficacy against PHN and available post-marketing studies also show high RZV effectiveness against PHN in the general population of adults aged ≥ 50 years, these effectiveness findings are limited to 3 studies. Only 2 of these studies have information on RZV effectiveness by year since vaccination, and only up to 4 years post-vaccination, constituting limited information on durability of RZV effectiveness against PHN. Further effectiveness studies against PHN in the general population of adults aged ≥ 50 years are needed to assess 1) the durability of RZV effectiveness of PHN in a larger population and beyond the 4 years currently available and 2) the durability of RZV effectiveness of PHN by age.

Observational studies have shown that immunization against HZ was associated with lower risks of MACE events including myocardial infarction and/or stroke, including events that occur independently of clinically manifested HZ [Helm, 2023; Klaric, 2019; Parameswaran 2023a; Parameswaran, 2023b; Nelson, 2023; Rayens, 2025; Yang, 2020; Yang, 2021; Xu, 2025], with some exceptions [Richardson, 2024]. Of note, most data were obtained from adults immunized with ZVL. To date, six studies have reported a

significantly reduced risk of myocardial infarction and/or stroke following immunization with RZV [Helm, 2023; Parameswaran 2023a; Parameswaran, 2023b; Nelson, 2023; Rayens, 2025; Xu, 2025]. These include 1 cohort study of HZ cases [Xu, 2025], 3 cohort studies of SHINGRIX vaccinated vs. unvaccinated individuals [Helm, 2023; Nelson, 2023; Rayens, 2025], and 2 analyses of VA datasets [Parameswaran 2023a; Parameswaran, 2023b]. A retrospective cohort study of KPSC members ≥ 50 YOA showed a decreased risk of hospitalized acute myocardial infarction (AMI) and stroke in adults who received RZV compared to matched RZV unvaccinated members (adjusted hazard ratio [aHR] of hospitalized AMI: 0.72 [95% CI: 0.59-0.88]; hospitalized stroke: 0.58 [95% CI: 0.53-0.62]) [Rayens, 2025]. A safety cohort study in VSD in 2018-2019 found the risk of AMI was significantly lower for RZV than for well-visit comparators (adjusted relative risk [aRR] of AMI: 0.82 [95% CI: 0.72, 0.94]) [Nelson, 2023]. One cohort study in the U.S. TriNetX database, with smaller of number of RZV-vaccinated adults 50-65 YOA found RZV was associated with a reduced risk of myocardial infarction but not stroke (aRR of myocardial infarction: 0.73 [95% CI: 0.55-0.96]); stroke: 0.97 [0.75-1.26]) [Helm, 2023]. A retrospective cohort study of HZ cases ≥ 50 YOA in US Optum Labs Data Warehouse found RZV was associated with a 21% reduced risk of HZ-associated cardiovascular disease (CVD) events within a year post-HZ (HR: 0.61 [95%CI: 0.43-0.87]), and that the reduced risk was significant for 2-dose RZV, but not significant for 1-dose RZV [Xu, 2025]. Analyses of patients ≥ 18 YOA who received care at a Veteran Affairs facility found a decreased odds of stroke within 30 days in patients who had received either RZV or ZVL, with a stronger effect observed with RZV (odds ratio of RZV 0.57 [95% CI: 0.46–0.72; $p < .001$]; ZVL 0.77 [95% CI: 0.65–0.91; $p = .002$]) and a decreased odds of MI within 30 days in patients who had received RZV (OR: 0.82 [95% CI: 0.74-0.92]); the publications are inconsistent in reporting the design of the study [Parameswaran 2023a; Parameswaran, 2023b]. While these studies found that RZV is associated with reduced risk of MACE events, the specific outcomes assessed in each study and definitions of those outcomes varied across studies. Further studies are needed to evaluate MACE outcomes more closely aligned to those used in randomized trials, such as 3-point MACE outcomes (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death). These prior studies have not had an appropriate design or sufficient CVD events after an HZ episode to provide information on VE against CVD outcomes after an HZ episode, particularly within shorter timeframes after HZ.

5.2. Rationale

Studies have demonstrated similar RZV effectiveness against PHN in adults ≥ 50 YOA and ≥ 65 YOA, but the follow-up time for those studies is short, and there is limited information on effectiveness against PHN by follow-up year since vaccination among ≥ 50 YOA. While prior studies have demonstrated that RZV is associated with reduced risk of CVD outcomes such as hospitalized AMI and hospitalized stroke, they have had the following limitations: 1) they did not assess cardiovascular death thus did not assess 3-point MACE as a composite outcome, 2) they were unable to report VE due to study design or smaller populations with insufficient sample size to assess RZV effectiveness against HZ-associated CVD events, and 3) they had a short duration of follow-up. Specifically, prior RZV studies with smaller populations did not have sufficient sample

size to evaluate CVD outcomes within short timeframes after an HZ episode, to provide information on VE against CVD outcomes after an HZ episode. Due to the high efficacy of RZV and relatively rare incidence of HZ complications such as PHN and CVD events after HZ, a very large retrospective observational study is the best opportunity to generate this data, with 100% of the Medicare FFS and the Medical Outcomes Research for Effectiveness and Economics Registry® (MORE² Registry®) databases being particularly fit for purpose. The 100% Medicare FFS and MORE² Registry® databases were selected for this study as each captures a distinct yet complementary population of adults eligible for RZV vaccination. Both data sources will be utilized to support the analysis, however results will be generated and presented separately for each database, and possibly aggregated via meta-analytic methods if scientifically appropriate (see Section 7.7.2.2.1.). This will preserve the integrity of the population and avoid inappropriate cross-database comparisons. The analyses will include stratification by age group, with a stratification by age ≥ 65 years for the MORE² Registry®, to allow evaluation of VE for the same age group in each database separately. Analyses performed using the MORE² Registry® will include an additional stratification by payer type (Medicare Advantage, managed Medicaid, commercial insurance). This multilevel stratification framework ensures an intensive, rigorous, and highly granular evaluation of VE across heterogeneous populations and coverage types.

Therefore, this study will assess RZV effectiveness against HZ complications, primarily 2-dose RZV (received 2-6 months apart) VE against PHN, and against CVD events after HZ, among individuals age ≥ 50 years enrolled in 100% Medicare FFS or the MORE² Registry® closed claims database at Inovalon.

The strengths of the study design (see Section 7) to address the current evidence gaps include the following:

- With the full population i.e., 100% of Medicare FFS, the study will draw from a total population of approximately 62.5 million unique individuals from all 50 U.S. states in that database alone across the years of the study. The MORE² Registry® database contains data on individuals with managed Medicaid (89% of the market), Medicare Advantage (22% of the market), or other commercial insurance (28% of the market), from all 50 U.S. states. The results from this study will reflect the entire population of Medicare FFS who meet study criteria, and be representative of all major U.S. healthcare payers. See Section 7.4. for additional information regarding these data sources. The results of this study will be generalizable to most U.S. adults with public or private insurance. Use of the full, 100% Medicare FFS database is a major strength of this research based on its comprehensive national coverage and longitudinal depth, which enables robust population-level analyses. The databases include detailed claims for all enrolled beneficiaries, allowing for complete capture of healthcare utilization, diagnoses, procedures, and prescription fills across diverse care settings. This breadth supports high statistical power and generalizability to the older U.S. adult population. Additionally, the ability to track individuals over time facilitates temporal analyses of exposures and outcomes while minimizing selection bias.

- The study design follows a conceptual approach from methods used in causal inference that address confounding and other sources of bias to generate robust estimates of RZV effectiveness against PHN, and against CVD events after HZ.
 - The study design to estimate 2-dose RZV (received 2-6 months apart) VE reflects some key aspects of the analyses of the modified vaccinated cohort who received 2 doses of RZV vs. placebo in the RZV clinical trials [Cunningham, 2016; Lal, 2015]. Specifically, the study design assigns the index date at receipt of dose 2 at the recommended interval after dose 1, and start of follow-up 30 days after dose 2 (see Section 7.1). This induction period of 30 days is included as 1) less than 30 days after vaccination (for RZV vaccinated individuals) is not long enough to allow full development of immunity and 2) HZ cases diagnosed less than 30 days after the index date may have truly began before the index date. Start of follow-up 30 days after RZV is commonly implemented across RZV effectiveness studies [Izurietta, 2021; Tseng, 2025; Zerbo, 2025]. To deal with potential confounding differences between RZV vaccinees and preventive-care-visit seekers (e.g., age, sex, certain chronic conditions, calendar time, etc.) and to address potential informative censoring, a marginal structural model [Robins, 2000] will be used (described in Section 7.7.1 below).
 - Currently, some studies of RZV vaccination have not implemented a concurrent comparator arm. The comparators in some previously published studies have been unvaccinated participants. Since Shingrix is a routine preventive vaccine, it follows that comparators drawn from those who are RZV unvaccinated at the time of a routine preventive care visit would be appropriate and would aid in mitigating healthy user bias. Therefore, this study will evaluate effectiveness among individuals who received 2-dose RZV (received 2-6 months apart) relative to comparators who had a preventive care visit, but did not receive the RZV vaccine (see Section 7.3.1).

6. RESEARCH QUESTION AND OBJECTIVE(S)

The study will assess RZV effectiveness against HZ complications, primarily 2-dose RZV (received 2-6 months apart) VE against PHN (outcome definition: PHN 90-180 days after HZ diagnosis; see Section 7.3.2.1), and against CVD events after HZ, among individuals age ≥ 50 years present in the 100% Medicare FFS or the MORE² Registry® closed claims database at Inovalon. Both databases will be utilized to support the analysis, however results will be generated and presented separately for each database, and possibly aggregated via meta-analytic methods if scientifically appropriate (see Section 7.7.2.2.1.).

The study will compare those who received RZV (“vaccinated”) to RZV unvaccinated comparators with a preventive care visit (“RZV unvaccinated comparators”), addressing the objectives below. While most objectives are among the population ≥ 50 YOA, the study will include individuals ≥ 18 YOA to address secondary objectives among adults ≥ 18 YOA with immunocompromise or autoimmune diseases (IC/AID; 18-49 YOA with IC/AID, plus a subpopulation of individuals ≥ 50 YOA that are ≥ 50 YOA with IC/AID). Objectives refer to 2 doses of RZV given 2 months to 6 months apart, except where noted (Secondary objectives to evaluate doses given 1 to 6 months apart in IC/AID cohort).

Where analyses by age groups are noted, age groups for the ≥ 50 YOA population will include 50-59, 60-69, 70-79, ≥ 80 years; analyses will also include an age grouping of all 50-64 and ≥ 65 years for each database, for comparison of results between databases as the study will only include Medicare FFS beneficiaries whose original reason for entitlement to Medicare is old age and survivor's insurance (Medicare enrollment is typically at age 65 years). Age groups for the ≥ 18 YOA with IC/AID population will include 18-49 and ≥ 50 years. Additional information on stratifications for each objective is available in Section 7.7.

6.1. PHN Objectives

The PHN objectives mostly evaluate PHN as the outcome of interest. Where noted, objectives will also assess other complications of HZ that occur during HZ events (HZ-associated hospitalizations, HZO).

6.1.1. PHN Primary Objective

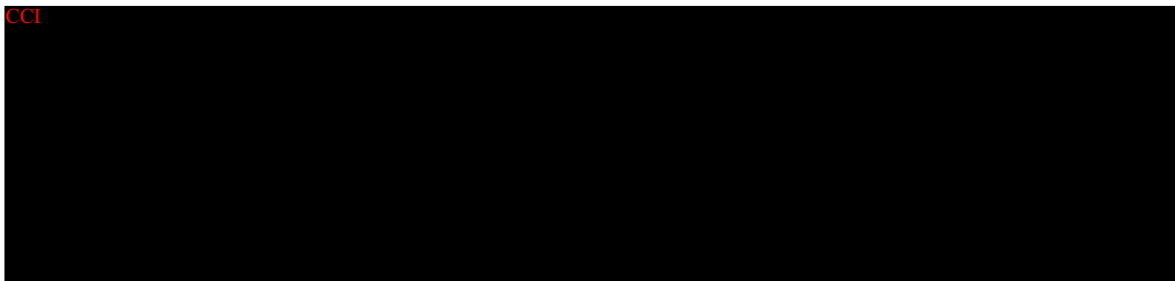
1. To estimate the VE of 2 doses of RZV (2-6 months apart) in preventing PHN in adults aged ≥ 50 years, overall and by follow-up year since vaccination.

6.1.2. PHN Secondary Objectives

Analyses for the following objectives will be conducted if there is sufficient sample size:

1. To estimate the VE of 2 doses of RZV (2-6 months apart) in preventing PHN in adults aged ≥ 50 years in stratified analyses (by age group, by follow-up year since vaccination within age groups, by payer type).
2. To estimate the VE of 2 doses of RZV (2-6 months apart) in preventing other HZ complications (HZO) and HZ-associated hospitalizations in adults aged ≥ 50 years, overall and in stratified analyses (by age group, by follow-up year since vaccination, by payer type).
3. To estimate the VE of 2 doses of RZV (1-6 months apart) in preventing PHN in adults aged ≥ 18 years with IC/AID, overall and in stratified analyses (by follow-up year since vaccination and within age groups, by payer type).

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6.2. CVD events after HZ Objectives

For CVD events after HZ, most objectives will assess 3-point MACE defined as 1) hospitalized AMI, 2) hospitalized stroke, or 3) cardiovascular death, after HZ. The objectives will primarily focus on 3-point MACE as a **composite**. Where noted, objectives will assess **3-point MACE components separately** after HZ, **all-cause MACE** (not limited to MACE occurring after HZ), and other CVD event outcomes (TIA) after HZ.

6.2.1. CVD events after HZ Primary Objective

1. To estimate the VE of 2 doses of RZV (2-6 months apart) in preventing 3-point MACE (composite of hospitalized AMI, hospitalized stroke, or cardiovascular death) occurring within 3 months after HZ diagnosis in adults aged ≥ 50 years, overall.

6.2.2. CVD events after HZ Secondary Objectives

Analyses for the following objectives will be conducted if there is sufficient sample size:

1. To estimate the VE of 2 doses of RZV (2-6 months apart) in preventing 3-point MACE (composite of hospitalized AMI, hospitalized stroke, cardiovascular death) occurring within 3 months after HZ diagnosis in adults aged ≥ 50 years, in stratified analyses (by age group, by selected comorbidities [see Section 7.7.3], by payer type).
2. To estimate the VE of 2 doses of RZV (2-6 months apart) in preventing 3-point MACE components: hospitalized AMI, hospitalized stroke, cardiovascular death, each separately occurring within 3 months after HZ diagnosis in adults aged ≥ 50 years, overall and in stratified analyses (by age group, by selected comorbidities [see Section 7.7.3], by payer type).
3. To estimate the VE of 2 doses of RZV (1-6 months apart) in preventing MACE composite and component outcomes (hospitalized AMI, hospitalized stroke, cardiovascular death) occurring within 3 months, 6 months, 1 year after HZ diagnosis, in adults ≥ 18 years with IC/AID, overall and in stratified analyses (by age group, by payer type).
4. To estimate the VE of 2 doses of RZV (2-6 months apart) in preventing MACE composite and component outcomes (hospitalized AMI, hospitalized stroke, cardiovascular death) occurring within different time periods (6 months, 1 year) after HZ diagnosis in adults aged ≥ 50 years overall and in stratified analyses (by age group, by payer type).
5. Assess association between 2 doses of RZV (2-6 months apart) and risk of all-cause MACE outcomes (all-cause hospitalized AMI, all-cause hospitalized stroke, all-cause cardiovascular death) in adults aged ≥ 50 years overall and in stratified analyses (by age group, by payer type).

CCI

6.3. Estimands for primary objectives

Estimand for PHN primary objective

Component	Description
Population	Eligible adults in 100% Medicare FFS and in MORE² Registry® between 01 January 2018 and 31 December 2024
Treatment(s)	- Vaccinated: RZV exposed individuals who completed 2-dose RZV, 2-6 months apart. Index date is defined as the date of RZV dose 2 - Unvaccinated comparators: RZV unexposed individuals, with no RZV before the index date and with a preventive care visit matched within 90 days - The index date will be set to the second RZV claim for RZV exposed or the preventive care visit for the RZV unexposed comparator. - The treatment comparison evaluates the effect of being RZV 2-dose vaccinated versus remaining RZV unvaccinated at the same time point
Endpoint	- Occurrence of PHN persisting 90-180 days after an incident HZ event during follow-up - PHN will be defined according to the protocol-specified algorithm using claims data from 100% Medicare FFS and MORE² Registry®
Strategy for Intercurrent events (ICE)	- Post-index RZV initiation among unvaccinated comparators will be treated as deviation - These individuals will be censored at time of vaccination - Other events include (1) end of the study period, (2) date of end of coverage, (3) date of death (for the main Cox model when death is treated as a competing risk), (4) date of ZVL, (5) date of third RZV vaccination for RZV vaccinated, or (6) PHN event date.
Summary Measure	- Marginal hazard ratio for PHN comparing 2-dose vaccinated with the unvaccinated comparators - The estimand will be estimated using a weighted Cox marginal structural model - IPTW will be used to adjust for measured baseline confounding at index date - IPCW will be used to account for informative censoring arising during follow-up - Time-to-event will be measured from index date until the earliest occurrence of PHN, censoring of end of follow-up - VE=1-HR

Estimand for CVD events after HZ primary objective

Component	Description
Population	Eligible adults in 100% Medicare FFS and in MORE2 Registry® between 01 January 2018 and 31 December 2024
Treatment(s)	- Vaccinated: RZV exposed individuals who completed 2-dose RZV, 2-6 months apart. Index date is defined as the date of RZV dose 2 - Unvaccinated comparators: RZV unexposed individuals, with no RZV before the index date and with a preventive care visit matched within 90 days - The index date will be set to the second RZV claim for RZV exposed or the preventive care visit for the RZV unvaccinated comparator. - The treatment comparison evaluates the effect of being 2-dose vaccinated versus remaining RZV unvaccinated at the same time point
Endpoint	- Occurrence of 3-point MACE (composite) occurring 3 months after an incident HZ event during follow-up 3-point MACE (composite) will be defined according to the protocol-specified algorithm using data from 100% Medicare FFS and MORE2 Registry®
Strategy for Intercurrent events (ICE)	- Post-index RZV initiation among unvaccinated comparators will be treated as deviation - These individuals will be censored at time of vaccination - Other events include (1) end of the study period, (2) date of end of coverage, (3) date of death (when death is treated as a competing risk), (4) date of ZVL, (5) date of third RZV vaccination for RZV vaccinated, or (6) 3-point MACE after HZ
Summary Measure	- Marginal hazard ratio for 3-point MACE after HZ comparing 2-dose vaccinated with the unvaccinated comparators - The estimand will be estimated using a weighted Cox marginal structural model - IPTW will be used to adjust for measured baseline confounding at index date - IPCW will be used to account for informative censoring arising during follow-up - Time-to-event will be measured from index date until the earliest occurrence of CVD, censoring of end of follow-up - VE=1-HR

7. RESEARCH METHODS

7.1. Study Design

The study design will be a retrospective, matched cohort study among adults ≥ 18 YOA using 100% of the Medicare FFS data plus the MORE² Registry® of closed claims database at Inovalon (analyses will be conducted separately for each database) from 01 October 2015 to 31 December 2024. While most objectives are among the population ≥ 50 YOA, the study will include individuals ≥ 18 YOA to address secondary objectives among adults ≥ 18 YOA with IC/AID (18-49 YOA with IC/AID from 20 October 2021, plus a subpopulation of individuals ≥ 50 YOA that are ≥ 50 YOA with IC/AID).

The MORE² Registry® database includes individuals with managed Medicaid, Medicare Advantage, or commercial insurance. The results from this study will reflect the entire population of Medicare FFS who meet study criteria, and be representative of all major U.S. healthcare payers. See Section 7.4 for additional information regarding these data sources. All analyses will be performed separately for each database, and results will be interpreted independently to ensure that conclusions accurately reflect the underlying population of each data source. There is heterogeneity between the 2 databases as they are different populations, they have different health care access, and confounding factors may be different. Results will be generated and presented separately for each database, and possibly aggregated via meta-analytic methods if scientifically appropriate (see Section 7.7.2.2.1.) . This will preserve the integrity of the population and avoid inappropriate cross-database comparisons. The analyses will include stratification by age group, with a stratification by age ≥ 65 years for the MORE2 Registry®, to allow evaluation of VE for the same age group in each database separately. Analyses performed using the MORE2 Registry® will include an additional stratification by payer type (Medicare Advantage, managed Medicaid, commercial insurance). This multilevel stratification framework ensures appropriate evaluation of VE across heterogeneous populations and coverage types.

This will involve constructing the following cohorts, which will be created separately within each database:

- Cohort #1: **‘ ≥ 50 years, RZV 2-dose 2-6 months cohort’** to address the primary objectives and most of the secondary objectives that will include individuals ≥ 50 YOA who received 2 doses of RZV given 2 months to 6 months apart matched to RZV unvaccinated comparators. Adults ≥ 65 YOA from Medicare FFS are a subpopulation of Cohort #1.
- Cohort #2: **‘ ≥ 18 years IC/AID, RZV 2-dose 1-6 months cohort’** to address Secondary objectives #3 that will include individuals ≥ 18 YOA with IC/AID who received 2 doses of RZV given 1 month to 6 months apart matched to RZV unvaccinated comparators

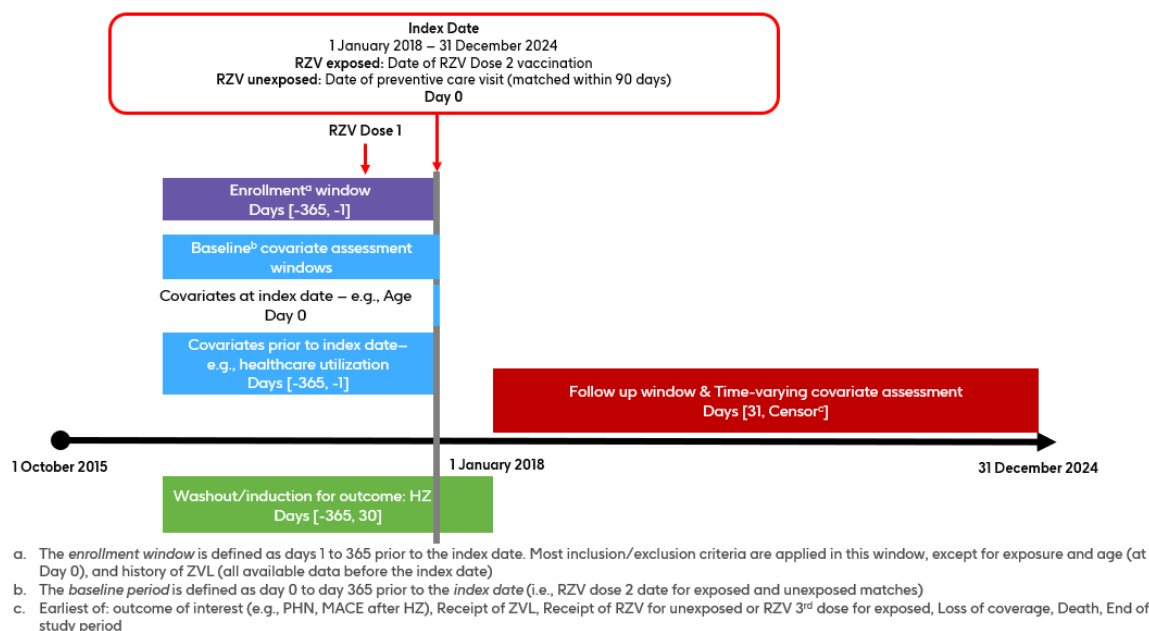
While accrual in the cohorts will start from 01 January 2018 (coinciding with the start of RZV uptake in the U.S.), the study time period extends back to 01 October 2015 to capture all available data on history of ZVL vaccination, as this date marks the federally mandated transition across all U.S. healthcare systems from International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) coding. Additional details of the study design are detailed below.

7.1.1. Cohort #1

Cohort #1: ≥ 50 years, RZV 2-dose 2-6 months cohort (PHN and CVD events after HZ Primary objectives; Secondary objectives 1, 2, 4, 5, and 6; CCI CCI

We will construct a retrospective, matched cohort using 100% Medicare FFS data and the MORE² Registry® of closed claims database at Inovalon from 1 October 2015 to 31 December 2024. The databases will be analyzed separately. The Cohort #1 study design reflects key aspects of the VE analyses for those who received 2 doses of RZV vs. placebo in the RZV clinical trials [Cunningham, 2016; Lal, 2015]. The study design overview is shown in Figure 1.

Figure 1. Study Schematic



The main study cohort will include adults ≥ 50 YOA, with adults from ≥ 50 YOA from the MORE² database and adults from ≥ 65 YOA from Medicare FFS; adults ≥ 65 YOA from Medicare FFS are a subpopulation of Cohort #1. The populations of interest are people who received RZV, compared to people who did not receive RZV but did have a preventive care visit in a ± 90 -day window of the RZV dose 2 date. RZV exposure will be defined as receipt of 2 doses of RZV, with 2–6-month (i.e., 60-183 days) dose spacing per U.S. label dose schedule, with a procedure code and/or National Drug Code (NDC)

for the second dose of RZV occurring any time between 01 January 2018 and 31 December 2024.

The RZV unexposed *comparator group* will be selected from individuals with a preventive care visit (see Section 7.3.1) who have not received RZV prior to or on the preventive care visit date. The comparators will be matched to the RZV exposed on age (e.g., within two-year bands), sex, race/ethnicity, payer, and IC/AID group. Using time-based exposure sets, an eligible age, sex, race/ethnicity, payer, and IC/AID group-matched comparator will be selected within 90-day calendar intervals of the RZV exposed index date to be matched 1:1 to every RZV exposed individual, without replacement. If more than 1 comparator has an eligible preventive care visit within the 90-day interval, the comparator whose preventive care visit date is closest to the matched RZV exposed participant's index date will be selected. The use of a comparator group with preventive visit (i.e., a comparator group that is observed during the same period of time as the RZV exposed group) as opposed to a historical preventive-care visit comparator group avoids potential confounding related to time (e.g., changes in health outcome of interest coding practices over time).

The *index date* will be defined as the date of receipt of RZV dose 2 for exposed participants and the preventive care visit date for the RZV unvaccinated comparator. The index date will be denoted as day 0 and does not contribute to the follow-up period.

The *enrollment window* will be continuous enrollment in the 1-year prior to the index date. All participants must be continuously enrolled in medical and pharmacy benefits for at least 365 days preceding the index date to be included in the analytic cohort [Medicare FFS: enrollment in Parts A, B, and D (allowing a 1 month gap in enrollment); MORE²: enrollment in medical and pharmacy benefits (allowing up to 30-day administrative gaps in coverage)]. This window will be used to evaluate most inclusion/exclusion criteria, the exceptions are exposure and age (at Day 0), and history of ZVL (all available data before the index date dating back to 01 October 2015). See Section 7.2.1 for the full inclusion and exclusion criteria.

The *baseline period* and *baseline covariate assessment window* will be day 0 to day 365 prior to the index date. The baseline covariates will be assessed either in the 1-year pre-index period (days 1 to 365 prior to the index date) or on the index date (day 0). Participant demographics (see Section 7.3.3) will be assessed on the index date. Clinical characteristics, health status/medical comorbidities, and risk factors for the outcome (see Section 7.3.3) will be examined during the 1-year pre-index period.

The study will also include a *washout/induction period* for the HZ outcome, and exclude any individual with HZ any time in the 12 months prior (washout period) to 30 days after (induction period) the index date. The *start of follow-up* begins when individuals will be at risk for the outcome, thus it will commence at day 31. This induction period is included as 1) less than 30 days after vaccination (for RZV vaccinated individuals) is not long enough to allow full development of immunity and 2) HZ cases diagnosed less than 30 days after the index date may have truly begun before the index date. This design, with the index date at receipt of dose 2 at the recommended interval after dose 1, and start of follow-up 30 days after dose 2, reflects key aspects of the VE analyses in the Phase 3

randomized controlled trials (RCTs) for RZV [Cunningham, 2016; Lal, 2015]; additionally, start of follow-up 30 days after RZV is commonly implemented across RZV effectiveness studies [Izurieta, 2021; Tseng, 2025; Zerbo, 2025].

The variable-length follow-up period will continue until the earliest of the outcome of interest (analysis specific) or a censoring event: receipt of ZVL, receipt of an RZV dose (RZV unexposed: a first dose; RZV exposed: a third dose), end of coverage (Medicare FFS: end of Medicare coverage or enrollment into Part C; MORE²: disenrollment from MORE² database), death, or the *end of the study period* on 31 December 2024. Note: for certain outcomes participants will be censored ahead of the end of the study period to ensure the capacity to fully observe the outcome among cohorts. For instance, for the PHN analysis the censoring date will be shifted 180 days prior to 31 December 2024 to ensure the capacity to fully observe subsequent PHN diagnosis after the start of an HZ episode among cohorts.

To deal with potential confounding differences between RZV vaccinees and preventive-care-visit seekers (e.g., age, sex, certain chronic conditions, calendar time, etc.) and to address potential informative censoring, a marginal structural model [Robins, 2000] will be used (described in Section 7.7.1 below).

7.1.2. Cohort #2

Cohort #2: **≥18 years IC/AID, RZV 2-dose 1-6 months cohort (Secondary objectives #3):**

For both PHN and CVD events after HZ secondary objectives #3, a separate retrospective matched cohort consisting of adults ≥18 YOA with IC/AID will be constructed. RZV exposure will be defined as receipt of 2 doses of RZV, with 1–6-month (i.e., 30-183 days) dose spacing per U.S. label dose schedule in this population. Individuals aged 18-49 years on their index date will only be included starting from 20 October 2021. Other aspects of the study design will be the same as described above.

7.2. Study Population and Setting

The study population will be selected from adults enrolled in 100% Medicare FFS and adults enrolled in MORE² (see Section 7.4). Starting on 01 January 2018, the cohorts will accrue commercially insured, managed Medicaid, Medicare Advantage, and Medicare FFS beneficiaries in the U.S. who are ≥18 YOA with IC/AID or ≥50 YOA (depending on the objective) at their index date (i.e., RZV vaccination date for RZV recipients or preventive visit date as index date for RZV unvaccinated comparators; see Section 7.3.1). The 365-day period prior to the index date will define the enrollment window. All analyses will be conducted separately by database in MORE² and Medicare FFS populations and possibly aggregated via meta-analytic methods if scientifically appropriate (see Section 7.7.2.1.).

This is a retrospective matched cohort study based on the 100% Medicare FFS and Inovalon MORE² closed claims databases. The study population will consist of the following cohorts:

- Cohort #1: ≥ 50 years, RZV 2-dose 2-6 months cohort
- Cohort #2: ≥ 18 years IC/AID, RZV 2-dose 1-6 months cohort (Secondary objectives #3)

These cohorts are described below.

7.2.1. Eligibility Criteria

See inclusion and exclusion criteria.

7.2.1.1. Inclusion Criteria

7.2.1.1.1. Cohort #1 - ≥ 50 years, RZV 2-dose 2-6 months cohort

An older adult cohort of all individuals in the Medicare FFS and MORE² databases who received RZV vaccination in the study period based on age (≥ 50 years) and as recommended i.e., 2 doses 2-6 months apart, 1:1 matched to an RZV unvaccinated comparator. Adults ≥ 65 YOA from Medicare FFS are a subpopulation of Cohort #1.

To be eligible for inclusion in cohort #1, a participant must meet all the following criteria:

- Receipt of 2 doses of RZV, 2-6 months apart for the RZV exposed group and at least one preventive care visit with no prior RZV for the RZV unvaccinated comparator.
 - *The index date will be set to the second claim for RZV exposed or the preventive care visit for the RZV unvaccinated comparator.*
- Age ≥ 50 years on the index date.
- Continuously enrolled with medical and pharmacy benefits for at least 365 days preceding the index date.
 - Medicare FFS databases: enrolled in Medicare Part A (hospitalization), B (office-based care) and Part D (prescription drug coverage). Continuous enrollment is determined by enrollment in the month of the index date and enrollment in at least 11 of the 12 preceding months, i.e., allowing a maximum of one calendar month gap in enrollment.
 - MORE²: Commercial insurance, Medicare Advantage, or Medicaid. Continuous enrollment is determined by no more than 30-day administrative gaps in coverage.
- Continuously enrolled with medical and pharmacy benefits for at least 30 days following the index date.

Note that a participant initially included in the RZV unvaccinated comparator group may later be classified in the RZV exposed group after their qualifying preventive care visit, if they receive RZV vaccination per the definition of the RZV exposed group and meet inclusion criteria.

7.2.1.1.2. Cohort #2 – ≥18 years IC/AID, RZV 2-dose 1-6 months cohort

An adult cohort of individuals in the Medicare FFS and MORE² databases ≥18 years who have an IC/AID and received RZV vaccination in the study period and as recommended i.e., 2 doses 1-6 months apart, 1:1 matched to an RZV unvaccinated comparator. IC/AID will include IC (hematologic malignancies, HIV/AIDS, solid organ transplant, solid tumors, and bone marrow transplant) and AID (inflammatory bowel disease, multiple sclerosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, and systemic lupus erythematosus). See [Annex 2](#) for specific algorithms that will be used to define IC/AID.

To be eligible for inclusion in cohort #2, a participant must meet all the following criteria:

- Receipt of 2 doses of RZV, 1-6 months apart for the RZV exposed group and at least one preventive care visit with no prior RZV for the RZV unvaccinated comparator.
 - *The index date will be set to the second claim for RZV for RZV exposed or the preventive care visit for the RZV unvaccinated comparator.*
- Age ≥18 years on the index date; Age 18-49 years on index date will only be included starting from 20 October 2021.
- Continuously enrolled with medical and pharmacy benefits for at least 365 days preceding the index date.
 - Medicare FFS databases: enrolled in Medicare Part A (hospitalization), B (office-based care) and Part D (prescription drug coverage). Continuous enrollment is determined by enrollment in the month of the index date and enrollment in at least 11 of the 12 preceding months, i.e., allowing a maximum of one calendar month gap in enrollment.
 - MORE²: Commercial insurance, Medicare Advantage, or Medicaid. Continuous enrollment is determined by no more than 30-day administrative gaps in coverage.
- Evidence of IC/AID during the 12-month baseline period preceding the index date:
 - IC includes hematologic malignancy, HIV/AIDS, solid organ transplant, solid tumor, and bone marrow transplant. AID includes inflammatory bowel disease, multiple sclerosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, and systemic lupus erythematosus. See [Annex 2](#) for specific algorithms that will be used to define IC/AID.
- Continuously enrolled with medical and pharmacy benefits for at least 30 days following the index date.

Note that a participant initially included in the RZV unvaccinated comparator group may later be classified in the RZV exposed group after their qualifying preventive care visit, if they receive RZV vaccination per the definition of the RZV exposed group and meet inclusion criteria.

7.2.1.2. Exclusion Criteria

The following exclusion criteria apply to all cohorts. An individual who meets any of the following criteria will be excluded from this study:

- History of ZVL any time prior to the index date (not limited to 1 year prior to the index date).
- HZ diagnosis in inpatient, emergency department (ED), or outpatient setting in the 1 year (365 days) prior to the index date or in the 30 days after index date.
- In a skilled nursing facility or on hospice in the 1 year (365 days) prior to or on the index date.
- Medicare FFS database: Original reason for entitlement to Medicare is based on disability insurance benefit, end-stage renal disease, or disability benefit and end-stage renal disease.

Note that for each analysis, individuals presenting evidence of the outcome of interest in the 1 year (365 days) prior to the index date or in the 30 days after index date will be excluded from that analysis.

7.3. Variables

7.3.1. Exposure definitions

For Cohort #1 **RZV vaccinated** will be defined as exposure to 2 doses of RZV received 2-6 months apart; this is the treatment strategy of interest for the primary and most secondary objectives.

For Cohort #2, addressing both Secondary Objectives #3, RZV vaccinated will be defined as exposure to two doses of RZV received 1-6 months apart.

RZV vaccination will be identified by means of the NDC and by the Current Procedural Terminology (CPT) code. The NDCs that will be used to identify RZV exposure as a prescription dispensing in an outpatient pharmacy setting are 58160-0828-01, 58160-0829-01, 58160-0819-12, 58160-0828-03, 58160-0829-03 and 58160-0823-11.

The CPT code 90750 for RZV will identify vaccine administration in a physician office setting claim.

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 the record will be deleted, but not the participant.

RZV unvaccinated comparator: individuals will be selected for the ‘no RZV’ unvaccinated comparator group from individuals with a preventive care visit who have no record of RZV vaccination prior to or on the preventive care visit date (see Section 7.1).

Preventive care visit definition: Preventive care visits for the RZV unvaccinated comparators will be identified by means of selected CPT, ICD-10-CM, and Healthcare Common Procedure Coding System (HCPCS) codes. The presence of any of the selected codes will qualify as an eligible “preventive care visit.” Note that a participant initially included in the RZV unvaccinated group may later be classified as RZV exposed if they receive RZV vaccination after their qualifying preventive care visit.

Study cohorts will be matched to an RZV unvaccinated comparator based on age, sex, race/ethnicity, payer, and IC/AID group (based on IC/AID status). For the matching, IC/AID status will be further categorized among individuals identified as having IC/AID (i.e., IC/AID = yes). Specifically, participants where IC/AID status is No will be assigned to “None” and participants where IC/AID status is Yes will be categorized into mutually exclusive IC/AID groups based on the groups listed below. If a participant qualifies for more than one IC/AID group, a hierarchical classification approach will be applied to assign the participant to a single IC/AID group. The hierarchy is ordered to reflect decreasing potential risk of adverse outcomes, with higher-risk conditions taking precedence over lower-risk conditions. The IC/AID group hierarchy is defined as follows (from highest to lowest priority), sample size permitting:

- Solid organ transplant and stem cell transplant (Transplant group)
- Human immunodeficiency virus (HIV)
- Hematologic malignancies and solid tumors (Cancer group)
- Systemic lupus erythematosus (SLE)
- Multiple sclerosis (MS)
- Rheumatoid arthritis (RA)
- Inflammatory bowel disease (IBD)
- Psoriasis and psoriatic arthritis (PsO/PsA group)

7.3.2. Outcome definitions

An overview of outcomes of interest is provided in [Table 1](#). Detailed definitions are provided in the following subsections.

Table 1. Outcomes of interest

Outcome	Objectives	Cohorts
PHN objectives		
PHN	Primary objective 1 Secondary objective 1 CCI	Cohort #1
	Secondary objective 3	Cohort #2
HZ-associated hospitalization	Secondary objective 2 CCI	Cohort #1
HZO	Secondary objective 2 CCI	Cohort #1
CCI		
CVD events after HZ objectives		
3-point MACE within 3 months after HZ - composite of hospitalized AMI, hospitalized stroke, or cardiovascular death	Primary objective 1 Secondary objective 1	Cohort #1
	Secondary objective 3	Cohort #2
3-point MACE within 3 months after HZ - components : hospitalized AMI within 3 months after HZ, hospitalized stroke within 3 months after HZ, cardiovascular death within 3 months after HZ	Secondary objective 2	Cohort #1
	Secondary objective 3	Cohort #2
3-point MACE within [timeframe] after HZ – composite and components	Secondary objective 4	Cohort #1
	Secondary objective 3	Cohort #2
All-cause 3-point MACE - composite	Secondary objective 5	Cohort #1
All-cause hospitalized AMI	Secondary objective 5	Cohort #1
All-cause hospitalized stroke (ischemic or hemorrhagic)	Secondary objective 5	Cohort #1
All-cause cardiovascular death	Secondary objective 5	Cohort #1
CCI		

7.3.2.1. PHN outcomes**7.3.2.1.1. Primary outcome**

Defining HZ: defining an HZ event is part of the algorithm for defining PHN. HZ can be identified with a high positive predictive value (PPV) >80% based on diagnosis codes, with additional accuracy established through requirement for use of an antiviral medication [Zhang, 2012]. A study showed a high PPV of 97.5% for an ICD-10-CM code for HZ accompanied by either a prescription or laboratory test results [Baxter, 2018].

- An event of HZ requires:
 - An inpatient claim with an ICD-10-CM diagnosis code (any position) for HZ (B02.xx)

OR Both:

- Any other medical claim with an ICD-10-CM diagnosis code (any position) for HZ (B02.xx).

AND

- Dispensing for an oral antiviral (acyclovir, valacyclovir, or famciclovir) within 7 days before or after the HZ diagnosis.

The HZ event date is the date of the medical visit with a qualifying HZ diagnosis code.

PHN: PHN has been examined in administrative claims data among patients diagnosed with HZ by using diagnoses of PHN in combination with a prescription for PHN treatment with PPV of 78-96% [Klompas, 2011; Klein, 2019]. An algorithm based on these studies and modified by Izurieta et al., 2021 will be used [Izurieta, 2021].

- At least one subsequent ICD-10-CM diagnosis code B02.xx (any position) in the 90-180 days after the HZ event.
- AND at least one of the following:
 - At least one incident dispensing for anti-PHN drugs (anticonvulsant or analgesic drugs) in the 0-60 days after the first HZ diagnosis without an anti-PHN drug in this drug class in the 365 days prior to initial HZ event (each drug class handled separately). The 0–60-day interval to identify anti-PHN medications is used because therapy for pain is typically started by clinicians in the first 60 days after HZ diagnosis.
 - An ICD-10-CM diagnosis B02.2x (HZ with other nervous system involvement) in the 90-180 days after HZ event.
 - A new ICD-10-CM diagnosis M79.2 (neuralgia and neuritis, unspecified) or M54.10 (radiculopathy, site unspecified) in the 0-180 days after HZ event, without neuralgia or radiculopathy in the 365 days prior to HZ event.

PHN is a joint outcome that requires both HZ diagnosis and PHN diagnosis within 90-180 days (an HZ code without a PHN code in the correct range will not be a censoring event as the intent is to identify the first episode that meets the criteria for PHN). The PHN event date is assigned as the time of the initial HZ event.

7.3.2.1.2. Secondary outcomes

- **HZ-associated hospitalization:** HZ-associated hospitalization includes only HZ events diagnosed in the hospital setting. This is a subset of HZ cases that are identified in the hospital setting (there is no time element). HZ-associated hospitalization date is the date of inpatient hospitalization with a diagnosis of HZ (ICD-10-CM code B02.xx) at any position.
- **HZO:** HZO will be defined as the subgroup of HZ patients with an ICD-10-CM diagnosis code of B02.3 - Zoster ocular disease. The HZO event date will be set to the HZ event date.

CCI

7.3.2.2. CVD events after HZ outcomes

7.3.2.2.1. Primary outcome

Defining an HZ event is part of the definition of a CVD event after HZ. See Section [7.3.2.1.1](#) for the definition of an HZ event.

3-point MACE within 3 months after HZ: composite outcome, any hospitalized AMI, hospitalized stroke, or cardiovascular death within 3 months after HZ diagnosis. Individuals who meet criteria for more than one MACE component will only be counted once for the composite outcome, at the earliest event for which they meet criteria.

Within 3 months after a first HZ ICD-10-CM code (B02.xx) during follow-up:

- **Hospitalized AMI within 3 months after HZ:** identified by ICD-10-CM codes in the primary position from inpatient encounters, or in any position from ED encounters if the patient was not hospitalized and if the patient died the same or next day. The date of the hospital admission or ED visit of the first AMI event after the HZ event date will define the AMI event date. PPVs 86-88% have been reported for the components of this algorithm using ICD-9-CM codes [[Wahl, 2010](#); [Cutrona, 2013](#); [Saunders-Hastings, 2021](#)].

Specifically, hospitalized AMI will be defined as:

- At least one ICD-10-CM AMI diagnosis code in the primary diagnosis position from the hospital setting.

OR

- At least one ICD-10-CM AMI diagnosis code from the ED setting, if the patient died the same or next day.

- **Hospitalized Stroke (ischemic or hemorrhagic) within 3 months after HZ:** identified by ICD-10-CM codes from inpatient encounters, or ED encounters if the patient was not hospitalized and if the patient died the same or next day. The date of the hospital admission or ED visit of the first stroke event after the HZ event date

will define the stroke event date. PPVs 93-96% have been reported for ischemic and hemorrhagic stroke components of this definition, based on ICD-9-CM codes, with requirement of diagnosis in the hospital setting and primary position showing the highest PPVs [Andrade, 2012; Wahl, 2010].

Specifically, hospitalized stroke will be defined as:

Inclusion criteria:

- Ischemic stroke:
 - At least one ischemic stroke ICD-10-CM diagnosis code in the primary diagnosis position from the hospital setting; or
 - At least one ischemic stroke ICD-10-CM diagnosis code from the ED setting if the patient died the same or next day.
- Hemorrhagic stroke:
 - At least one hemorrhagic stroke ICD-10-CM diagnosis code in the primary diagnosis position from the hospital setting; or
 - At least one hemorrhagic stroke ICD-10-CM diagnosis from the ED setting if the patient died the same or next day.

Exclusion criteria:

- Stroke events with a hospital claim with a traumatic brain injury code in the primary diagnosis position on the same date as the stroke diagnosis will be excluded. The exclusion of strokes with a traumatic event during the same admission or on the same day or claim is consistent with the Medicare Chronic Conditions Warehouse algorithm and ensures that strokes possibly resulting from traumatic events are excluded.
- **Cardiovascular Death within 3 months after HZ:** identified by ICD-10 codes or Centers for Disease Control and Prevention (CDC) group 113 level found within Veritas Cause of Death (COD) database. Specifically, deaths from major cardiovascular diseases ICD-10 codes: I00–I78. Cardiovascular related death includes deaths from Diseases of heart (ICD–10 codes I00–I09, I11, I13, I20–I51); Essential hypertension and hypertensive renal disease (I10, I12, I15) and Cerebrovascular diseases (I60–169) [Miniño, 2010]. In MORE² and Medicare FFS data will be linked to the Veritas Fact of Death (FOD) data to capture over 90% of U.S. deaths within weeks of occurrence, drawing from sources such as the Social Security Administration’s data, obituaries, cemeteries, and other death announcements. This data will include information on facts of death including date of death and location when available as well as the cause of death from the COD database. A recent validation analysis of a composite mortality variable in a data source that linked to Veritas FOD for mortality data found a 96% PPV compared to the National Death Index [Kapilivsky, 2025]. See Section 7.4.3 for additional details on this data source.

7.3.2.2.2. Secondary outcomes

Secondary outcomes will include the 3-point MACE within 3 months after HZ composite outcome and each of the separate 3-point MACE within 3 months after HZ component outcomes defined in Section 7.3.2.2.1. Additionally, secondary outcomes will include the following, applying the definitions in Section 7.3.2.2.1 for different timeframes after HZ:

- **3-point MACE within [timeframe] after HZ**
- **Hospitalized AMI within [timeframe] after HZ**
- **Hospitalized Stroke (ischemic or hemorrhagic) within [timeframe] after HZ**
- **Cardiovascular Death within [timeframe] after HZ**

Secondary outcomes will include the following, applying the definitions in Section 7.3.2.2.1 but removing the requirement that the event occur after an HZ event:

- **All-cause 3-point MACE**
- **All-cause Hospitalized AMI**
- **All-cause Hospitalized Stroke (ischemic or hemorrhagic)**
- **All-cause Cardiovascular Death**

CVD events after HZ secondary objective #5 uniquely pertains to *all-cause CVD events occurring at any time*, rather than being limited to CVD events following an HZ event. The date of the hospital admission or ED visit of the first AMI event after the index date will define the all-cause AMI event date. The date of the hospital admission or ED visit of the first stroke event after the index date will define the all-cause stroke event date.

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7.3.3. Confounders and effect modifiers

Table 2 identifies possible covariates that will be used in the study analysis to describe the population and adjust for confounding. Categories listed may be modified or combined for analysis. Variables may also be collapsed or removed as needed to facilitate the analysis or for computational limitations.

Table 2. Data Items/Variables and Data Sources

Variable	Categories
Baseline/sociodemographic variables	
Age	Continuous; 18-49, 50-59, 60-69, 70-79, ≥80 years; 50-64, ≥65
Sex	Male/Female
Race/ethnicity	White, non-Hispanic; Black or African American, non-Hispanic; Asian, Native Hawaiian, or other Pacific Islander, non-Hispanic; Hispanic or Latino; Other/Unknown, non-Hispanic
Census region	West, Midwest, South, Northeast, U.S. Territory/Unknown
Payer	MORE ² Only: Managed Medicaid, Medicare Advantage, Commercial
Dual eligibility status	Y/N
Original reason for entitlement to Medicare	Old age and survivor's insurance; Disability insurance benefit; End-stage renal disease; Disability insurance benefit and end-stage renal disease; N/A – not Medicare
Index Year	2018 - 2024
Alcohol use	Y/N
Tobacco use	Y/N
Hospitalization stays	0, 1-2, 3+
Outpatient-ER visits	0, 1-2, 3+
Outpatient general medical visits	0, 1-2, 3+
Other vaccines	
Pneumococcal vaccine	Y/N
Hepatitis B vaccine	Y/N
Tetanus vaccine	Y/N
Influenza vaccine	Y/N
COVID-19 vaccine	Y/N
Any IC/AID condition ^{a,b}	Y/N
Any IC condition ^{a,b}	Y/N
Individual IC condition – Yes ^{a,b}	Hematologic malignancies, HIV/AIDS, Solid Organ Transplant, Solid Tumor, Stem Cell Transplant
Any AID condition ^{a,b}	Y/N
Individual AID Condition – Yes ^{a,b}	Inflammatory Bowel Disease, Multiple Sclerosis, Psoriasis, Psoriatic Arthritis, Rheumatoid Arthritis, Systemic Lupus Erythematosus
Deyo-Charlson Comorbidity Index (DCI) [Deyo, 1992] – Score and specific DCI comorbidities	
DCI score ^a	0, 1, 2, 3, 4+
AMI ^a	Y/N
Congestive heart failure ^a	Y/N
Peripheral vascular disease ^a	Y/N
Cerebrovascular disease ^a	Y/N
COPD ^a	Y/N
Rheumatic disease ^a	Y/N
Peptic ulcer disease ^a	Y/N
Hemiplegia or paraplegia ^a	Y/N
Renal disease ^a	Y/N
Diabetes without complications ^a	Y/N
Diabetes with complications ^a	Y/N
Mild liver disease ^a	Y/N
Moderate/severe liver disease ^a	Y/N
Malignancy ^a	Y/N
AIDS/HIV ^a	Y/N
Metastatic solid tumor ^a	Y/N
Other health conditions	
Asthma ^a	Y/N

Variable	Categories
Other chronic lung disease	Y/N
Blood disorders	Y/N
Depression ^a	Y/N
Angina ^a	Y/N
Atrial fibrillation ^a	Y/N
Congestive heart failure	Y/N
Carotid stenosis ^a	Y/N
Ischemic heart disease/coronary artery disease	Y/N
Hypertension ^a	Y/N
Hypercholesterolemia/ Hyperlipidemia ^a	Y/N
Hypothyroidism ^a	Y/N
Dementia	Y/N
Other neurological conditions	Y/N
CVD medications	Y/N

a) Denotes a potential time-varying covariate

b) Algorithms in [Annex 2](#)

7.4. Data sources

This study will leverage 1) 100% Medicare FFS data, 2) the MORE² Registry® database at Inovalon and 3) Veritas Death data. Analysis will be conducted separately across the Medicare FFS and the MORE² Registry® databases, and possibly aggregated via meta-analytic methods if scientifically appropriate (see Section 7.7.2.2.1.). [Table 3](#) presents a summary of the data elements across the 100% Medicare FFS and MORE² Registry® data sources. Detailed information on each data source is described in the subsections below.

Table 3. Summary of Medicare FFS and MORE² Registry® Data Elements

Data Elements	Details
Plan Enrollment Details & Demographics	Plan type: Medicare FFS, Commercial [private, exchange], Medicare Advantage, Managed Medicaid Member enrollment dates Sex, age, race/ethnicity (where available), geographic region Validated date of death for FFS enrollees; Linkage to Veritas FOD data for MORE ² Registry®
Medical Encounters	Hospitalizations, including readmissions ED visits Post-acute care services, including skilled nursing and rehabilitation, long term acute care hospitalization, hospice, and home health Durable medical equipment Outpatient services including dialysis services, surgical procedures and physician-administered treatments, primary care, and specialist visits
Outpatient Lab Tests	HCPCS codes for all general labs and therapeutic drug monitoring (no lab results)
Pharmacy Records	Fill date, drug name, class, strength, formulation, days' supply from retail, specialty, and mail order pharmacies
Healthcare Expenditures	MORE ² Registry®: Standardized allowed amount for services rendered Medicare FFS: Medicare payment amounts, secondary payments, OOP contributions

7.4.1. MORE² Registry®

The Inovalon MORE² Registry® of closed claims is a real-world database that is inclusive of medical and pharmacy claims primary sourced by over 160 health plans and statistically de-identified. The Inovalon MORE² Registry® contains data pertaining to over 1.1 million physicians, 667,000 clinical facilities, 386 million unique patients, and more than 83 billion medical events. Claims data in the dataset are longitudinally matched and cover all major U.S. payer lines of business including commercial (28% of market), Medicare Advantage (22% of market), and managed Medicaid (89% of market). All 50 U.S. states are represented, and enrollment/dates of service range from 2000 to the present.

The claims data are available in 4 different datasets and a unique identification (ID) is used to link an individual across all data sets:

Member File: This dataset includes information pertaining to the members enrolled in an insurance company provided health plan including but not limited to sex, race, and state.

Member Enrollment File: This dataset includes information on the payer type and enrollment date.

Claims: This data contains claim service line information for medical services and may also include information relating to lab services (without an associated result), pharmaceuticals administered from the practitioner's office and medical encounter data. The claims file contains up to 25 diagnosis codes per claim as well as CPT codes.

RX Claims: The RX Claims file contains attributes associated with pharmacy (prescription) claims. The NDC variable will be used in this study to identify all medications dispensed during the baseline and follow-up period.

7.4.2. 100% Medicare FFS Claims for Part A, B, and D

Under a research data use agreement (DUA) between Inovalon and the Centers for Medicare and Medicaid Services (CMS), Inovalon has direct access to 100% Medicare FFS enrollment information and claims for Parts A, B, and Part D Prescription Drug Event (PDE) data for all Part D plans. The DUA allows for collaboration with life sciences companies to utilize the in-house 100% FFS claims data to further Medicare research in the domains of access to care, healthcare resource utilization, and quality of care. The proposed analyses will draw from the 100% sample which includes all Part A/B medical encounters for Medicare FFS beneficiaries, including hospital claims, ED visits, skilled nursing facility (SNF) stays, hospital outpatient services/ambulatory surgical center services, physician office visits (including physician administered treatments), home health services/durable medical equipment (DME), hospice care and the PDE file. The claims data are available in seven different datasets and a unique identification (ID) is used to link an individual across all data sets.

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.

Home Health Claim File: This data set includes fee-for-service claims for a range of health care services provided in one's home for those who have difficulty leaving their home (i.e., using an assisted device such as a wheelchair) due to an illness. The home health files contain 25 diagnosis fields.

Hospice Claim File: This dataset includes fee-for-service claims for routine care provided in the home or other facility, including an inpatient hospice facility. The hospice files contain 25 diagnosis fields.

DME Claim File: This data set includes use of equipment used for a medical reason and can be used in one's home. The DME files contain up to 12 diagnosis fields.

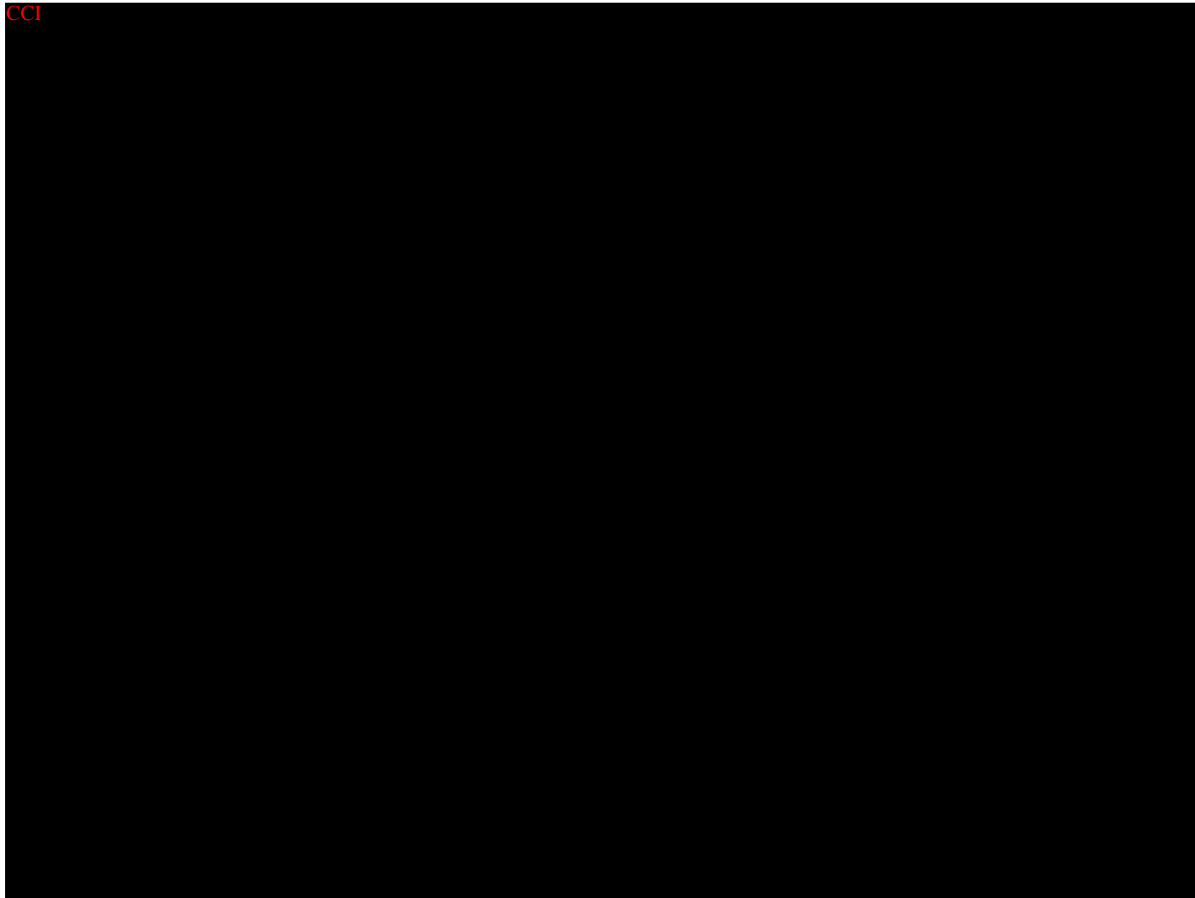
PDE File: This dataset includes all medications filled at an *outpatient pharmacy* that have been submitted by the prescription drug plan. The NDC variable will be used in this study to identify all medications dispensed during the baseline and follow-up period.

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 RZV exposure, IC/AID group, the outcomes, and the baseline covariates. The PDE file will be used to ascertain RZV exposure, baseline vaccinations, and IC/AID medications. Use of home health, hospice and DME will be used to assess RZV exposure, IC/AID group, baseline covariates, and exclusion criteria.

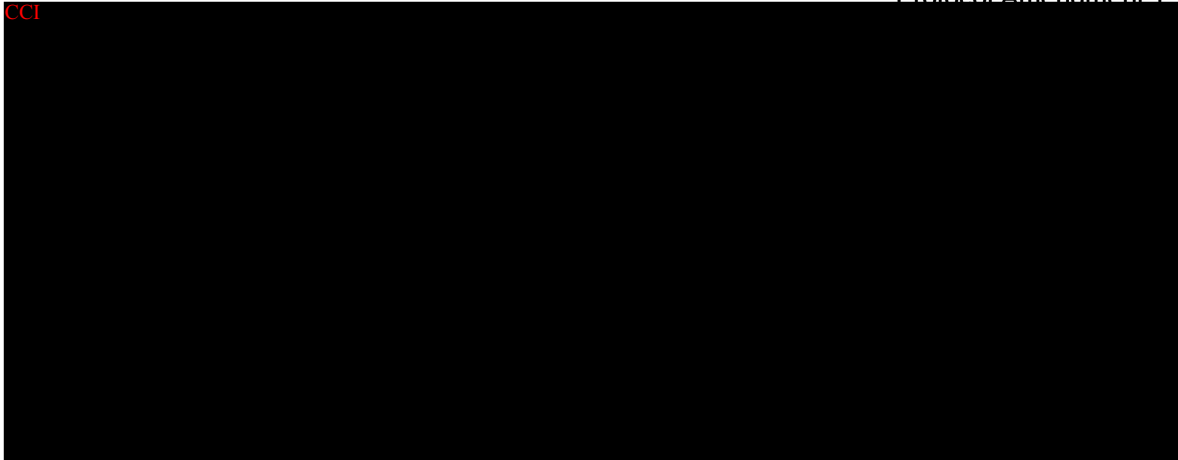
7.4.3. Veritas Death data

Veritas FOD is a comprehensive, curated mortality dataset produced by Veritas Data Research that aggregates and validates U.S. death records from tens of thousands of public and private sources to create the most complete, timely, and transparent index of mortality data available. It captures over 90% of U.S. deaths within weeks of occurrence, drawing from sources such as the Social Security Administration's data, obituaries, cemeteries, and other death announcements, and consolidates them into a single deduplicated, quality checked record. This data will include information on facts of death including date of death and location when available. Additionally, the Veritas COD dataset will be used to identify cardiovascular death. Veritas COD provides cause-of-death information for more than 22 million deceased individuals in the United States from 2017 onward, including one primary and up to five secondary causes of death. [[Veritas, 2026](#)]

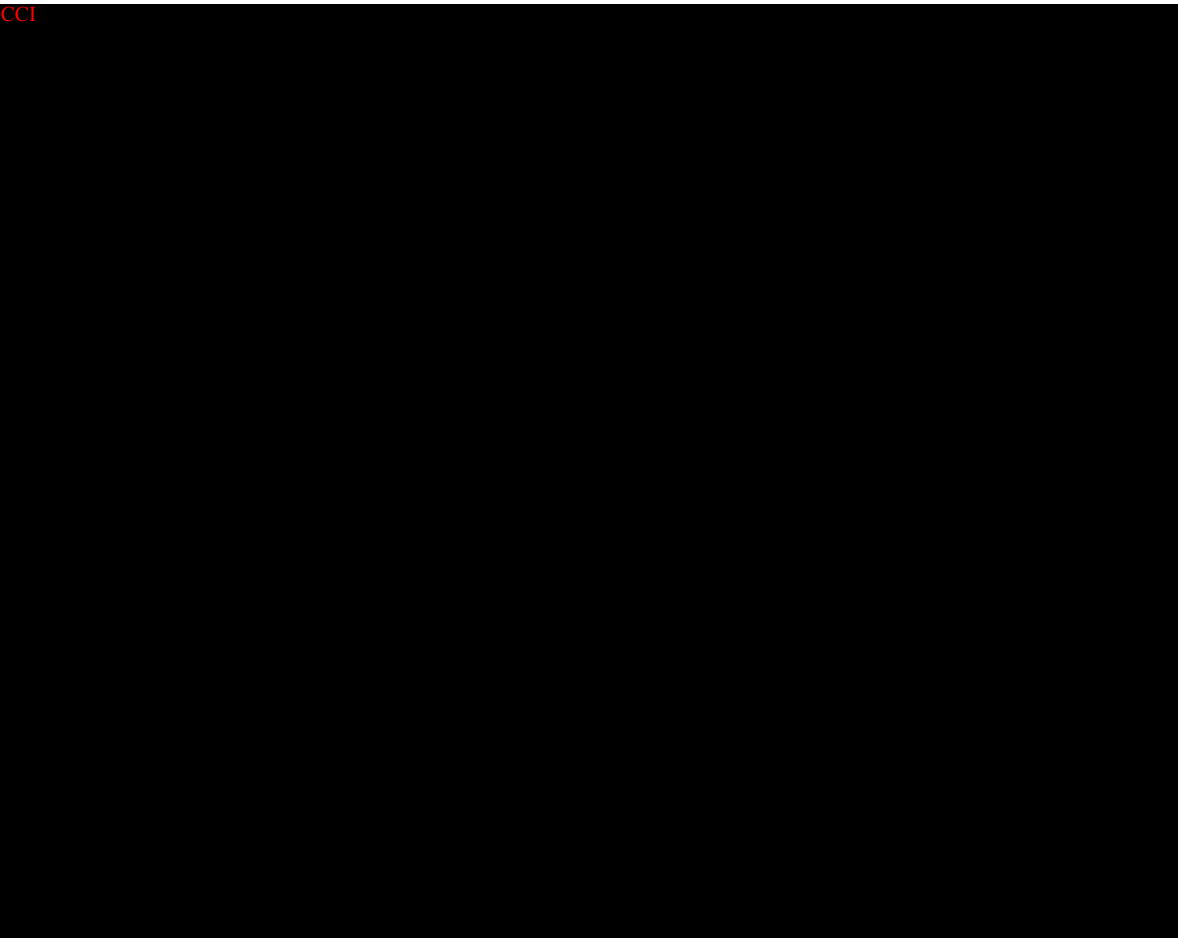
7.5. Study size



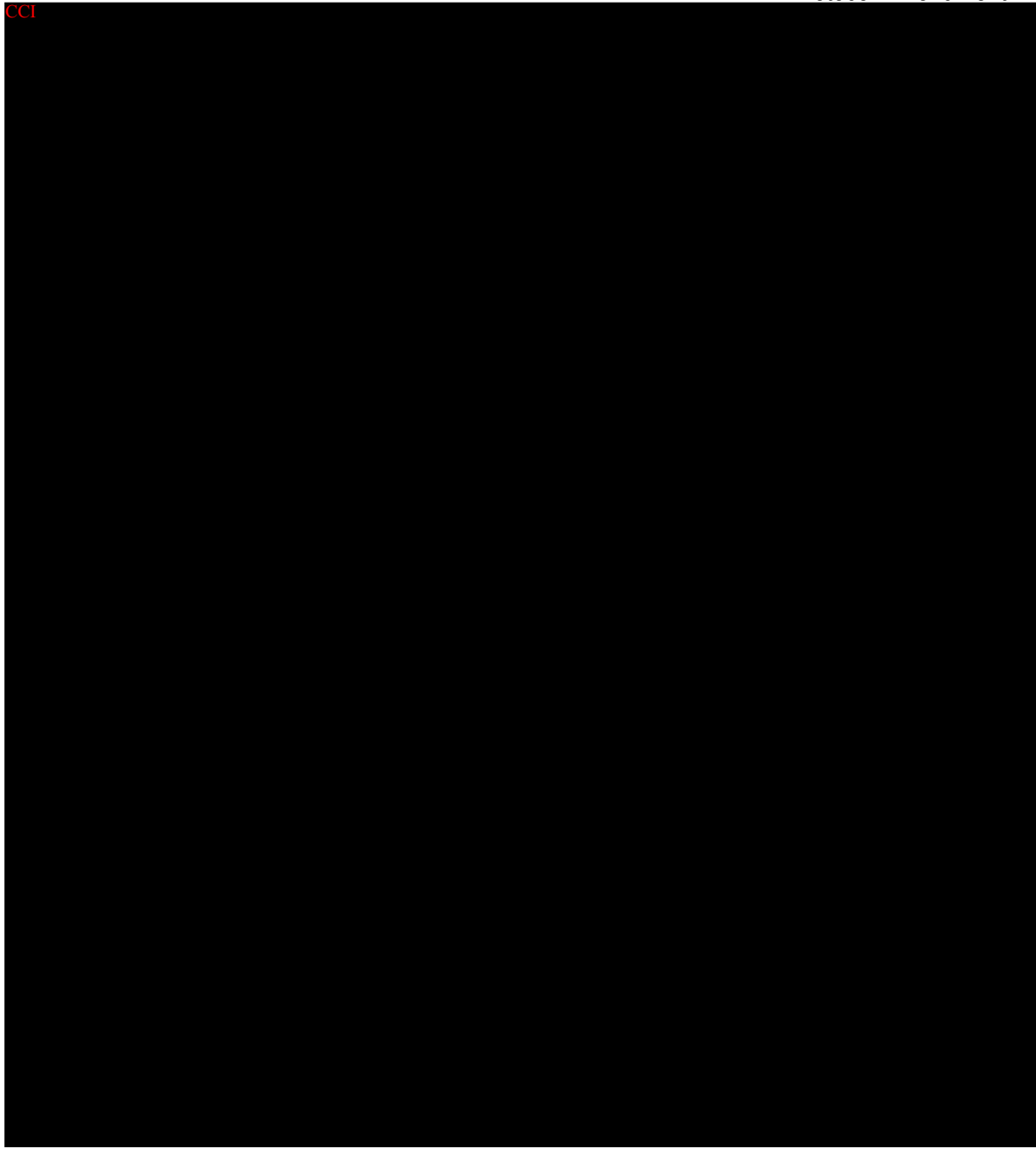
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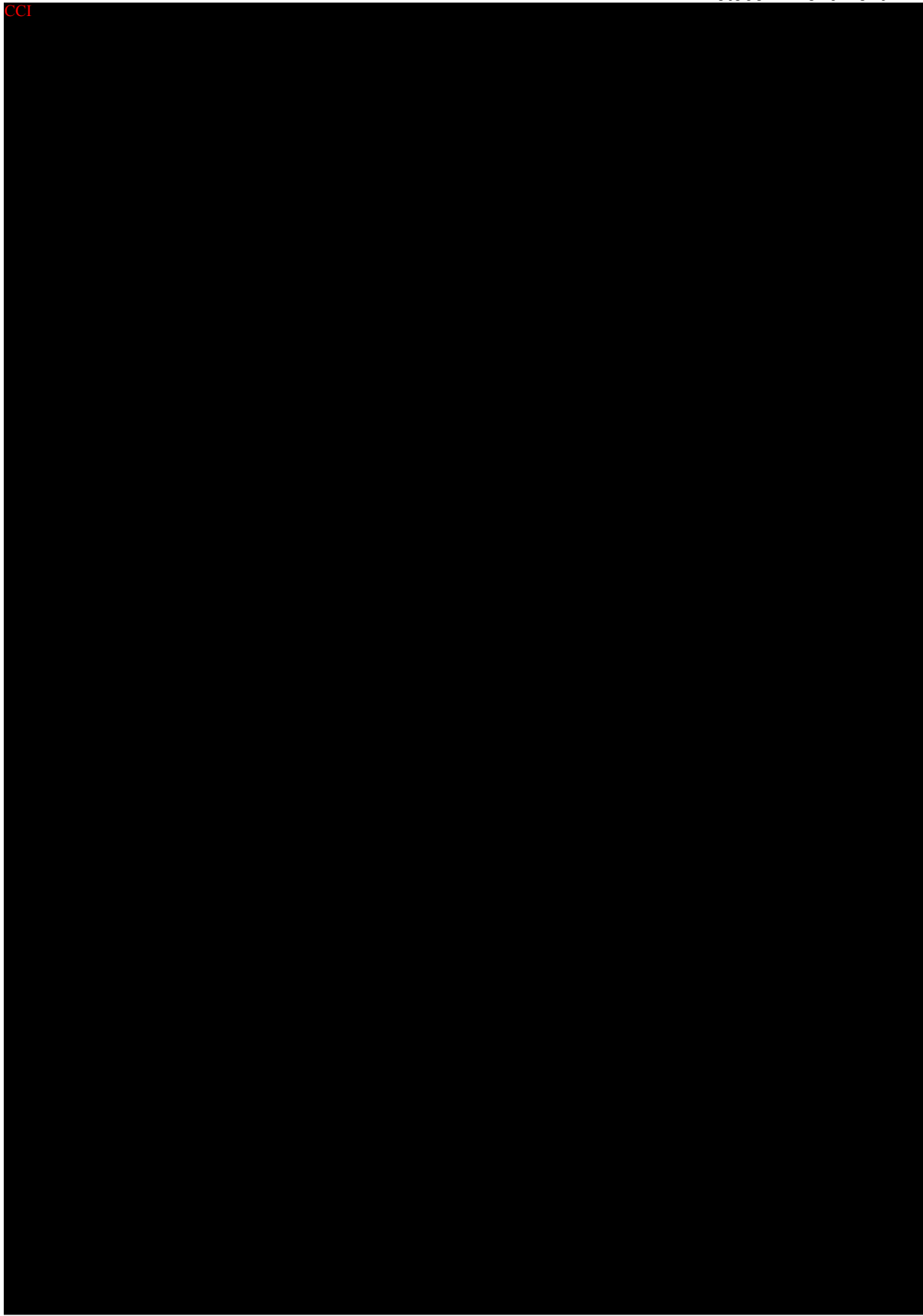
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7.6. Data management

The databases used in this study are maintained in-house at Inovalon. As required by the DUA with CMS, GSK will not have access to the raw CMS data. Analysis results from Medicare FFS and the MORE² Registry® will only be provided in aggregate.

All manual and automated processes used for data retrieval, curation, transformation, and preparation of the study-specific analytic datasets will be thoroughly assessed from initial data ingestion through completion of the final study report to ensure data integrity, with verification steps. Since only structured data (e.g., enrollment files, medical and pharmacy claims) will be used, no unstructured data or natural language processing methods will be employed. Quality control procedures—including use of unique patient identifiers, cross-file reconciliation, verification of join logic, and record-level consistency checks—will prevent patient duplication or over representation, with automated procedures supplemented by manual review as needed. Data management and handling conventions are discussed further in Section 7.7.2.2.

7.7. Data analysis

A series of matched, multivariable, and weighted analyses will be conducted to address the research objectives focused on assessing the VE (including incidence rate and hazard ratio) of new diagnosis of PHN and 3-point MACE after HZ as well as other HZ complications among individuals aged ≥ 50 YOA included in the MORE² Registry® or individuals aged ≥ 65 receiving Medicare FFS benefits. Outcomes will be presented separately for each data source (Medicare FFS and MORE² Registry®). Note that for each analysis, individuals with the outcome in the 1 year (365 days) prior to the index date or in the 30 days after index date will be excluded from that analysis.

7.7.1. Statistical methods overview

The primary objectives of this study will assess the overall effect of per-label RZV vaccination (i.e., having initiated RZV and receiving dose 2 at time t) versus remaining unvaccinated at the nearest eligible preventive visit relative to the matched vaccinated participant's RZV dose 2 separately for each data source. The analysis will utilize a marginal structural Cox model estimated using stabilized IPTW and inverse probability of censor weighting (IPCW) which are widely recognized as supporting potential causal inference/strong association in observational studies [Chakladar, 2022; Yiu, 2022].

Treatment weights will be estimated in a regression model, regressing exposure (vaccination) on study covariates. We will include covariates listed in Section 7.3.3 to estimate the propensity score model. In order to protect against extreme propensity score weights we will stabilize weights [SAS Help Center, 2024] as well as potentially trim/truncate weights based in quantiles of their distribution (it is usual to consider 1st and 99th percentiles as thresholds but we will be flexible). We will also estimate censoring weights to address potential informative censoring that may arise by any competing risks.

7.7.1.1. IPTW and IPCW

IPTW will be constructed to balance measured confounders between vaccinated and unvaccinated comparator groups, conditional on covariates assessed during the 12-month lookback prior to each individual's index date (and any additional baseline windows specified in the protocol). The IPTW model will include prespecified covariate domains such as demographics, comorbidities, medication use and healthcare utilization. To improve precision and reduce variability, stabilized IPTW will be used.

$$\text{logit}(e_i) = \log\left(\frac{e_i}{1 - e_i}\right) = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \dots + \beta_p X_{pi}$$

where e_i is the PS (probability of vaccination) for participant i , and $X_{1i}, X_{2i}, \dots, X_{pi}$, represent the set of baseline covariates included in the PS model.

Stabilized weights will be calculated to improve precision and reduce the influence of extreme weights:

$$\text{Vaccinated } SW_i = \frac{P(T = 1)}{e_i}$$

$$\text{Unvaccinated } SW_i = \frac{P(T = 0)}{1 - e_i}$$

where T is the treatment (vaccination), $P(T = 1)$ and $P(T = 0)$ represent the marginal probabilities of being vaccinated and unvaccinated, respectively.

IPCW will address bias due to differential censoring, particularly the initiation of RZV by unvaccinated comparators (censored at receipt of RZV Dose 1 during follow-up). IPCW will be estimated using pooled time-to-censoring models that will incorporate such as the baseline covariates, medication use and healthcare utilization during follow-up (e.g., updated monthly or quarterly). To improve precision and reduce variability, stabilized IPCW will be used.

$$\begin{aligned} \text{logit}(p_i(t)) &= \log\left(\frac{p_i(t)}{1 - p_i(t)}\right) \\ &= \gamma_0(t) + \gamma_1 X_{1i} + \gamma_2 X_{2i} + \dots + \gamma_b X_{bi} + \gamma_{b+1} X_{(b+1)i}(t) + \dots + \gamma_p X_{pi}(t) \end{aligned}$$

where

- $p_i(t)$ is the conditional probability that participant i remains uncensored at time t
- $X_{1i}, \dots, X_{bi}$ represent the baseline covariates that do not change over time included in the censoring model
- $X_{(b+1)i}(t), \dots, X_{pi}(t)$ represent the time-varying covariates (e.g., MCI diagnosis, medication status, healthcare resource utilization)
- $\gamma_0(t)$ is a time-indexed intercept that allows the baseline probability of remaining uncensored to vary across time intervals

Stabilized IPC weights will be calculated to reduce variability and mitigate the influence of extreme weights:

$$SW_i(t) = \frac{P(C(t) = 1)}{p_i(t)}$$

where $P(C(t) = 1)$ denotes the marginal probability of remaining uncensored at time t . Combining stabilized IPTW and IPCW, the final weights will be applied to the following product

$$W(t) = \text{IPTW} * \text{IPCW}(t)$$

To assess the weight stability, we will summarize stabilized IPTW and IPCW distributions (e.g., mean, SD, percentiles, minima/maxima) and evaluate overlap. If needed, we will apply prespecified remedies such as truncation/trimming, collapsing sparse covariate levels, or alternative weight specifications (e.g., overlap-type approaches), guided by diagnostics and finalized prior to outcome modeling.

Full details will be prespecified in the SAP.

Assessment of Covariate Balance

Covariate balance between groups will be assessed using standardized mean differences (SMDs) comparing unweighted and weighted distributions; absolute SMD > 0.10 will be considered indicative of meaningful imbalance [Austin, 2009].

For continuous covariates, we will additionally use graphical checks (e.g., side-by-side boxplots and distributional comparisons). If residual imbalance remains after weighting, the affected covariates may be included as additional adjustment terms in the weighted outcome model.

7.7.1.2. Cox proportional hazards model

Rationale for model selection

The Cox proportional hazards model will serve as the primary analytical approach for estimating the hazard of each outcome (PHN, 3-point MACE after HZ) comparing RZV vaccinated individuals versus RZV unvaccinated comparators.

Model specification

The Cox proportional hazards model related the hazard of an event at time t to baseline covariates through the following equation:

$$h(t|X_i(t)) = h_o(t) \exp (\beta_{vacc} T_i + \beta_1 X_{1i} + \beta_2 X_{2i} + \dots + \beta_b X_{bi} + \beta_{b+1} X_{(b+1)i}(t) + \dots + \beta_k X_{ki}(t))$$

where

- $h(t|X_i(t))$ is the hazard function for participant i at time t , conditional on the history of covariates up to t
- $h_0(t)$ is the baseline hazard function (unspecified)
- T_i is the treatment indicator
- $X_{1i} \dots X_{bi}$ are baseline covariates that do not change over time
- $X_{(b+1)i}(t) \dots X_{ki}(t)$ are time-varying covariates (e.g., medication status, healthcare resource utilization)
- β_{vacc} is the log hazard ratio for treatment effect
- $\exp(\beta_{vacc})$ is the hazard ratio comparing vaccinated participants to unvaccinated comparators

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). Nonparallel lines or non-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.

The model will be weighted using the product of the stabilized IPTW and IPCW described above. The combined weighting approach adjusts for time-varying confounding as well as potential informative censoring during follow-up. The primary parameter of interest is $\exp(\beta_{vacc})$, representing the hazard ratio for PHN and CVD event after HZ comparing RZV vaccinated participants versus RZV unvaccinated comparators. Robust sandwich variance estimators will be used to account for the combined weighting and provide valid confidence intervals.

Censoring

As specified in Section 7.1, participants will be censored at the earliest of: (1) end of the study period, (2) date of end of coverage, (3) date of death (for the main Cox model when death is treated as a competing risk), (4) date of Zostavax or RZV vaccination for initially RZV unvaccinated comparators, (5) date of third RZV vaccination for RZV vaccinated comparators, or (6) date of first evidence of outcome of interest. The censoring mechanism is assumed to be independent of the outcome process conditional on measured covariates.

7.7.1.3. Fine-Gray sub-distribution hazard model

Rationale for model selection

The cumulative incidence function will be estimated using the Fine–Gray subdistribution hazard model, which accounts for competing risks by modeling the hazard of the event of interest in the presence of competing events. Unlike the Kaplan–Meier method, the Fine–Gray approach appropriately incorporates competing risks rather than treating them as censored observations. Given that the study population consists of Medicare enrollees and MORE² Registry® older participants in whom death is expected to occur with non-negligible frequency, death from other causes may be a competing risk. Failure to account for competing risk may result in biased estimates, where in general the potential for bias increases with the larger percentage of competing events or longer follow-up time [Austin, 2016; Berry, 2010]. As such, the proportion of participants who experience death from other causes will be evaluated to assess whether the proportion of participants who experience the competing event of death from other causes is equal to or greater than the proportion of participants who experience the outcome of interest, or if the absolute percentage on competing events is >10% [Austin, 2016; Berry, 2010; Schuster, 2020]. If at least one of these conditions is met, cumulative incidence will be estimated using cumulative incidence function (CIF). The CIF produces unbiased estimates of the cumulative incidence unlike the Kaplan Meier which may overestimate the cumulative incidence [Austin, 2016; Berry, 2010].

7.7.1.4. Missing data

Participants with missing data in covariates required for PS estimation will be excluded from the analysis. Missingness is expected to be minimal. Demographic information, with the exception of race/ethnicity, is well-populated in the 100% Medicare FFS and MORE² Registry® databases and the absence of evidence of clinical characteristics will be interpreted as the absence of the condition rather than missing data. On average, 20% of race/ethnicity data is missing in MORE². Participants with other or unknown race/ethnicity will be retained in the study sample, and matched to other participants with other/unknown race/ethnicity. Nonetheless, the extent and pattern of missingness will be described, and sensitivity analyses may be conducted if missingness exceeds predefined thresholds.

7.7.2. Primary analysis

7.7.2.1. Main Analytical approach

PHN:

In execution of the primary objective focused on assessing VE against PHN, a descriptive analysis of new onset PHN among cohort #1 (≥50 years) will be performed independently across both MORE² Registry® and Medicare FFS databases applying the same analytic approach. The count and proportion of participants presenting evidence of new PHN diagnosis will be reported overall and stratified by time since vaccination (follow-up year since vaccination: Year 1, Year 2, etc.; data permitting). Incidence rates

will be calculated as the number of incident cases divided by the total PYs of follow-up and expressed per 1,000 PYs. The 95% confidence intervals will be obtained using a Poisson regression (or a negative binomial model if overdispersion is present).

Following matching on age group, sex, race/ethnicity, payer type, and IC/AID group, IPTW will be used to account for differences in baseline participant characteristics between the study cohorts, and IPCW will be applied to account for potential informative censoring during follow-up. Cox proportional hazards models will be utilized to further assess the time from vaccination or preventive care visit to the first diagnosis of PHN. If competing risks are present, such as death prior to a PHN diagnosis, Fine-Gray subdistribution hazard models will be employed to estimate the subdistribution hazard ratios for PHN, explicitly accounting for these competing events. In this case, the Fine-Gray subdistribution hazard model approach will be the primary method, and the standard Cox proportional hazards model will be used as a sensitivity analysis.

The final vector of covariates will be determined by the research teams following a review of the descriptive analyses but will likely include participant demographics and clinical characteristics. Final hazard ratios, 95% Wald confidence intervals, and p-values will be reported for each variable included in the final models. Estimates of VE (%) will be calculated as $(1 - \text{adjusted HR}) \times 100$.

CVD events after HZ:

In execution of the primary objective focused on assessing VE against CVD events after HZ, a descriptive analysis of 3-point composite MACE within 3 months after HZ diagnosis among adults aged ≥ 50 years will be performed independently across both MORE² Registry[®] and Medicare FFS databases applying the same analytic approach. The count and proportion of participants presenting evidence of composite MACE within 3 months of HZ will be reported overall. Incidence rates will be calculated as the number of incident cases divided by the total PYs of follow-up and expressed per 1,000 PYs. The 95% confidence intervals will be obtained using a Poisson regression (or a negative binomial model if overdispersion is present).

Following matching on age group, sex, race/ethnicity, payer type, and IC/AID group, IPTW will be used to account for differences in baseline participant characteristics between the study cohorts, and IPCW will be applied to account for potential informative censoring during follow-up. Cox proportional hazards models will be utilized to further assess the time from vaccination or preventive care visit to the first diagnosis of a CVD event. If competing risks are present, such as death prior to a CVD event, Fine-Gray subdistribution hazard models will be employed to estimate the subdistribution hazard ratios for CVD events, explicitly accounting for these competing events. In this case, the Fine-Gray subdistribution hazard model approach will be the primary method, and the standard Cox proportional hazards model will be used as a sensitivity analysis.

The final vector of covariates will be determined by the research teams following a review of the descriptive analyses but will likely include participant demographics and clinical characteristics. Final hazard ratios, 95% Wald confidence intervals and p-values will be reported for each variable included in the final models. Estimates of VE (%) will be calculated as $(1 - \text{adjusted HR}) \times 100$.

7.7.2.2. Data handling conventions

Analysis and programming will commence after protocol and SAP approval; all data for this study will be obtained, processed, and managed by Inovalon, and all analyses will be conducted by Inovalon separately in both Medicare FFS and MORE² Registry[®] databases. Within both databases, identical cohort definitions, exposure definitions, outcome definitions, and covariate adjustment strategies as described in Section 7.7.1 will be applied across all databases to the extent feasible. Analyses will be conducted independently within each database using harmonized programming specifications. The study programmer will be responsible for developing all SAS code, including a log detailing methodological and analytic changes agreed to by the study teams over the course of the project. Upon receipt of each of the respective data extracts, edit, range, and logic checks will be performed on each data field by the project programmer using SAS[®] 9.4 for Windows[®] to ensure the quality and completeness of the study databases and all of the variables therein. All data files and statistical programs used to generate results will be archived on secured servers.

7.7.2.2.1. Cross-database consistency and meta-analysis

The full study team will examine all programming output prior to the creation of the descriptive results tables. The Inovalon study lead will be responsible for validating all the results tables to confirm that results are consistent across analysis tables and databases and that the results make logical sense. Additionally, consistency/concordance across study results will be assessed based on whether the estimates across databases are consistently statistically significant ($p < 0.05$) in the same direction, or if estimates are consistently non-significant but directionally aligned. Any discordance in significance alone (e.g., one significant, one not) will not be considered sufficient evidence of inconsistency if direction and magnitude are similar. For discordant findings, pre-specified stratified analyses will be performed to check whether this discordance may be due to a difference in their distribution. Stratification on other potential effect-modifying variables will be considered if discordant results remain.

Provided the results stratified by payer type are consistent, as per above definition, random-effect meta-analyses may be performed on VE estimates of the four payer types from Medicare FFS and MORE² databases (Medicare FFS, Commercial, Medicare Advantage, and Medicaid) for the PHN and 3-point MACE endpoints. If residual heterogeneity, as measured by the width of the 95% prediction interval of the meta-analysis estimate as well as by I^2 , remains high, other approaches, such as meta regression or other appropriate methods, may be considered.

All study results will be communicated transparently, emphasizing (1) consistency of evidence vs. variability across both data sources and (2) plausible explanations for discrepancies. Results will be presented separately for each database, and possibly aggregated via meta-analytic methods if scientifically appropriate (per criteria above).

If applicable, results may be compared with previous literature to ensure consistency.

7.7.3. Secondary analysis

PHN:

Secondary Objective 1: To estimate the VE of 2 doses of RZV (i.e., having initiated RZV and receiving dose 2 at time t) versus remaining unvaccinated at the nearest eligible preventive visit relative to the matched vaccinated participant's RZV dose 2 in preventing PHN in adults aged ≥ 50 years, stratified by age group (50-59, 60-69, 70-79, ≥ 80 years; 50-64, ≥ 65) and within each age group across pre-specified categories of time since vaccination (follow-up year since vaccination: Year 1, Year 2, etc.; data permitting), and by payer type within the MORE2 database (Medicare Advantage, managed Medicaid, commercial insurance), we will employ similar methods as for the primary VE analysis. Additional details on the objective stratification will be included in the SAP. Descriptive analyses and Cox proportional hazards regression or Fine-Gray model will be conducted by strata and estimates of VE (%) will be calculated as $(1 - \text{adjusted HR}) \times 100$.

Secondary Objective 2: To estimate the VE of 2 doses of RZV (i.e., having initiated RZV and receiving dose 2 at time t) versus remaining unvaccinated at the nearest eligible preventive visit relative to the matched vaccinated participant's RZV dose 2 in preventing other HZ complications (HZ-associated hospitalizations, HZO) in adults aged ≥ 50 years, stratified by age group (50-59, 60-69, 70-79, ≥ 80 years; 50-64, ≥ 65), by pre-specified categories of time since vaccination (follow-up year since vaccination: Year 1, Year 2, etc.; data permitting), and by payer type within the MORE² database (Medicare Advantage, managed Medicaid, commercial insurance), we will employ similar methods as for the primary VE analysis. Additional details on the objective stratification will be included in the SAP. Descriptive analyses and Cox proportional hazards regression or Fine-Gray model will be conducted by strata and estimates of VE (%) will be calculated as $(1 - \text{adjusted HR}) \times 100$.

Secondary Objective 3: To estimate the VE of 2 doses of RZV (i.e., having initiated RZV and receiving dose 2 at time t) versus remaining unvaccinated at the nearest eligible preventive visit relative to the matched vaccinated participant's RZV dose 2 in preventing HZ and PHN in adults ≥ 18 years with IC/AID, overall and stratified by time since vaccination (follow-up year since vaccination: Year 1, Year 2, etc.; data permitting), within each age group (18-49, ≥ 50 years) across pre-specified categories of time since vaccination (follow-up year since vaccination: Year 1, Year 2, etc.; data permitting), and by payer type within the MORE² database (Medicare Advantage, managed Medicaid, commercial insurance), we will employ similar methods as for the primary VE analysis. Additional details on the objective stratification will be included in the SAP. Descriptive analyses and Cox proportional hazards regression or Fine-Gray model will be conducted overall and by strata and estimates of VE (%) will be calculated as $(1 - \text{adjusted HR}) \times 100$.

CVD events after HZ:

Secondary Objective 1: To estimate the VE of 2 doses of RZV (i.e., having initiated RZV and receiving dose 2 at time t) versus remaining unvaccinated at the nearest eligible preventive visit relative to the matched vaccinated participant's RZV dose 2 in preventing 3-point MACE (composite of hospitalized AMI, hospitalized stroke, cardiovascular death) within 3 months after HZ diagnosis among adults aged ≥ 50 years, stratified by age group (50-59, 60-69, 70-79, ≥ 80 years; 50-64, ≥ 65), within selected comorbidities (renal disease, heart disease, lung disease, liver disease, diabetes), and by payer type within the MORE² database (Medicare Advantage, managed Medicaid, commercial insurance), we will employ similar methods as for the primary VE analysis. Additional details on the objective stratification will be included in the SAP. Descriptive analyses and Cox proportional hazards regression or Fine-Gray model will be conducted by strata and estimates of VE (%) will be calculated as $(1 - \text{adjusted HR}) \times 100$.

Secondary Objective 2: To estimate the VE of 2 doses of RZV (i.e., having initiated RZV and receiving dose 2 at time t) versus remaining unvaccinated at the nearest eligible preventive visit relative to the matched vaccinated participant's RZV dose 2 in preventing 3-point MACE components: hospitalized AMI, hospitalized stroke, cardiovascular death, each separately within 3 months after HZ in adults aged ≥ 50 years, overall and stratified by age group (50-59, 60-69, 70-79, ≥ 80 years; 50-64, ≥ 65), within selected comorbidities (renal disease, heart disease, lung disease, liver disease, diabetes), and by payer type within the MORE² database (Medicare Advantage, managed Medicaid, commercial insurance), we will employ similar methods as for the primary VE analysis. Additional details on objective stratification will be included in the SAP. Descriptive analyses and Cox proportional hazards regression or Fine-Gray model will be conducted by strata and estimates of VE (%) will be calculated as $(1 - \text{adjusted HR}) \times 100$.

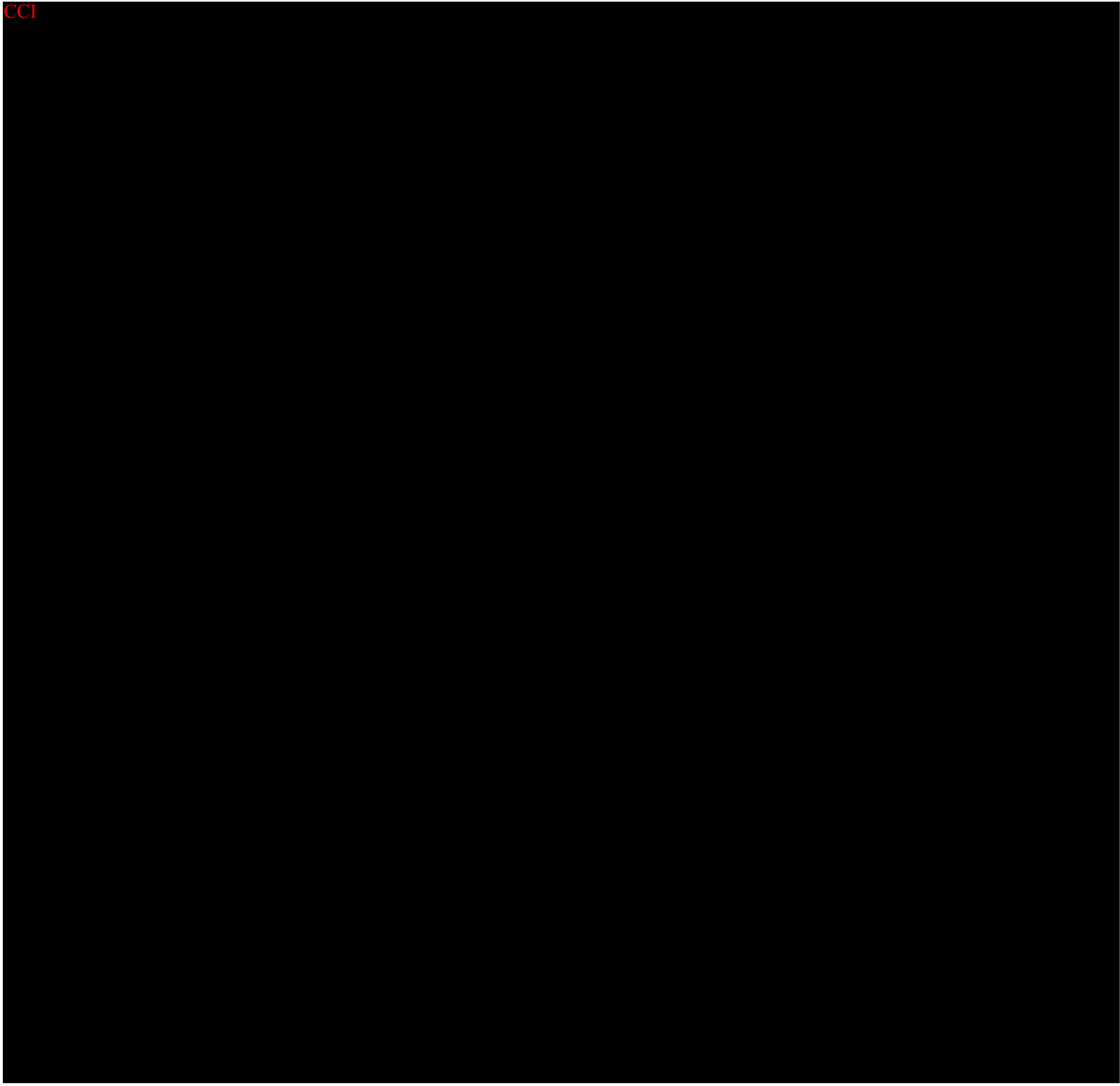
Secondary Objective 3: To estimate the VE of 2 doses of RZV (i.e., having initiated RZV and receiving dose 2 at time t) versus remaining unvaccinated at the nearest eligible preventive visit relative to the matched vaccinated participant's RZV dose 2 in preventing MACE composite and component outcomes (hospitalized AMI, hospitalized stroke, cardiovascular death) within 3 months, 6 months, 1 year after HZ, in adults ≥ 18 years with IC/AID, overall and stratified by age group (18-49, ≥ 50 years), and by payer type within the MORE² database (Medicare Advantage, managed Medicaid, commercial insurance), we will employ similar methods as for the primary VE analysis. Additional details on objective stratification will be included in the SAP. Descriptive analyses and Cox proportional hazards regression or Fine-Gray model will be conducted by strata and estimates of VE (%) will be calculated as $(1 - \text{adjusted HR}) \times 100$.

Secondary Objective 4: To estimate the VE of 2 doses of RZV (i.e., having initiated RZV and receiving dose 2 at time t) versus remaining unvaccinated at the nearest eligible preventive visit relative to the matched vaccinated participant's RZV dose 2 preventing MACE composite and component outcomes (hospitalized AMI, hospitalized stroke, cardiovascular death) within different time periods (6 months, 1 year) after HZ in adults aged ≥ 50 years, overall and stratified by age group (50-59, 60-69, 70-79, ≥ 80 years; 50-64, ≥ 65), and by payer type within the MORE² database (Medicare Advantage, managed Medicaid, commercial insurance), we will employ similar methods as for the primary VE

analysis. Additional details on objective stratification will be included in the SAP. Descriptive analyses and Cox proportional hazards regression or Fine-Gray model will be conducted by strata and estimates of VE (%) will be calculated as $(1 - \text{adjusted HR}) \times 100$.

Secondary Objective 5: To assess association between 2 doses of RZV (i.e., having initiated RZV and receiving dose 2 at time t) versus remaining unvaccinated at the nearest eligible preventive visit relative to the matched vaccinated participant's RZV dose 2 in the risk of all-cause key CVD outcomes (hospitalized AMI, hospitalized stroke, cardiovascular death) in adults aged ≥ 50 years, overall and stratified by age group (50-59, 60-69, 70-79, ≥ 80 years; 50-64, ≥ 65), and by payer type within the MORE² database (Medicare Advantage, managed Medicaid, commercial insurance), we will we will employ similar methods as for the primary analysis to estimate adjusted HR. Descriptive analyses and if sample size allow, Cox proportional hazards regression or Fine-Gray model will be conducted by strata to calculate adjusted HR. Additional details on objective stratification will be included in the SAP.

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7.7.5. Sensitivity analyses

To conduct sensitivity analysis of the primary objectives, we will fit either the Cox proportional hazards regression model or the Fine-Gray model (as described in Section 7.7.1). These analyses may include the following cases, if there is sufficient sample size:

- For the PHN Primary Objective
 - Evaluate a composite negative control outcome
 - The composite NCO will be similar to the one used in [Taquet, 2024], which included wrist fracture, acute pancreatitis, appendicitis, acute cholecystitis, adhesive capsulitis of the shoulders, and trigeminal neuralgia.
 - Alternative 2-dose analyses: 2 doses of RZV 4 weeks-6 months apart, 2 doses of RZV > 6 months apart (>6-18 months, >18-24 months, >24 months)
- For the CVD events after HZ Primary Objective
 - Evaluate a composite negative control outcome
 - The composite NCO will be similar to the one used in [Taquet, 2024], which included wrist fracture, acute pancreatitis, appendicitis, acute cholecystitis, adhesive capsulitis of the shoulders, and trigeminal neuralgia.
 - Alternative timeframes after HZ: 4 months, 1 month
 - Alternative 2-dose analyses: 2 doses of RZV 4 weeks-6 months apart, 2 doses of RZV > 6 months apart (>6-18 months, >18-24 months, >24 months)
 - Alternative hospitalized stroke definition: ischemic stroke only

Quantitative bias analysis to test for unmeasured confounders: One assumption underlying the main 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 a quantitative bias analysis is to estimate the magnitude of effect of an unobserved confounder that is needed to change the statistical inference [Ding, 2016; VanderWeele, 2011; Schneeweiss, 2006]. This can be accomplished by estimating the bounding (or bias) factor and dividing the observed risk ratio by the bounding factor to obtain the most that unmeasured confounders could alter the effect estimate [VanderWeele, 2017]. One could also estimate the E-value, which is the minimum strength of association an unmeasured confounder would need to have to nullify the treatment-outcome association [VanderWeele, 2017]. Quantitative bias analysis will be conducted for the primary objectives.

7.8. Quality control and Quality Assurance

This study will be conducted according to local quality control processes. This procedure requires documented evidence that the study protocol has been correctly interpreted and executed.

Quality assurance will be an ongoing process throughout the project. All data for this study will be obtained, processed, and managed by Inovalon, and all analyses will be conducted by Inovalon. The study programmer will be responsible for developing all SAS code, including a log detailing methodological and analytic changes agreed to by the study teams over the course of the project. Upon receipt of each of the respective data extracts, edit, range, and logic checks will be performed on each data field by the project programmer using SAS® 9.4 for Windows® to ensure the quality and completeness of the study databases and all of the variables therein.

Additionally, a second, independent programmer will perform code review to confirm that SAS code is written with correct syntax and generates results as specified per the protocol. The primary study programmer will resolve any issue identified by the code reviewer. All data files and statistical programs used to generate results will be archived on secured servers.

The full Inovalon team (i.e., study lead, analytic lead, and study support) will examine all programming output prior to the creation of the descriptive results tables. The Inovalon study lead will be responsible for validating all the results tables to confirm that results are consistent across analysis tables and that the results make logical sense. If applicable, results may be compared with previous literature to ensure consistency.

Additionally, Inovalon will conduct a pre-specified data quality assessment (DQA) of the MORE² source data prior to the primary analysis. The DQA will evaluate coding completeness and consistency for key study elements, including SHINGRIX exposure, study outcomes, and critical covariates, overall and stratified by payer type. Variability in coding patterns and data completeness across payer types will be quantified and reported transparently. Pre-specified data quality thresholds and decision rules will be applied to identify potential data quality concerns, and the potential impact of any observed heterogeneity on exposure ascertainment, outcome identification, and confounding control will be assessed and documented. Findings from the DQA will be incorporated into the interpretation of vaccine effectiveness estimates and any limitations related to cross-payer heterogeneity will be explicitly acknowledged.

7.9. Limitations of the research methods

- The use of the full, 100% Medicare FFS database is a major strength of this research based on its comprehensive national coverage and longitudinal depth, which enables robust population-level analyses. The inclusion of the MORE² Registry® database is an additional strength of this study, as it allows capture of data for the general population of adults from 50 YOA, as Medicare FFS enrollment is typically at 65 YOA. These data sources ensure coverage of the entire age range of US adults indicated and who receive SHINGRIX, and coverage of all major US payer types; this ensures the analyses will be generalizable to most US adults with public or private insurance. While a limitation of Medicare FFS claims data is that the data only capture vaccination after individuals enroll in Medicare FFS, which could lead to misclassification of exposure status for those vaccinated before 65 YOA who then enroll in Medicare FFS, this limitation is minimized through the study design. Study accrual starts from January 2018, thus capturing the period of SHINGRIX introduction in the U.S.; this ensures that the time period where SHINGRIX would be received for most of the study population from Medicare FFS is covered. Therefore, this limitation is only relevant for individuals in the study population who newly enroll or age into Medicare FFS (turn 65 YOA) over the period of the study. For context, in 2023 ~6% of all Medicare beneficiaries (including Medicare FFS and Medicaid Advantage) were new enrollees [CMS, 2025]. Additionally, misclassification of exposure status for individuals who age into Medicare FFS (turn 65 YOA) is less likely in the first years of the study when vaccination uptake was relatively low. Even in the most recently updated U.S. CDC estimates from the 2023 NHIS, SHINGRIX coverage (≥ 2 doses) was 17.5% among those 50–59 YOA and 24.3% for those 60–64 YOA [CDC, 2026]. Based on these percentages, we expect newly enrolled and previously SHINGRIX vaccinated would not be more than ~2% in a given year. If misclassification of RZV exposure is present, it would cause the observed effect sizes to underestimate the true association between RZV vaccination and the study outcomes, due to dilution of the exposed and unexposed groups. Overall, these considerations limit the concern for misclassification of RZV exposure status among Medicare beneficiaries in our study. Misclassification of ZVL history based at all available data will likely be higher in Medicare FFS cohort since data from 50–64 YOA will not be available, but is likely non-differential.
- Administrative claims data are collected for the purpose of billing and reimbursement, not for coordinating medical care or conducting outcomes research. Coding errors and underreporting of clinical conditions that do not trigger a billable event are possible. As such, there is some chance that the data on medical conditions and outcomes are not documented correctly. This can lead to participant misclassification either due to miscoding or misdiagnosis. Nonetheless, the primary outcomes will be assessed using algorithms that have been validated for use in claims data.

- Observational bias may be another limitation if there is a significantly different length of follow-up between the RZV vaccinated and unvaccinated comparator groups. In a previous GSK sponsored study using a 20% random sample of Medicare beneficiaries, there was a slight difference in follow-up time, primarily due to unvaccinated individuals becoming vaccinated. However, this study will report the mean/median length of follow-up time for all cohorts, and we will address the potential bias by using time-varying IPCW to address informative censoring.
- Another limitation is lack of generalizability to uninsured populations. However, for the primary analyses of individuals ≥ 50 YOA, the combination of the use of the 100% Medicare FFS database and the MORE² database including participants from a broad set of insurance types from all major U.S. healthcare payer types ensures the analyses is representative of most U.S. adults with public or private insurance. Use of the full, 100% Medicare FFS database is a major strength of this research based on its comprehensive national coverage and longitudinal depth, which enables robust population-level analyses. The dataset includes detailed claims for all enrolled beneficiaries, allowing for complete capture of healthcare utilization, diagnoses, procedures, and prescription fills across diverse care settings. This breadth supports high statistical power and generalizability to the older U.S. adult population. Additionally, the ability to track individuals over time facilitates temporal analyses of exposures and outcomes while minimizing selection bias.

7.9.1. Study closure/uninterpretability of results

Not applicable for this study.

7.10. Other aspects

Not applicable.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

This study will comply with all applicable laws regarding participant privacy. No direct subject contact or primary collection of individual human subject data will occur. Under a research DUA between Inovalon and CMS, Inovalon has direct access to 100% Medicare FFS enrollment information and claims for Parts A, B and Part D PDE data for all Part D plans. The DUA allows for collaboration with life sciences companies to utilize the in-house 100% FFS claims data to further Medicare research in the domains of access to care, healthcare resource utilization, and quality of care. Study results will be in tabular form and aggregate analyses that omits subject identification, therefore informed consent is not required. Any publications and reports will not include subject identifiers.

The protocol will be submitted to an Institutional Review Board (IRB) for Exempt Determination under 45 CFR 46.104(d)(4). The study involves the secondary research use of data originally collected for non-research purposes. Study initiation, including any data access or analysis, will commence only upon receipt of formal IRB determination.

8.2. Subject confidentiality

The MORE² Registry® and 100% Medicare FFS databases are de-identified and in compliance with the confidentiality requirements outlined in the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Additionally, all cells with a value less than 11 will be suppressed when sharing results of our analyses, per CMS reporting requirements.

9. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

The authors confirm that study data is Individual Human Data (IHD) not owned by GSK, but that the proposed use of the IHD aligns with the ‘purpose of use’ outlined in the source contract and/or the terms and conditions of use of the data source and it will comply with any specified prohibitions of use.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study does not have safety objectives. Safety collection and reporting will correspond to the following study type:

Study type 4: Secondary data collection studies based on structured data or unstructured data without human review without safety objectives. Structured data includes de-identified/anonymised healthcare data or health data are converted to a structured forms using automated/computer algorithms e.g., natural language processing. Unstructured data without human review, includes use of an automated algorithm and/or natural language processing for data extraction.	<i>These studies will not identify safety events as per study objective and cannot identify spontaneous events</i>
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Collection of adverse events/reactions (Solicited Events)

The study outcomes are endpoints unrelated to safety that will not be collected and reported as solicited safety events.

Reporting of adverse events/reactions (Spontaneous Events)

There is no potential to collect serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK product during the conduct of this research, as the minimum criteria of identifiable patient, reporter, exposure and event, needed to collect and report individual case safety reports are not present in the data source. The study is based on secondary anonymized healthcare data which lack an identifiable patient and reporter and are insufficient to establish attribution between a potential safety event and an individual patient using a GSK product.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study protocol and results will be registered in an appropriate registry as per GSK policy. Results may be presented at local, national, or international professional conferences and will be submitted as manuscripts for peer-reviewed publication within policy defined timelines.

CMS Requirement: Public Dissemination

The Medicare DUA with the CMS has two requirements with which Inovalon must comply. First, Inovalon will analyze no more than a 20% cohort of total Medicare population in any given year. Should the final analysis sample exceed the 20% threshold, Inovalon will conduct random sampling to meet this requirement. While CMS limits final cohort sizes to no more than 20% of total Medicare beneficiaries in any given year, we do not anticipate any concerns with that threshold for this study. Second, all cells with a value less than 11 will be suppressed when sharing results of our analyses.

Second, Inovalon has an obligation to disseminate certain findings of our research that utilizes the Medicare FFS data. In the case that GSK does not publish findings in an abstract, poster, and/or manuscript, Inovalon may pursue an “Insight” to fulfil the CMS public dissemination requirement.

Authorship

This study will adhere to the International Committee of Medical Journal Editors (ICMJE) recommendations for authorship.

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ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2 VARIABLE DEFINITION DETAIL**IC/AID Algorithms:**

Validated algorithms in the CBER BEST assessment report [[Saunders-Hastings, 2021](#)] will be used to identify IC conditions; including HIV, hematologic malignancies, solid tumor, solid organ transplant ICD-10-CM Codes (Section [7.2.1.1.2](#)) and validated coding algorithms that have high positive predictive values (**PPVs**), i.e., >75%, will be used to identify study participants who have IC status.

For all definitions below, the claim can be taken from any setting (inpatient, outpatient, ED, etc.) and from any position of the code in the claim:

Annex Table 1: Identification of Immunocompromised (IC) cohorts

IC	Algorithm
HIV/AIDs	≥2 claims for ANY HIV/AIDS diagnostic codes that were at least 30 days apart during the 15-month baseline period. This category is viewed as immunocompromised regardless of treatment status {treatment (RX)-independent}.
Hematologic malignancies	≥2 claims for ANY relevant diagnostic codes that were at least 30 days apart during the 15-month baseline period. This category is viewed as immunocompromised regardless of treatment status (RX-independent).
Solid tumor	≥2 claims for ANY solid malignancy diagnostic codes (at least 30 days apart) during the 15-month baseline period AND one of: • ≥2 claims for ANY codes for chemotherapy or radiation that were at least 30 days apart during the 15-month baseline period • ≥2 claims for ANY codes for immune-modulating or immunosuppressant therapy that were at least 30 days apart during the 15-month baseline period
Solid organ transplant	• ≥1 claims for ANY transplant or related condition diagnostic codes during the 15-month baseline period AND • ≥2 claims for ANY codes for immune-modulating or immunosuppressant therapy that were at least 30 days apart during the 15-month baseline period
Stem cell transplant	• ≥1 claims for ANY stem cell transplant diagnostic codes during the 15-month baseline period AND • one of: a. ≥2 claims for ANY codes for chemotherapy or radiation that were at least 30 days apart during the 15-month baseline period. b. ≥2 claims for ANY codes for immune-modulating or immunosuppressant therapy that were at least 30 days apart during the 15-month baseline period.

Claims-based algorithms obtained from the published literature defining AID conditions and are validated with demonstrated PPV will be used to identify participants with AID. Information on PPVs for each condition are described below.

Annex Table 2: Identification of Individuals with Autoimmune Diseases (AIDs)

AID	Algorithm
Systemic lupus erythematosus (SLE)	≥1 inpatient claim with a diagnosis code for SLE OR ≥2 physician outpatient claims with SLE diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 15-month baseline period prior to the index date OR ≥ 1 rheumatologist visit/encounter/claim for SLE. - The algorithm that includes ≥1 rheumatologist visit/encounter/claim has demonstrated a PPV of 95% and sensitivity of 83% [Hanly, 2014].
Multiple sclerosis (MS)	≥3 claims from any inpatient ICD-10-CM diagnoses of MS, from ambulatory visit (AV) diagnoses of MS, emergency department (ED) diagnoses of MS, or MS-specific disease-modifying therapy fills/infusions during the 15-month baseline period (at any position at least one day apart). At least one of these must be an inpatient, AV, or ED diagnosis of MS (i.e., all three claims cannot be from MS-specific disease modifying therapy fills/infusions). - This algorithm has demonstrated a PPV of 95-97% and sensitivity of 85-93% [Culpepper, 2019].
Rheumatoid arthritis (RA)	- Any 2 outpatient claims with an ICD-10-CM diagnosis code for RA from any position at least 3 months apart during the 15-month baseline period - The above algorithm has a PPV of 81% (95% CI: 79%-83%) [Callhoff, 2022]
Inflammatory bowel disease (IBD)	≥1 inpatient claim with an ICD-10-CM diagnosis code for IBD from any position OR ≥2 physician outpatient claims with IBD diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 15-month baseline period prior to the index date. - The above algorithm has no demonstrated PPV but has been used extensively in the literature [Weng, 2007].
Psoriasis (PsO)	≥1 dermatologist recorded ICD-10-CM diagnosis code (from any setting) for PsO from any position, in the 15-month baseline period prior to the index date. - The above algorithm has demonstrated a PPV of 90% (95% CI, 83-95) and sensitivity of 88% (95% CI, 80-93) based on ICD-9 codes [Asgari, 2013].
Psoriatic arthritic (PsA)	≥2 rheumatologist recorded ICD-10-CM diagnosis codes for PsA from any position, that were at least 30 days apart, in the 15-month baseline period prior to the index date. - The above algorithm has demonstrated a PPV of 81% (95% CI, 68-90) and sensitivity of 77% (95% CI, 64-87%) based on ICD-9 codes [Asgari, 2013].

[Annex Table 3](#) presents results of initial queries of the Medicare FFS and MORE² databases between 1 January 2017 and 31 December 2023 (latest data available at the time of database query) exploring the study subgroups of interest.

Annex Table 3: Participant Feasibility Counts – Subgroups of Interest

Step description	MORE ²
	N
Number of individuals that turn 50 years old between October 21, 2017 and October 20, 2018 (i.e., move from 49 to 50 years old)	3,507,729
Step description	MORE²
	N
Number of individuals 18-49 YoA who present ≥1 claim for a condition classifying the patient as immunocompromised or as having an autoimmune disease any time between October 21, 2020 and October 20, 2021.	1,120,922

ANNEX 3 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	☒	☐	☐	4
1.1.2 End of data collection ²	☒	☐	☐	4
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.	☒	☐	☐	4

Comments:

1.1.3 and 1.1.4: no formal progress or interim reports planned

1.1.5: Registration is planned prior to start of data analysis

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)	☒	☐	☐	5, 6
2.1.2 The objective(s) of the study?	☒	☐	☐	6
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	5, 6

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 2: Research question	Yes	No	N/A	Section Number
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	5, 6
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☒	☐	

Comments:

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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)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	10
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7.7.2.1
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))	☒	☐	☐	7.7.2.1
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)	☐	☐	☒	10

Comments:

3.5: N/A, Section 10 explains the rationale

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	7.1, 7.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	7.1, 7.2

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.2 Age and sex	☒	☐	☐	7.1, 7.2
4.2.3 Country of origin	☐	☐	☒	
4.2.4 Disease/indication	☒	☐	☐	7.1, 7.2
4.2.5 Duration of follow-up	☒	☐	☐	7.1, 7.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	7.2.1

Comments:

4.2.2. Age group is defined, no inclusion/exclusion by sex
4.2.3. The study will be conducted in US claims databases, no inclusion/exclusion by country of origin

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)	☒	☐	☐	7.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☒	☐	☐	7.3.1, 7.9
5.3 Is exposure categorized according to time windows?	☒	☐	☐	7.3.1
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	7.3.1
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?	☒	☐	☐	7.3.1

Comments:

5.4: Number of doses is defined

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?	☒	☐	☐	7.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.2
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)	☒	☐	☐	7.3.2
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)	☒	☐	☐	7.3.2

Comments:

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Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	5.2, 7.3.3., 7.7
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	5.2, 7.7
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	5.2, 7.7

Comments:

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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, subgroup analyses, anticipated direction of effect)	☒	☐	☐	6, 7.3.3, 7.7

Comments:

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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)	☒	☐	☐	7.3.1
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	7.3.3
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)	☒	☐	☐	7.4
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.4
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-mediations, lifestyle)	☒	☐	☐	7.4
9.3 Is a coding system described for:				

Section 9: Data sources	Yes	No	N/A	Section Number
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	7.3.1
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	7.3.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	7.3.3, 7.4
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	7.3.2, 7.4

Comments:

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Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7.1
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.5
10.3 Are descriptive analyses included?	☒	☐	☐	7.7
10.4 Are stratified analyses included?	☒	☐	☐	7.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	7.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	7.7
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	7.7.1.4
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	7.7.5

Comments:

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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)	☒	☐	☐	7.6
11.2 Are methods of quality assurance described?	☒	☐	☐	7.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

11.3: There is not a system in place for independent review of the study results. However, study deliverables including data tables and summaries of results (study reports) will be reviewed by all stakeholders including Inovalon and GSK staff.

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?	☒	☐	☐	5.2, 7.7, 7.9
12.1.2 Information bias?	☒	☐	☐	5.2, 7.7, 7.9
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).	☒	☐	☐	5.2, 7.7, 7.9
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)	☒	☐	☐	7.5

Comments:

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Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	8.2

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?	☒	☐	☐	3

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)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

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