Kaiser Permanente Research

EPI-ZOSTER-031 VE US, Long-Term Effectiveness Study of Shingrix in Adults ≥ 50 Years of Age in the US

Project Name	Zoster
GSK e-Track study number and Abbreviated Title	209570 (EPI-ZOSTER-031 VE US)
Date of protocol	26 May 2020
Date of protocol amendment 1	17 February 2022
Study Delivery Lead (SDL)	PPD
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Protocol Sponsor Signatory Approval

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Sponsor signatory	Agnes Mwakingwe-Omari Clinical and Epidemiology Project Lead (CEPL) for Zoster, Clinical R&D
Signature	_____
Date	_____

Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol and with the terms of the study agreement.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, "Good Pharmacoepidemiology Practice" (GPP) and "Good Epidemiologic Practices" (GEP) as well as all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

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Investigator name	_____
Signature	_____
Date	_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 1 (17 February 2022):

Overall rationale for the current amendment: To include race/ethnicity as a possible matching variable to minimize the impact of bias and confounding in the study design.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 7.2 **Identification of Study Cohorts**	***Added the following sentence: Further matching will be done on race/ethnicity (with categories being White, Black, Hispanic, Asian, and Other) if 95% of exposed individuals can be fully matched to 4 unexposed individuals.*** ***Updated matching in Figure 1 to include race/ethnicity***	***The amendment aligns the protocol with the SAP to reflect the inclusion of race/ethnicity as a matching variable to minimize potential bias and confounding in the study design***
Section 8.4 **Sample Size and Power Estimation**	***Added "race/ethnicity" to the list of matching variables.***	***The amendment aligns the protocol with the SAP to reflect the inclusion of race/ethnicity as a matching variable***
Section 8.5 **Projected Timelines**	***Table 7. Study timelines updated.***	***Timelines were updated as the cohort accrual was achieved one year earlier than planned.***

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ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AMI	Acute Myocardial Infarction
CI	Confidence Interval
EHR	Electronic Health Record
EMA	European Medicines Agency
FDA	Food and Drug Administration
GSK	GlaxoSmithKline Biologicals SA
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
HZ	Herpes Zoster
HZO	Herpes Zoster Ophthalmicus
ICD	International Classification of Diseases
IRB	Institutional Review Board
KPSC	Kaiser Permanente Southern California
NLP	Natural Language Processing
PHI	Protected Health Information
PHN	Post-Herpetic Neuralgia
RCT	Randomized Controlled Trial
RIPC	Regional Immunization Practice Committee
RZV	Recombinant Zoster Vaccine
Tdap	Tetanus, diphtheria and pertussis vaccine
US	United States
VE	Vaccine Effectiveness
VZV	Varicella Zoster Virus
ZOE-50	Zoster Efficacy Study in Adults 50 Years of Age or Older
ZOE-70	Zoster Efficacy Study in Adults 70 Years of Age or Older
ZVL	Zoster Vaccine Live

1. SYNOPSIS

Herpes zoster (HZ), or shingles, is an often painful vesicular rash caused by reactivation of varicella zoster virus (VZV) persisting latently in dorsal root ganglia [1, 2]. The pain from acute HZ can be disabling, and if complicated by the development of post-herpetic neuralgia (PHN), can last for months or years. Before zoster vaccine live (*Zostavax*, ZVL) was introduced, about one million episodes of HZ occurred in the United States (US) annually [3]. A study among the Medicare population showed that the effectiveness of ZVL against incidence of HZ and PHN was 48% and 59%, respectively [4]. Subsequent studies have shown the protection of ZVL wanes over time [5-7].

Recombinant zoster vaccine (*SHINGRIX*, RZV), a two-dose subunit zoster vaccine containing recombinant glycoprotein E in combination with a novel adjuvant ($AS01_B$), was licensed by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2017. This decision was based on two large parallel Phase III randomized controlled trials (RCTs): the Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50) and the Zoster Efficacy Study in Adults 70 Years of Age or Older (ZOE-70). Vaccine efficacy against HZ was 97.2% in adults ages ≥50 years in ZOE-50 and 89.8% in adults ≥70 in ZOE-70. Vaccine efficacy against PHN was 91.2% in pooled analyses [8]. Subsequent to FDA approval for the prevention of HZ in individuals ≥50 years of age, the Advisory Committee on Immunization Practices (ACIP) made three recommendations: (1) RZV is recommended for immunocompetent adults aged 50 years and older; (2) RZV is recommended for immunocompetent adults previously vaccinated with ZVL; and (3) RZV is the preferred vaccine over ZVL [9].

While the clinical trial data provided evidence that RZV works under ideal conditions (*i.e.,* vaccine efficacy), confirmation of these results is needed in real-world conditions (*i.e.,* vaccine effectiveness [VE]) to show whether benefits of the vaccine can be generalized to conditions of real-world clinical practice [10-12].

We will conduct a long-term, observational, cohort study in adults aged ≥ 50 years at Kaiser Permanente Southern California (KPSC), a large integrated health care organization serving approximately 4.6 million racially and ethnically diverse members. Comprehensive electronic health records (EHR) at KPSC integrate all aspects of patient care, including patient demographics, diagnoses, vaccinations, medications, procedures, and laboratory results. The KPSC vaccine team has extensive experience in vaccine safety and effectiveness research and has access to EHR data in near real-time to facilitate research.

The primary objectives of the study are (1) to estimate the VE of 2 doses of RZV in preventing HZ and (2) to estimate the VE of 2 doses of RZV in preventing PHN when used in a real-world setting. HZ incidence and PHN incidence among individuals who received 2 doses of RZV will be compared to a cohort of individuals who did not receive RZV, (*i.e.,* RZV unvaccinated). Individuals will be followed until the end of their 10-year follow-up period, death, receipt of a dose of RZV among the RZV unvaccinated cohort, or termination of KPSC membership (allowing for a 31-day gap in membership), whichever comes first. For both HZ and PHN outcomes, crude VE (%) will be estimated. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) comparing incidence in the 2-dose RZV vaccinated and RZV unvaccinated cohorts will be estimated by Cox proportional hazards regression models adjusting for potential confounders. Adjusted VE will be computed as 1-adjusted HR. Secondary analyses will be conducted to assess VE of 1 or 2 doses of RZV in various subgroups of adults ages ≥50 years, using similar methods as the primary analysis.

2. BACKGROUND

Herpes zoster (HZ), or shingles, is an often painful vesicular rash caused by reactivation of varicella zoster virus (VZV) persisting latently in dorsal root ganglia [1, 2]. The pain from acute HZ can be disabling, and if complicated by the development of post-herpetic neuralgia (PHN), can last for months or years. Before a vaccine was introduced, about one million episodes of HZ occurred in the United States (US) annually [3]. Aside from increasing age and immunosuppression, the other risk factors for this condition are not well known [13], but some evidence suggests sex, race / ethnicity, family history, and comorbidities may be associated with HZ [14].

Zostavax (zoster vaccine live [ZVL]), a live-attenuated vaccine prepared from the Oka/Merck strain of VZV, was licensed by the Food and Drug Administration (FDA) in 2006 and recommended by the Advisory Committee on Immunization Practices (ACIP) for healthy adults aged 60 years and older [3]. ZVL was licensed for adults aged 50-59 years in 2011, but due to ZVL shortages and waning protection, ACIP never recommended routine vaccination with ZVL in this age group. A study among the Medicare population showed that the effectiveness of ZVL against incidence of HZ and PHN is 48% and 59%, respectively [4]. Subsequent studies have shown the protection of ZVL wanes over time [5-7].

Recombinant zoster vaccine (*SHINGRIX*, RZV), a two-dose subunit zoster vaccine containing recombinant glycoprotein E in combination with a novel adjuvant ($AS01_B$), was licensed by the FDA in 2017. This decision was based on two large parallel Phase III randomized controlled trials (RCTs): the Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50) and the Zoster Efficacy Study in Adults 70 Years of Age or Older (ZOE-70). ZOE-50 assessed whether RZV reduced the risk of HZ in adults 50 years of age or older. During a mean follow-up of 3.2 years, HZ was confirmed in 6 out of 7,698 participants in the vaccine group and in 210 out of 7,713 participants in the placebo group (incidence rate 0.3 vs. 9.1 per 1,000 person-years). Overall vaccine efficacy against HZ was 97.2% and ranged between 96.6% and 97.9% for all age groups evaluated [15]. In ZOE-70, the overall vaccine efficacy against HZ was 89.8% (6,541 vaccinated participants and 6,622 placebo participants) and was similar in participants 70-79 years of age (90.0%) and participants 80 years of age and older (89.1%) [16]. Although these Phase III RCTs were not powered to show statistical significance in serious adverse events, there were no observed differences between subjects vaccinated with RZV and comparison populations for the overall reported rates of serious adverse events [15]. Per indication, RZV is not contraindicated in persons with immunosuppressive conditions or treatments. Subsequent to FDA approval, ACIP made three recommendations: (1) RZV is recommended for immunocompetent adults aged 50 years and older; (2) RZV is recommended for immunocompetent adults previously vaccinated with ZVL; and (3) RZV is the preferred vaccine over ZVL [9].

While the clinical trial data provided evidence that RZV works under ideal conditions (*i.e.,* vaccine efficacy), confirmation of these results is needed in field conditions (*i.e.,* VE including storage and handling) to show whether benefits of the vaccine can be generalized to conditions of clinical practice [10-12]. This is particularly important for RZV, given that the elderly population for whom the vaccine is indicated often has multiple comorbidities. Moreover, a large observational study allows for exploration of vaccine benefits and durability of protection among important patient subgroups that would be infeasible in most RCTs. With our experience in HZ and HZ vaccine [7, 17-30], Kaiser Permanente Southern California (KPSC) will conduct an RZV effectiveness study in the US.

3. STUDY OBJECTIVES

We will conduct a study to assess VE among individuals at KPSC who received RZV ("vaccinated") compared to individuals who did not receive RZV ("RZV unvaccinated") with 10 years of follow-up, addressing the objectives below.

Although RZV should be administered as 2 doses separated by 2-6 months, ACIP guidance followed at KPSC specifies that a second dose administered <4 weeks after the first dose should be repeated, but a second dose administered ≥4 weeks after the first dose does not need to be repeated [9]. Furthermore, due to variation in real-world practice, the second dose may be given earlier than 2 months after the first dose. Therefore, objectives refer to 2 doses of RZV given 4 weeks to 6 months apart, except where indicated otherwise (secondary objectives 8-9 and exploratory objective 1).

Primary objectives:

1. To estimate the VE of 2 doses of RZV in preventing HZ in adults aged ≥ 50 years
2. To estimate the VE of 2 doses of RZV in preventing PHN in adults aged ≥ 50 years

Secondary objectives:

1. To estimate the VE of 2 doses of RZV in preventing HZ in adults aged ≥ 50 years by age, by sex, and by race/ethnicity
2. To estimate the VE of 2 doses of RZV in preventing PHN in adults aged ≥ 50 years stratified by age, by sex, and by race/ethnicity
3. To estimate the VE of 2 doses of RZV in preventing HZ in adults aged ≥ 50 years, by prevalent comorbidities at baseline (kidney disease, heart disease, lung disease, liver disease, diabetes)
4. To estimate the VE of 2 doses of RZV in preventing HZ in adults aged ≥ 50 years, by history of ZVL
5. To calculate the incidence of HZ in vaccinated (2 doses of RZV) and RZV unvaccinated adults ≥ 50 years, by prior history of HZ
6. To estimate the VE of 2 doses of RZV in preventing herpes zoster ophthalmicus (HZO) in adults aged ≥ 50 years
7. To estimate the VE of 2 doses of RZV in preventing hospitalized acute myocardial infarction (AMI), and hospitalized stroke in adults aged ≥ 50 years
8. To estimate the VE of 1 dose of RZV in preventing HZ in adults aged ≥ 50 years
9. To estimate the VE of 1 dose of RZV in preventing PHN in adults aged ≥ 50 years

Exploratory objectives:

1. To estimate the VE of 2 doses of RZV in preventing HZ and PHN, when the second dose is received more than 6 months after the first dose in adults aged ≥ 50 years
2. To estimate the VE of 2 doses of RZV in preventing HZ, by presence of concomitant vaccination (*e.g.,* receipt of influenza vaccine, pneumococcal vaccine, or tetanus, diphtheria and pertussis vaccine [Tdap]) at the time of receiving either the first or second dose of RZV) in adults aged ≥ 50 years

3. To assess clinical characteristics associated with the acute HZ episode for a sample of cases (100 RZV vaccinated [2-dose] HZ cases and 100 RZV unvaccinated HZ cases) in adults aged ≥ 50 years
4. To estimate the VE of 2 doses of RZV in preventing HZ-related meningoencephalitis and bacterial superinfection in adults aged ≥ 50 years
5. To estimate the relative risk of disseminated HZ among vaccinated (2 doses of RZV) and RZV unvaccinated adults ≥ 50 years who are immunocompromised at the time of their incident HZ diagnosis

4. RESEARCH INSTITUTION OVERVIEW

4.1 Study Setting

Kaiser Permanente is one of the nation's largest not-for-profit health plans. As an integrated health care system, KPSC provides an ideal environment for population-based research. The health plan's population includes more than 4.6 million members who represent 260 different ethnicities and speak more than 150 different languages. The demographic makeup of the KPSC membership closely mirrors the Southern California population [31] and the California census population. Compared to the racial/ethnic distribution of the US population, KPSC membership is comprised of twice as many individuals of Asian/Pacific Island descent and three times as many Hispanic individuals.

KPSC facilities include hospitals and medical offices, all linked by an information infrastructure that supports both clinical practice and business needs. Health information from this infrastructure can be leveraged for research purposes. More than 90 percent of members remain in the health plan after one year; more than three-quarters remain after three years. The large, diverse, and stable population permits the rapid accrual of a representative sample size and offers the ability to evaluate long-term implications of immunization.

KPSC began administering ZVL in late 2006 when it was first recommended by the ACIP and KPSC Regional Immunization Practice Committee (RIPC). As of January 1, 2018, over 380,000 doses of ZVL had been administered. In 2017, ACIP recommended RZV preferentially over ZVL. As of April 2018, RZV is the preferred HZ vaccine for routine use and the standard care for the prevention of HZ in adults aged 50 years and older at KPSC. As of April 30, 2019, 60,481 individuals have received at least 1 dose of RZV and 26,887 have received 2 doses, despite limited supply of RZV that has since increased.

4.2 Electronic Health Records

Kaiser Permanente Health Connect is the largest and most advanced civilian electronic health record (EHR) system available in the US. In addition to supporting patient care, this robust system facilitates research, providing access to EHR for the KPSC vaccine research team. Up-to-date details of patient care are available and accessible to researchers. Data regarding demographics, services, and diagnoses are tracked from the outpatient, Emergency Department and hospital settings.

Pharmacy and vaccination utilization are linked through patients' unique medical record numbers. As KPSC is a pre-paid health care system, recommended vaccines such as RZV are provided to KPSC members at no charge and can be obtained at no-cost nurse visits or on a walk-in basis without appointment, which is an incentive for members to receive immunizations within the system. Vaccinations received outside of the health plan with appropriate documentation are also recorded in KPSC databases.

KPSC members have very strong motivation to use services internally. For outside providers to be reimbursed by the health plan for covered emergent or contract care, claims must be submitted with documentation of the episode of care, which is integrated into administrative data systems. Thus, the

capture of care is considered to be very comprehensive. Care received at KPSC is updated and available to researchers in near real time. Claims data are over 90% complete after 3 months.

4.3 Study Population Demographics

As of January 1, 2018, KPSC membership consisted of 1,495,838 KPSC members aged 50 years and older, 899,592 members aged 60 years and older, and more than 130,000 members aged 80 years and older (Table 1). Approximately 53% of KPSC members were female, and the racial/ethnic composition included White (43%), Hispanic (30%), Asian/Pacific Islander (11%), and African American (9%). Geographically, KPSC covers the entire Southern California region from Bakersfield to San Diego.

Table 1. Demographic distribution of KPSC members 50 years and older on January 1, 2018

Age on January 1, 2018 (years)	Frequency	Percent
50-59	596,246	39.86
60-69	493,190	32.97
70-79	275,722	18.43
80+	130,680	8.74
Sex		
Female	793,381	53.04
Male	702,457	46.96
Race/Ethnicity[1]		
White	636,438	42.55
Hispanic	452,243	30.23
Asian and Pacific Islander	167,298	11.18
African American	138,879	9.28
Multiple/other/unknown	100,980	6.75
Total	1,495,838	100
[1]All categories other than Hispanic are non-Hispanic ethnicity.		

Table 2 shows the length of retention of KPSC membership by age group beginning January 1, 2008. Approximately 52% of members aged 50-59, 61% of members aged 60-69 years, and 57% of members aged 70-79 years had completed 10 years of membership at KPSC. For members aged 80 years and older, the percentage of members who completed 10 years of membership at KPSC decreased to 24%. The stability of KPSC membership allows the unique opportunity to follow patients over time and conduct long-term effectiveness studies.

Table 2. Prospective length of KPSC membership among individuals aged ≥50 years on January 1, 2008

		Membership length (years)			
		0-5	>5-10	>10	Total
Age on January 1, 2008 (years)					
50-59	N	145,613	77,164	239,563	462,340
	Row %	31.49	16.69	51.82	
60-69	N	76,378	37,055	176,036	289,469
	Row %	26.39	12.8	60.81	
70-79	N	33,640	34,072	88,441	156,153
	Row %	21.54	21.82	56.64	
80+	N	34,335	23,808	18309	76,452
	Row %	44.91	31.14	23.95	
Total	Frequency	289,966	172,099	522,349	984,414

5. STUDY DESIGN OVERVIEW

We will conduct a long-term, observational cohort study in adults aged ≥ 50 years at KPSC with primary objectives of (1) estimating the VE of 2 doses of RZV in preventing HZ and (2) estimating the VE of 2 doses of RZV in preventing PHN.

A cohort design is ideal to examine multiple outcomes, estimate annual VE and evaluate waning effectiveness, and observe rare events (*e.g.,* breakthrough HZ, PHN, HZO), taking advantage of the EHR system at KPSC. For the primary analyses, HZ incidence and PHN incidence among individuals who received 2 doses of RZV separated by 4 weeks to 6 months will be compared to a cohort of individuals who did not receive RZV (*i.e.,* RZV unvaccinated). Individuals will be followed until the end of their 10-year follow-up period, death, receipt of a dose of RZV among the RZV unvaccinated cohort, termination of KPSC membership (allowing for a 31-day gap in membership), or occurrence of event of interest (for event-specific analyses), whichever comes first. Additional analyses will be conducted to address the secondary and exploratory objectives exploring the VE of 1 or 2 doses of RZV in various subgroups.

The study will be conducted in accordance with regulations and guidelines from the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (GPP), International Epidemiological Association Guidance on Good Epidemiological Practice (GEP), and the Council for International Organizations of Medical Sciences International Ethical Guidelines for Epidemiological Studies (CIOMS). [32-34]

6. MEASURES

6.1 Exposure Definitions

We will identify RZV vaccinations from the EHR, which is available and accessible in real-time, providing the ability to view vaccine details and collect patient immunization history at the point of care. Since the EHR captures the dates the vaccinations were given, we are able to determine the dose sequence based on the dates.

The index dose will be defined as the second RZV dose received 4 weeks to 6 months after the first dose for primary objectives 1-2, secondary objectives 1-7, and exploratory objectives 2-5. The index dose will be defined as the first RZV dose for secondary objectives 8-9. The index dose will be defined as the second RZV dose received more than 6 months after the first dose for exploratory objective 1. The index date corresponds to the index dose for the respective objectives.

6.1.1 Exposure for primary objectives

The exposure of interest for primary objectives 1-2 is receipt of 2 doses of RZV, with the second dose received 4 weeks to 6 months after the first dose.

6.1.2 Exposure for secondary objectives

The exposure of interest for secondary objectives 1-7 is receipt of 2 doses of RZV, with the second dose received 4 weeks to 6 months after the first dose. The exposure of interest for secondary objectives 8-9 is receipt of 1 dose of RZV.

6.1.3 Exposure for exploratory objectives

The exposure of interest for exploratory objective 1 is 2 doses of RZV, with the second dose received more than 6 months after the first dose. The exposure of interest for exploratory objectives 2-5 is 2 doses of RZV, with the second dose received 4 weeks to 6 months after the first dose.

6.2 Outcome Definitions

6.2.1 Identification of HZ

HZ will be defined by International Classification of Diseases (ICD)-10 codes (B02.xx) from hospital, outpatient, and Emergency Department settings with an antiviral prescription (acyclovir, valacyclovir, famciclovir) within 7 days before or after the date of HZ diagnosis. Inclusion of an antiviral prescription as part of the HZ definition ensures identification of new HZ diagnoses, rather than carry-over codes from prior HZ episodes.

6.2.2 Identification of PHN

PHN will be defined as HZ-related pain persisting >3 months after HZ diagnosis [35]. HZ-related pain will be defined as pain consistent with the HZ episode which is not explained by other obvious causes (e.g., rheumatoid arthritis). We will use targeted chart review to identify PHN from encounters in the >3- to 6-month period after HZ diagnosis.

6.2.3 Identification of other outcomes

Secondary and exploratory objectives, described further in Sections 0 and 0 respectively, include the following outcomes:

- HZO during the follow-up period will be identified using natural language processing (NLP) of EHR notes, as described in our previous study [36].
- Hospitalized AMI will be identified by ICD-10 codes from inpatient encounters, or Emergency Department encounters if the patient was hospitalized or if the patient died the same or next day.
- Hospitalized stroke will be identified by ICD-10 codes from inpatient encounters, or Emergency Department encounters if the patient was hospitalized or if the patient died the same or next day.
- Characteristics of the clinical presentation of the initial acute HZ episode will be identified from chart review.
- HZ-related meningoencephalitis will be identified by targeted chart review of inpatient encounters with ICD-10 codes and/or cerebrospinal fluid (CSF) test results positive for VZV.
- HZ-related bacterial superinfection will be identified by ICD-10 codes and antibiotic prescriptions.
- Disseminated HZ will be identified by targeted chart review of EHR of vaccinated and unvaccinated individuals who are immunocompromised at the time of their incident HZ diagnosis.

6.3 Other Variable Definitions

Other variables will be identified from EHRs and considered in analyses when appropriate as covariates or stratification variables, including:

- Demographic variables: age at index date, sex, race/ethnicity
- Health care utilization (number of outpatient/emergency/inpatient encounters) in year prior to index date
- Comorbidities (*e.g.,* kidney disease, heart disease, lung disease [*i.e.,* chronic obstructive pulmonary disease], liver disease, diabetes) in year prior to index date
- Immunocompromised status during follow-up (time-varying). Immunocompromised status will be identified from ICD-10 codes of immunocompromising conditions and pharmacy dispense data of immunosuppressing medications
- History of ZVL prior to index date based on dates of vaccinations in the EHR
- History of HZ prior to index date identified using ICD-10 codes (B02.xx) and ICD-9 codes (053.xx) from hospital, outpatient, and Emergency Department settings
- Concomitant vaccinations at time of exposure (*e.g.,* receipt of influenza vaccine, pneumococcal vaccine or Tdap)

7. STUDY POPULATION

7.1 Eligibility Criteria

Individuals will be eligible for inclusion in the study if the following criteria are met:

- Age 50 years or more at the index date for all study objectives
- At least 1 year of continuous KPSC membership before the index date (allowing for a 31-day gap in membership)

Certain individuals will be excluded from the study. Individuals who receive a second dose less than 4 weeks after the first dose will be excluded, since ACIP guidelines state that these individuals must repeat the second dose. Individuals with an HZ diagnosis in the 6 months prior to index date will be excluded to ensure that HZ diagnoses after index date are new, rather than carried over from HZ episodes prior to index date. Individuals with HZ occurring within 30 days after the index date for both exposed and unexposed groups will also be excluded since it is unclear if HZ began before or after index date and whether the length of time since vaccination (for RZV vaccinated individuals) is long enough to allow development of immunity.

Individuals with immunocompromising conditions (*e.g.,* leukemia, lymphoma, human immunodeficiency virus) or who received immunosuppressant agents in the year prior to index date will not be excluded from the study, but VE estimates will be adjusted for time-varying immunocompromised status (Section 0).

7.2 Identification of Study Cohorts

The study will comprise 3 RZV analytic cohorts (**Figure 1**). The "2-dose (4 weeks to 6 months) RZV cohort" will be used to address primary objectives 1-2, secondary objectives 1-7, and exploratory objectives 2-5. The "1-dose RZV cohort" will be used to address secondary objectives 8-9, and the "2-dose (> 6 months) RZV cohort" will be used for exploratory objective 1. RZV vaccinated individuals can contribute person-time to both the 1-dose and one of the 2-dose RZV cohorts. Unvaccinated individuals who are matched to RZV vaccinated individuals (as described below) can also contribute person-time to vaccinated cohorts if they receive RZV.

The 2-dose (4 weeks to 6 months) RZV cohort will include eligible individuals who received 2 doses of RZV separated by 4 weeks to 6 months. The date of the second RZV dose will be considered the index date. RZV unvaccinated individuals corresponding to the 2-dose (4 weeks to 6 months) RZV cohort will be randomly selected from the RZV unvaccinated population and 4:1 matched to the 2-dose (4 weeks to 6 months) RZV vaccinated individuals by age and sex. ***Further matching will be done on race/ethnicity (with categories being White, Black, Hispanic, Asian, and Other) if 95% of exposed individuals can be fully matched to 4 unexposed individuals. (Amended 17 February 2022.)*** The matching ratio was selected by optimizing the sample size of the 2-dose (4 weeks to 6 months) RZV cohort while considering the anticipated larger censoring rate in the RZV unvaccinated cohort due to receipt of RZV. The index date for the 2-dose (4 weeks to 6 months) RZV unvaccinated match will be the same as his/her matched 2-dose (4 weeks to 6 months) RZV vaccinated counterparts. The match will allow a sufficient sample size

of RZV unvaccinated individuals, as these individuals can eventually receive RZV during the study period. The match is also feasible given the KPSC population of 1.5 million members ages ≥50 years.

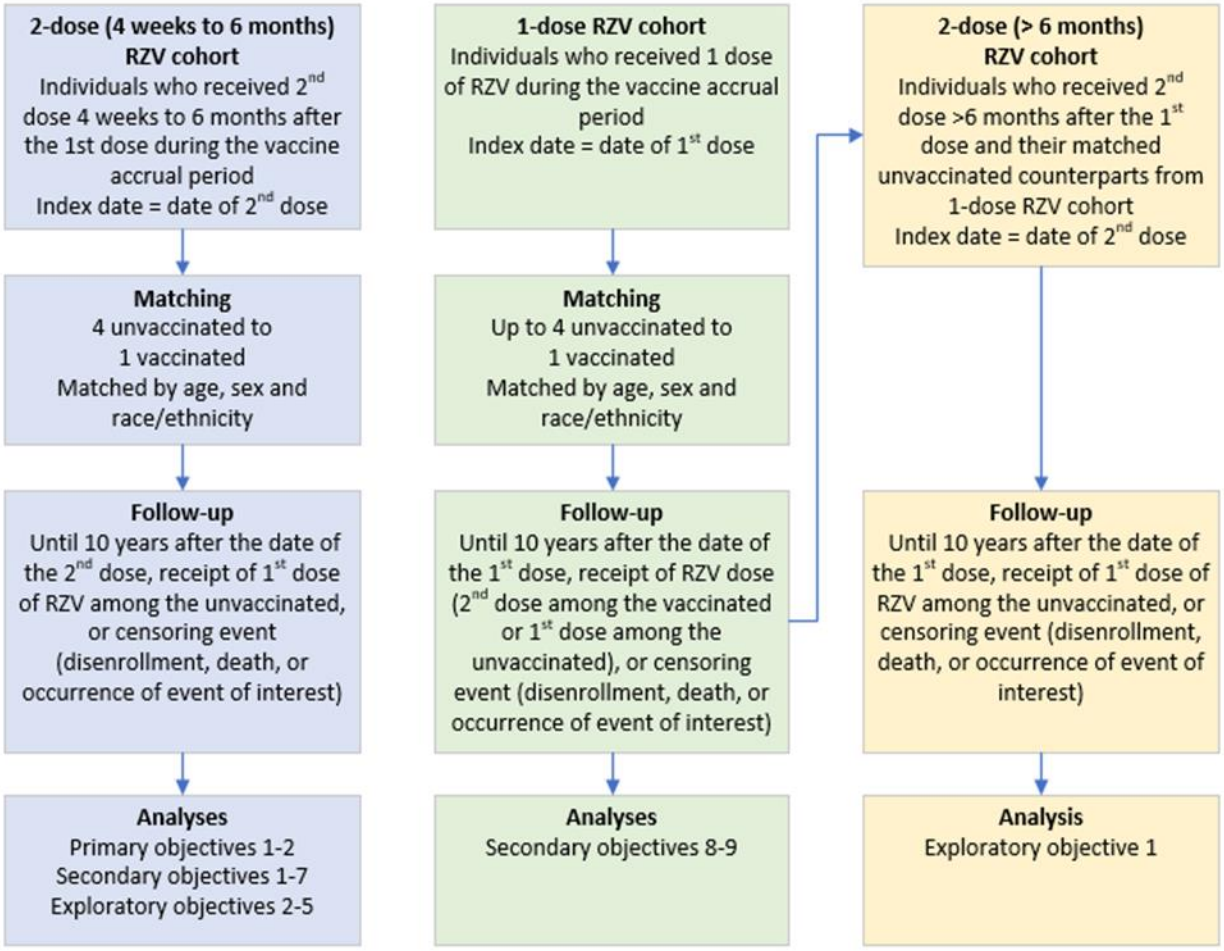
The 1-dose RZV cohort will consist of eligible individuals who receive 1 dose of RZV. Such individuals may go on to receive a second RZV dose within 4 weeks to 6 months of the first dose, a second RZV dose >6 months after the first dose, or no subsequent RZV doses. The index date for the 1-dose RZV cohort will be the date of the first dose of RZV. RZV unvaccinated individuals corresponding to the 1-dose RZV cohort will be randomly selected from the RZV unvaccinated population and up to 4:1 matched to the 1-dose RZV vaccinated individuals by age and sex. ***Further matching will be done on race/ethnicity (White, Black, Hispanic, Asian, and Other) if 95% of exposed individuals can be fully matched to 4 unexposed individuals. (Amended 17 February 2022.)*** The index date for the 1-dose RZV unvaccinated match will be the same as his/her matched 1-dose RZV counterpart. The same unvaccinated individual can be matched to both an individual in the 2-dose (4 weeks to 6 months) RZV cohort and an individual in the 1-dose RZV cohort. This increases the likelihood of being able to find an appropriate RZV unvaccinated match.

The 2-dose (>6 months) RZV cohort will comprise individuals who receive a second dose of RZV more than 6 months after the first dose. The date of the second RZV dose will be considered the index date. These individuals will retain the same unvaccinated matches that they had in the 1-dose RZV cohort. This is because the interval between the first dose and the second dose is unpredictable and could be very long (e.g. years), and it would not be feasible to indefinitely extend the study in order to match and follow-up these individuals. Some of the unvaccinated matches to the 1-dose RZV cohort may experience a censoring event (i.e., unvaccinated match receives RZV, terminates membership, dies, or develops the event of interest) and will no longer be available as an unvaccinated match at the time of the second RZV dose (>6 months) index date. These unvaccinated matches will not be replaced, so the matching ratio for the 2-dose (>6 months) RZV cohort will be less than 4:1.

Individuals will be followed for 10 years. For individuals and their matches in the 2-dose (4 weeks to 6 months) RZV cohort, this will be 10 years after the date of the second dose. For individuals in the 1-dose RZV cohort or 2-dose (>6 months) RZV cohort, this will be 10 years after the date of the first dose. Follow-up will end upon the occurrence of a censoring event (i.e., death, termination of KPSC membership (allowing for a 31-day gap in membership), or occurrence of event of interest (for event-specific analyses), whichever comes first.

Individuals in the 1-dose RZV cohort and their unvaccinated matches will contribute person-time to the 1-dose cohort until they receive an RZV dose, reach the end of follow-up, or experience a censoring event (i.e., termination of membership, death, or development of event of interest), upon which time they will stop contributing person-time to the 1-dose RZV cohort. Individuals who receive a second dose 4 weeks to 6 months after the first dose will enter the 2-dose (4 weeks to 6 months) RZV cohort, and they will receive new independently-selected unvaccinated matches, as described for the 2-dose (4 weeks to 6 months) RZV cohort above. Individuals who receive a second dose more than 6 months after the first dose will enter the 2-dose (>6 months) RZV cohort, but they will keep the same matches that they had in the 1-dose RZV cohort. However, only person-time contributed after the date of the second dose (>6 months) for vaccinated individuals and their unvaccinated matches will be included in the 2-dose (>6 months) analyses.

Figure 1. Construction of study cohorts (Amended 17 February 2022)



8. ANALYSIS

8.1 Primary Analyses

We will describe and compare the number and characteristics of individuals in each cohort. Categorical variables such as those listed in Section 0 will be presented as absolute numbers and percentages with p-values for the χ^2 test. Continuous variables such as age in years will be presented as the mean with standard deviation and/or median with interquartile ranges, with p-values for the two-sample t-test or Wilcoxon rank-sum test, as appropriate. Overall incidence rates of HZ for 2-dose (4 weeks to 6 months) RZV vaccinated cohort and the matched unvaccinated cohort will be calculated by dividing the number of HZ cases by the total number of person-years.

To calculate the crude VE by follow-up year after vaccination, the number of HZ cases occurring within that year and the number of person-years of follow-up for subjects in that year will be assessed for the 2-dose (4 weeks to 6 months) RZV cohort and the matched unvaccinated cohort. Crude VE (%) will be estimated as (1 – [incidence rate of HZ among 2-dose (4 weeks to 6 months) RZV recipients / incidence rate of HZ among RZV unvaccinated individuals]) x 100.

Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) comparing HZ incidence rates in the 2-dose (4 weeks to 6 months) RZV cohort and the matched unvaccinated cohort will be estimated by Cox proportional hazards regression models adjusting for potential confounders (Section 0). If the vaccine effect wanes over time and the proportional hazard assumption does not hold, time-varying Cox regression models which model the risk of HZ by time interval will be used to estimate the adjusted HRs and 95% CIs. Estimates of VE (%) will be calculated as (1 – adjusted HR) × 100. Competing risks such as death will be assessed and will be accounted for in the analyses as appropriate.

Similarly, to calculate the crude VE for preventing PHN by follow-up year after vaccination, the number of PHN cases occurring within that year and the number of person-years of follow-up for subjects in that year will be assessed for the 2-dose (4 weeks to 6 months) RZV cohort and the matched unvaccinated cohort. Crude VE (%) will be estimated as (1 – [incidence of PHN among the 2-dose (4 weeks to 6 months) RZV vaccine recipients / incidence of PHN among RZV unvaccinated individuals]) x 100. The adjusted HRs and 95% CIs comparing PHN incidence in the 2-dose (4 weeks to 6 months) RZV cohort and the matched unvaccinated cohort will be estimated by Cox proportional hazards regression models adjusting for potential confounders (Section 0). In addition, for primary objective 2, adjusted relative risks for PHN among HZ cases that were 2-dose (4 weeks to 6 months) RZV vaccine recipients compared to RZV unvaccinated HZ cases will be calculated using Poisson regression with robust error variance [37]. Matching will be broken for this analysis.

8.2 Secondary Analyses

Analyses will be conducted to address the secondary objectives described in Section 3. Matched sets will not be maintained in stratified analyses (except in stratified analyses by age, by sex***, and by race/ethnicity) (Amended 17 February 2022)***; therefore, matching variables will be adjusted in the Cox proportional hazards regression models.

Secondary objectives 1 and 2: The primary analyses for HZ and PHN comparing the 2-dose (4 weeks to 6 months) RZV cohort with the matched unvaccinated cohort will be stratified by age at index date (50-59, 60-69, 70-79, ≥80 years), by sex, and by race / ethnicity. For each stratum, we will calculate HZ incidence and PHN incidence, adjusted HRs and 95% CIs, and VE (Section 0).

Secondary objective 3 and 4: The primary analyses for HZ comparing the 2-dose (4 weeks to 6 months) RZV cohort with the matched unvaccinated cohort will be stratified by (a) each of the following comorbidities in the year prior to index date: kidney disease, heart disease, lung disease, liver disease, diabetes and (b) history of ZVL prior to the index date. For each stratum, we will calculate HZ incidence, adjusted HRs and 95% CIs, and VE. The methods will be similar to those used in the primary analyses (Section 0).

Secondary objective 5: We will describe HZ incidence in the 2-dose (4 weeks to 6 months) RZV cohort and the matched unvaccinated cohort, stratified by history of HZ (defined as any diagnosis of HZ 6 months prior to the index date).

Secondary objective 6: We will assess the VE of 2 doses of RZV (among the 2-dose (4 weeks to 6 months) RZV cohort) in preventing HZO. Individuals with HZO in the 6 months prior to the index date will be excluded and the first occurrence after index date will be identified. Analyses will use similar methods to the primary analyses (Section 0).

Secondary objective 7: We will assess the VE of 2 doses of RZV (among the 2-dose (4 weeks to 6 months) RZV cohort) in preventing hospitalized AMI and in preventing hospitalized stroke in two ways. The first set of analyses for this objective will include all individuals in the 2-dose (4 weeks to 6 months) RZV cohort and their unvaccinated matches. Individuals with AMI or stroke in the 6 months prior to the index date will be excluded from the cohorts for their respective analyses. For both hospitalized AMI and hospitalized stroke (Section 6.2.3), the first occurrence after index date will be identified. Analyses will use similar methods to the primary analyses (Section 0). For the second set of analyses, the outcome will consist of the first occurrence of hospitalized AMI and hospitalized stroke after index date that occurs within 1 month after incident HZ diagnosis and within 3 months after incident HZ diagnosis (as the true risk window is not known). Analyses will use similar methods to the primary analyses (Section 0).

Secondary objectives 8 and 9: We will estimate the VE of 1 dose of RZV (among the 1-dose RZV cohort) in preventing HZ and in preventing PHN in adults aged ≥ 50 years. The study cohorts for these objectives are described in Section 0. Overall incidence of HZ and PHN for the 1-dose RZV cohort and the matched unvaccinated cohort will be calculated by dividing the number of HZ and of PHN cases by the total number of person-years, respectively. Adjusted HRs and 95% CIs comparing the HZ and PHN incidence in the 1-dose RZV cohort and the matched unvaccinated cohort will be estimated by Cox proportional hazards regression models adjusting for potential confounders.

8.3 Exploratory Analyses

Exploratory objective 1: We will estimate the VE of RZV in preventing HZ and PHN in adults aged ≥ 50 years who completed 2 doses of the vaccine, but the second dose was received more than 6 months after the first dose (2-dose (>6 months) RZV cohort). The date of the second RZV dose will be the index date. We will use a similar analysis approach as was described for the primary objectives in Section 0.

Exploratory objective 2: We will assess VE of 2 doses of RZV (among the 2-dose (4 weeks to 6 months) RZV cohort) with concomitant vaccination (*e.g.,* receipt of influenza vaccine, pneumococcal vaccine, or Tdap) at the time of receiving either the first or second dose of RZV in preventing HZ in adults aged ≥ 50 years. We will compare HZ incidence in individuals who received 2 doses of RZV and received another vaccine on the same day as either the first or second dose of RZV with RZV unvaccinated individuals. We will also compare the HZ incidence in individuals who received 2 doses of RZV and did not receive another vaccine on the same day as both the first and second dose of RZV with RZV unvaccinated individuals. For each of these analyses, we will estimate adjusted HRs and 95% CIs, and VE using methods similar to those described in Section 0.

Exploratory objective 3: We will conduct chart reviews to assess clinical characteristics related to the initial acute HZ episode for a sample of cases (100 2-dose (4 weeks to 6 months) RZV vaccinated HZ cases and 100 unvaccinated HZ cases). We will abstract clinical characteristics on the HZ episode from medical encounters 30 days before and after the initial HZ diagnosis, including: date of rash onset, date of HZ diagnosis, number of days from onset of rash to HZ diagnosis, affected dermatomes, location of rash, rash characteristics, severity of HZ, complications related to acute HZ, whether there was a positive test result for VZV (if available), specialty of provider making diagnosis, and antiviral prescription information. Clinical characteristics for vaccinated and unvaccinated cases will be presented as absolute numbers and percentages with p-values for the χ^2 test (categorical variables) or mean with standard deviation and/or median with interquartile ranges, with p-values for the two-sample t-test or Wilcoxon rank-sum test (continuous variables).

Exploratory objective 4: We will assess VE of 2 doses of RZV in preventing HZ-related meningoencephalitis and HZ-related bacterial superinfection in adults aged ≥ 50 years. For both meningoencephalitis and bacterial superinfection outcomes (Section 6.2.3), the first occurrence after index date will be identified. Analyses will use similar methods to the primary analyses (Section 0).

Exploratory objective 5: We will conduct chart reviews for disseminated HZ among a sample of HZ cases with immunocompromised status at the time of HZ diagnosis (Section 6.2.3) (up to 100 2-dose (4 weeks to 6 months) RZV vaccinated HZ cases and 100 unvaccinated HZ cases per year for 10 years). We will calculate the relative risk of disseminated HZ between these two groups.

8.4 Sample Size and Power Estimation

We computed the sample size needed to assess RZV effectiveness against HZ and PHN. We estimated that the incidence of HZ ranges from 10 to 15/1,000 person-years in the RZV unvaccinated group, and that the incidence of PHN ranges from 1.0 to 1.5/1,000 person-years in the RZV unvaccinated group, and the censoring rates in the RZV vaccinated and RZV unvaccinated groups are 7% and 15% per year, respectively. We expect a higher drop out over time in the RZV unvaccinated group due to receipt of RZV.

The sample size calculation was conducted using a two-sided log rank test with alpha=0.05, to achieve 80% statistical power, based on certain assumptions for incidence rate in the RZV unvaccinated group, follow-up period, censoring rate, matching ratio, and detectable HR (or VE). The calculation was performed using SAS software package (version 9.3) PROC POWER procedure.

Assumptions for sample size calculation:

- Incidence of HZ in the RZV unvaccinated group: 10, 12, 15/1,000 person-years
- Incidence of PHN in the RZV unvaccinated group: 1.0, 1.2, 1.5/1,000 person-years
- Follow-up period: 5 or 10 years after the second dose of RZV
- Censoring rate in the RZV vaccinated group: 7%
- Censoring rate in the RZV unvaccinated group: 15%
- Ratio of RZV unvaccinated to RZV vaccinated group: 4:1
- Detectable HR (or VE): 0.1, 0.2, 0.3, or 0.4 (VE=90%, 80%, 70%, or 60%)

Table 3 to Table 6 below present the sample size estimated to be sufficient to detect a HR of PHN and HZ between the vaccinated and unvaccinated cohorts with a follow-up period of 5 years (interim report) or 10 years (complete follow-up period). The study sample size is determined based on a conservative approach for subgroup analysis of VE against PHN. Given a PHN incidence of 1/1,000 person-years in the RZV unvaccinated group, application of censoring rates in the RZV vaccinated and RZV unvaccinated groups, and 5 years of follow-up, we need 5,836 patients with completion of two doses of RZV for a subgroup analysis to achieve 80% of power of detecting a HR of 0.4 (60% VE).

Assuming that Black race/ethnicity is a reasonably small subgroup (which contributes 6.5% of vaccinated patients), that 40% of patients who receive one dose of RZV will not complete their second dose between 4 weeks and 6 months of their first dose, and that 7% of patients will not meet the requirement of 1-year membership prior to index date, the proposed sample size receiving at least one dose of RZV during the vaccine accrual period will be 160,900 patients (=5836/0.065/0.6/0.93). The target sample size of the 2-dose RZV cohort meeting eligibility criteria and with their second dose between 4 weeks and 6 months of their first dose is 89,785 (=5836/0.065). Given 1.67 million current active members aged 50 years and older in KPSC, we estimate that 1.4 million unvaccinated members will be eligible for matching. It is feasible to match unvaccinated patients 4:1 to vaccinated patients in the 2-dose (4 weeks to 6 months) RZV cohort by age, ***sex and race/ethnicity (Amended 17 February 2022)***.

Table 3. Sample size estimation for PHN with 5 years follow-up

Incidence rate in RZV unvaccinated group (cases/1,000 person- years)	HR	VE (%)	Total Sample Size	Sample size of RZV vaccinated group
1.0	0.1	90	11,890	2,378
	0.2	80	15,505	3,101
	0.3	70	20,845	4,169
	0.4	60	29,180	5,836
1.2	0.1	90	9,910	1,982
	0.2	80	12,920	2,584
	0.3	70	17,370	3,474
	0.4	60	24,320	4,864
1.5	0.1	90	7,930	1,586
	0.2	80	10,340	2,068
	0.3	70	13,900	2,780
	0.4	60	19,460	3,892

Table 4. Sample size estimation for HZ with 5 years follow-up

Incidence rate in RZV unvaccinated group (cases/1,000 person- years)	HR	VE (%)	Total Sample Size	Sample size of RZV vaccinated group
10	0.1	90	1,190	238
	0.2	80	1,555	311
	0.3	70	2,095	419
	0.4	60	2,935	587
12	0.1	90	990	198
	0.2	80	1,295	259
	0.3	70	1,745	349
	0.4	60	2,450	490
15	0.1	90	795	159
	0.2	80	1,035	207
	0.3	70	1,400	280
	0.4	60	1,965	393

Table 5. Sample size estimation for PHN with 10 years follow-up

Incidence rate in RZV unvaccinated group (cases/1,000 person- years)	HR	VE (%)	Total Sample Size	Sample size of RZV vaccinated group
1.0	0.1	90	7,090	1,418
	0.2	80	9,300	1,860
	0.3	70	12,570	2,514
	0.4	60	17,685	3,537
1.2	0.1	90	5,910	1,182
	0.2	80	7,750	1,550
	0.3	70	10,475	2,095
	0.4	60	14,740	2,948
1.5	0.1	90	4,730	946
	0.2	80	6,200	1,240
	0.3	70	8,385	1,677
	0.4	60	11,800	2,360

Table 6. Sample size estimation for HZ with 10 years follow-up

Incidence rate in RZV unvaccinated group (cases/1,000 person- years)	HR	VE (%)	Total Sample Size	Sample size of RZV vaccinated group
10	0.1	90	715	143
	0.2	80	940	188
	0.3	70	1,275	255
	0.4	60	1,795	359
12	0.1	90	595	119
	0.2	80	785	157
	0.3	70	1,065	213
	0.4	60	1,505	301
15	0.1	90	475	95
	0.2	80	630	126
	0.3	70	855	171
	0.4	60	1,210	242

8.5 Projected Study Timelines

In order to accrue a sufficient number of vaccinated individuals to power our primary analyses and certain secondary analyses covering a 5-year and 10-year follow-up period, we estimate that we will need 160,900 eligible individuals receiving at least one dose of RZV, or 89,785 eligible 2-dose (4 weeks to 6 months) RZV recipients with their second dose between 4 weeks and 6 months after their first dose. We will stop accrual when we reach our target sample size. Beginning with retrospective data from the first dose of RZV administered in April 2018, we expect to accrue the number of individuals receiving at least one dose of RZV in approximately 3-3.5 years, and allow an additional 6 months for receipt of the second dose. The sample size is based on assumptions made for numerous factors noted in Section 0, including incidence rates of HZ and PHN, censoring rates, matching ratio, VE, 2-dose completion rate, and membership requirements. The following timeline (Table 7) is based on vaccine accrual and on the assumption that KPSC will not experience any interruption in RZV supply.

We estimate 50,000 persons per year will receive at least one dose of RZV (40,000 based on initial annual ZVL uptake plus an additional 10,000 annually due to eligibility of individuals aged 50-59 years to receive RZV). The total duration of the study activities will be approximately 16 years contingent upon assumptions and RZV supply. It is therefore feasible to accrue 160,900 eligible individuals receiving at least one dose of RZV and 89,785 eligible 2-dose (4 weeks to 6 months) RZV recipients over approximately 3-4 years and to have sufficient RZV unvaccinated individuals for the matched design.

Table 7. Study timelines and milestones (Amended 17 February 2022)

STUDY PHASE	ESTIMATED DATES	DESCRIPTION
FIXED TIMELINES		
Estimated accrual period	April 2018 – Dec ***2020***	***2.7*** years of accrual
RZV follow-up period	Jan ***2021*** – Dec ***2030***	10 years following administration of last completed 2-dose vaccination series
Data settling	Jan ***2031***– March ***2031***	~3 months after follow-up period to allow data settling for long hospitalizations and claims
MILESTONES (DELIVERY DATE TO GSK)		
Final report (10-year follow-up)	***October 2032***	

We plan to submit brief annual progress report tables describing vaccine uptake during the estimated accrual period. After the accrual period is complete, we will provide more substantive annual reports including descriptive outcome information. We propose to report on the formal analyses of the objectives in the final report (10-year follow-up).

9. DATA MANAGEMENT AND DATA QUALITY

Data management activities will be performed by KPSC. The KPSC EHR will be the data source for extracting information on exposures, outcomes, and covariates. KPSC will develop the study datasets, maintain documentation, and perform data quality checks.

Programmers will extract data per protocol and reference documentation for KPSC EHR databases. They will conduct data quality checks which includes data integrity control, double programming, and program review. Data integrity control will include checks such as sample size, duplications, formatting, etc. Double programming (i.e., programming independently conducted by 2 people) will be performed on the cohort extraction as well as key outcome variables. The results of the original and validation programming will be compared, discrepancies will be investigated, and action will be taken to resolve discrepancies. Program review (i.e. a second person reviews the code of the lead programmer) will be performed on all programs that are not double-programmed. All decisions made during data extraction and data quality checks will be documented in a programming decision log.

10. ETHICAL AND LEGAL REQUIREMENTS

Federal Policy for the Protection of Human Subjects is codified by the Department of Health and Human Services 45 Code of Federal Regulations Part 46 which outlines the basic regulations governing the protection of human subjects in research, including requirements for assuring compliance by research institutions, requirements for obtaining and documenting informed consent, and requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping.

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule governs the use and disclosure of protected health information (PHI) from covered entities. Throughout the course of the study, no human subjects will be contacted or enrolled, and no PHI will be disclosed; however, PHI will be accessed through the EHR. This information will only be accessed by those authorized to do so and will not be shared with GSK or anyone outside of the KPSC study team. The KPSC team will obtain institutional approval to use PHI for research activities. Since this access to PHI presents no more than minimal risk to individuals, and the research could not be practically done if required to obtain written authorization for usage, we will obtain a waiver for written HIPAA authorization for research involving use of the EHR to conduct the study.

Additionally, all investigators and project managers are trained in the protection of human research participants, Good Pharmacoepidemiology Practices, and HIPAA. The KPSC Department of Research and Evaluation has policies in place to govern the conduct and administration of research at KPSC. These policies support compliance with federal and state regulatory requirements. Policies include conflict of interest, misconduct, sensitive data, and system access control. Policies are in place to ensure compliance with the Sunshine Act. All KPSC staff undergo annual compliance training and certification. The Principles of Responsibility is KPSC's code of conduct that addresses such issues as protection of confidential information and anti-bribery and corruption.

11. LIMITATIONS

A potential limitation of this study is that there could be differences between vaccinated and unvaccinated individuals that are difficult to control and measure. We will adjust for differences in demographic characteristics, health care utilization, and comorbidities, but differences in other unmeasured factors could result in residual confounding.

During the initial months of the vaccine accrual period, RZV vaccine at KPSC was prioritized for individuals ages 60 years and older. However, this should not bias results since individuals are matched on age.

Despite high validity of diagnostic algorithms, misclassification of HZ status could occur inherently in EHR studies using automated data, but this would only be a concern if misclassification was differential between exposure groups.

It is unknown if HZ vaccination leads to modified or atypical HZ presentations that are more likely to be underdiagnosed or misdiagnosed. If these cases are never diagnosed or are diagnosed as other conditions, they will not be identified through ICD-10 codes for HZ. This would lead to a potential over-estimation of VE. This is less of a concern in this study, however, since the outcome of interest is defined to be medically-attended HZ diagnoses. It is also possible that there is differential misclassification of HZ due to differential health care seeking behaviors, but to address this, prior health care utilization is included as a covariate.

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13. APPENDIX: PROTOCOL AMENDMENT HISTORY

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

DOCUMENT HISTORY	
Document	**Date of Issue**
Protocol Amendment 1	17 February 2022
Final Protocol	26 May 2020

Detailed description of the current protocol amendment:

The amendment aligns the protocol with the SAP to reflect the inclusion of race/ethnicity as a matching variable to minimize potential bias and confounding in the study design.