NON-INTERVENTIONAL STUDY PROTOCOL

TITLE PAGE

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Title:	A post-marketing active surveillance study to evaluate the risk of Guillain-Barré syndrome, acute disseminated encephalomyelitis, and atrial fibrillation in adults 50 years and older vaccinated with GSK's *Arexvy* vaccine in the United States
Compound Number:	GSK3844766A
Effective Date:	13 Jan 2025
Subject:	Safety, *Arexvy,* Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), atrial fibrillation (AF)
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STUDY INFORMATION

Title	A post-marketing active surveillance study to evaluate the risk of Guillain-Barré syndrome, acute disseminated encephalomyelitis, and atrial fibrillation in adults 50 years and older vaccinated with GSK's *Arexvy* vaccine in the United States
Protocol version identifier	220149 (EPI-RSV-041 OA VS US DB)
Date of last version of protocol	27 Nov 2024
EU PAS (ENCEPP) register number	Study not registered
Active substance	Recombinant respiratory syncytial virus pre-fusion F protein (RSVPreF3)
Medicinal product	*Arexvy* (Recombinant, adjuvanted RSV vaccine)
Product reference	For Food and Drug Administration (FDA): IND number 18540
Procedure number	Not applicable
Marketing authorisation holder(s)	GlaxoSmithKline Biologicals SA Rue de l'Institut, 89, 1330 Rixensart, Belgium
Joint PASS	No
Research question and objectives	The study will address the question of whether *Arexvy*, a recombinant adjuvanted RSV vaccine RSVPreF3 OA, is associated with an increased risk of new-onset Guillain-Barré syndrome (GBS), new-onset acute disseminated encephalomyelitis (ADEM), and new-onset atrial fibrillation (AF), within specified time periods after vaccination in people ≥50 years of age. The primary objectives are to assess the risk of new-onset GBS and new-onset ADEM identified within 42 days following *Arexvy* vaccination as compared to the risk in the self-controlled comparison window, in adults ≥50 years of age using administrative claims data from health plans participating in the United States (US) Food and Drug Administration (FDA) Sentinel System.
Country of study	United States

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MARKETING AUTHORISATION HOLDER(S)

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REVISION CHRONOLOGY

Date	Version	Change(s) since last version
25 Apr 2024	Original	N/A
27 Nov 2024	Amendment 1	A new publication by Britton, 2024, and a presentation by Lloyd, 2024, were added to the Rationale and Background, Section 5; Study Design and Variables, Section 7. Study timeline and milestones were updated to reflect end of data collection by June 30, 2033, and final report delivery by December 31, 2034 (Section 2, Section 4, Section 7). Cohort selection criteria were updated to exclude individuals receiving any medical product indicated for RSV disease prevention prior to receipt of *Arexvy* vaccination or through the end of the follow-up (Section 2 and Section 7). Sample size calculations for the GBS outcome were updated to detect an RR of ≥2 with a background incidence rate of 4.5 per 100,000 person-years (Table 8). A publication by Moll, 2023 was added in addition to Lloyd, 2024 as references for the GBS background rate (Section 7.5). Sensitivity analyses for the GBS and ADEM outcomes have now been included that will use risk and control windows of (a) 1-21 days and 43-84 days, respectively and (b) risk and control windows of 8-28 days and 43-84 days, respectively (Section 7.3). The primary analysis for the AF outcome has been updated to use risk and control windows of 1-8 days and 9-16 days, respectively (Figure 3 and Table 4). Sample size calculations were updated accordingly (Table 9). Sensitivity analyses have been added that will use risk and control windows of: a) 1-28 days and 29-56 days, respectively; and b) 1-3 days and 4-8 days, respectively (Section 7.3).

Date	Version	Change(s) since last version
		Section 7.9 and Section 7.9.1 were revised with an updated plan of action. Vaccinees identified with AF via the claims-based algorithm will be assessed for a prior AF diagnosis code >365 days before the AF event; the number of such individuals will be reported descriptively (Section 7.3). The criteria used for AF case confirmation were edited for clarity. Additional covariates have been added to describe vaccinees identified with GBS, ADEM, or AF via claims-based algorithms (Section 7.3.3).
13 Jan 2025	Amendment 2	Study timeline and milestones were updated to reflect end of data collection by June 30, 2030, and final report delivery by December 31, 2031 (Section 2, Section 4, Section 7). New publications by Boos, 2020, Gundland, 2020, Parsons, 2020, and Tenembaum, 2007 were added to the Covariates, Section 7.3.3.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
AE	Adverse Events
AF	Atrial fibrillation
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CPT	Current Procedural Terminology
CVX	Vaccine administered code
ECG	Electrocardiogram
ED	Emergency Department
ENCePP	European Network of Centres for Pharmacoepidemiology & Pharmacovigilance
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GSK	GlaxoSmithKline Biologicals SA
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPHCI	Harvard Pilgrim Health Care Institute
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICSR	Individual case safety reporting
IEC	Independent Ethics Committee
IHD	Individual Human Data
IR	Incidence rate
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
LRTD	Lower Respiratory Tract Disease
NDC	National Drug Code
OA	Older adult
PCORnet	National Patient-Centered Clinical Research Network

PPV	Positive Predictive Value
preF	Pre-fusion F
QA	Quality assurance
RP	Research Partner
RR	Relative risk
RSV	Respiratory Syncytial Virus
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCDM	Sentinel Common Data Model
SCRI	Self-Controlled Risk Interval
SOP	Standard Operating Procedure
US	United States
ZIP	Zonal improvement plan

TRADEMARK INFORMATION

Trademarks of the GSK group of companies	**Trademarks not owned by the GSK group of companies**
Arexvy	NA

1. RESPONSIBLE PARTIES

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1.1. SPONSOR SIGNATORY

Title: A post-marketing active surveillance study to evaluate the risk of Guillain-Barré syndrome, acute disseminated encephalomyelitis, and atrial fibrillation in adults 50 years and older vaccinated with GSK's *Arexvy* vaccine in the United States

Compound Number: GSK3844766A

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

STUDY ADVISORY COMMITTEE

Not applicable

2. SYNOPSIS

Title

A post-marketing active surveillance study to evaluate the risk of Guillain-Barré syndrome, acute disseminated encephalomyelitis, and atrial fibrillation in adults 50 years and older vaccinated with GSK's *Arexvy* vaccine in the United States.

Rationale and background

Across GlaxoSmithKline Biologicals SA (GSK) respiratory syncytial virus (RSV) vaccine trials in adults 60 and older up to initial marketing authorization by Food and Drug Administration (FDA) in May 2023, inflammatory neurologic events were reported in 3 of 17 922 participants within 42 days after receipt of *Arexvy*. Reported events included 1 case of Guillain-Barré syndrome (GBS) and 2 cases of acute disseminated encephalomyelitis (ADEM), though the reporting investigator later revised the 2 ADEM diagnoses as hypoglycemia and dementia for 1 event and a cerebrovascular event for the other.

In addition, in the pivotal efficacy Phase 3 trial, a higher number of participants in the intervention group reported atrial fibrillation (AF) within 30 days after injection than the control group. This imbalance was no longer observed within 6 months after vaccination. After administration of a second dose of *Arexvy* in participants from this Phase 3 trial, an imbalance in AF events was observed within 6 months after vaccination, but not within 30 days after vaccination. In a Phase 3 trial evaluating the safety and the non-inferiority of the immune response of *Arexvy* in adults 50-59 years of age compared to adults ≥60 years of age, 1 AF event was reported among the 769 adults 50-59 years of age and 4 events were reported among the 381 adults ≥60 years of age.

Arexvy was approved for use in adults 60 years of age and older in May 2023, and the approval extended to individuals 50 through 59 years of age who are at increased risk for lower respiratory tract disease (LRTD) caused by RSV in June 2024. This study will include adults ≥50 years of age.

Research question and objectives

The study will evaluate whether *Arexvy*, a recombinant adjuvanted RSV vaccine RSVPreF3 OA, is associated with an increased risk of new-onset GBS, new-onset ADEM, and new-onset AF within specified time periods after vaccination among people ≥50 years of age.

The primary objectives are to assess the risk of: 1) new-onset GBS, and 2) new-onset ADEM, identified within 42 days after *Arexvy* vaccination and confirmed by clinician review of hospital records.

A secondary objective is to assess the risk of new-onset AF identified within 8 days after *Arexvy* vaccination.

Study Design

Self-controlled risk interval (SCRI) design.

Population

Health plan members ≥50 years of age will be eligible if they: 1) received one dose of *Arexvy*; 2) had 365 days of continuous medical and pharmacy enrolment prior to *Arexvy* receipt; 3) had continuous enrolment through the end of the follow-up period; 4) had no evidence of a second dose of *Arexvy* during the follow-up period; and 5) had no evidence of another medical product indicated for RSV disease prevention prior to receipt of *Arexvy* or during the follow-up period.

Variables

Arexvy receipt; new-onset GBS; new-onset ADEM; new-onset AF.

Data sources

Five Research Partners (RPs) (Carelon, CVS Health, HealthPartners, Humana, Point32Health) participating in the United States (US) FDA's Sentinel System.

Study size

Using a background rate for GBS of 4.5 cases per 100 000 person-years, a total of 69 GBS cases in the combined risk and control intervals will provide 80% power to reject the null hypothesis of no association when the true relative risk (RR) is ≥2.0. Approximately 4.4 million vaccinated patients are expected to be needed to accrue the number of cases of GBS. Using a background rate for ADEM of 0.45 cases per 100 000 person-years, a total of 12 cases in the combined risk and control intervals provides 80% power to reject the null hypothesis of no association when the true RR is ≥7.0. Approximately 3.9 million vaccinated patients are expected to be needed to accrue the number of cases of ADEM.

Data analysis

SCRI-based analyses will use conditional Poisson regression to determine incidence rate ratios (IRRs) of outcomes with 95% confidence intervals (CIs).

Milestones

Data collection will begin CCI [redacted] (the month when vaccinations began) and continue through 30 June 2030 or until the number of cases needed to power the study with adequate precision have been accrued, whichever is earlier. An inferential analysis of each outcome will be conducted when the required number of cases have accrued. A final report will be submitted to the US FDA by 31 December 2031.

3. AMENDMENTS AND UPDATES

Protocol dated 25 April 2024 was amended based on feedback from the US FDA received November 2024 (Amendment 1) and January 2025 (Amendment 2).

Amendment number	Date	Amendment or update	Section of study protocol	Reason
1	27 Nov 2024	A new publication by Britton, 2024, and a presentation by [Lloyd, 2024], were added.	5, 7	These contain new information relevant to RSV vaccines and GBS.
		Study timeline and milestones were updated to reflect end of data collection by June 30, 2033 and final report delivery by December 31, 2034	2, 4, 7	Based on feedback received from the US FDA
		Cohort selection criteria were updated to exclude individuals receiving any medical product indicated for RSV disease prevention prior to receipt of Arexvy vaccination or through the end of the follow-up	2, 7.2, 7.3.1, 7.7.2.2	Language was made broad to allow for the possibility of erroneous coding for the infant monoclonal antibodies among adults older than 50 years or future innovations in RSV disease prevention for the older adult population

Amendment number	Date	Amendment or update	Section of study protocol	Reason
		Sample size calculations for the GBS outcome were updated to detect an RR of ≥2 with a background incidence rate of 4.5 per 100,000 person-years (Table 8). A publication by Moll, 2023 was added in addition to Lloyd, 2024 as references for the GBS background rate.	2, 7.5	These calculations were updated based on more recent data available on RSV vaccines and GBS.
		Sensitivity analyses for the GBS and ADEM outcomes were added to observe outcomes over (a) a risk window of 1-21 days and control window of 43-84 days and (b) risk window of 8-28 days and control window of 43-84 days. (Table 4).	6, 7.3.2, 7.5, 7.7.2	Due to timing of postmarketing reports of GBS, other studies of post-vaccination GBS, and the timing of the 1 reported GBS case and 2 reported ADEM cases in the Arexvy clinical trials, all indicating a clinically relevant risk window of 21 days. Unpublished data by Lloyd et al (2024) demonstrated that GBS cases occurred in days 8-28.
		The primary analysis for the AF outcome will use risk and control windows of 1-8 days and 9-16 days, respectively (Figure 3 and Table 4). Sample size calculations were updated accordingly (Table 9). Sensitivity analyses have been added that will use risk and control windows of: a) 1-28 days and 29-56 days, respectively; and b) 1-3 days and 4-8 days, respectively.	2, 7	Due to the timing of various unpublished postmarketing reports of AF indicating a variable maximum time to onset of 8 days and 3 days.
		Vaccinees identified with AF via the claims-based algorithm will be assessed	7.3.2	There is interest in assessing whether a longer lookback period will

Amendment number	Date	Amendment or update	Section of study protocol	Reason
		for a prior AF diagnosis code >365 days before the AF event; the number of such individuals will now be reported descriptively.		identify prior AF history among those meeting the new-onset AF algorithm.
		The criteria used for confirmation of AF cases during medical record review were edited for clarity.	7.3.2	The original language was redundant.
		Additional covariates were added to describe vaccinees identified with GBS, ADEM, or AF via the claims-based algorithms.	7.3.3	There is interest in assessing whether other factors that may precipitate the outcomes of interest are documented in the individuals' claims history.
		Section 7.9 and Section 7.9.1 were revised with an updated plan of action in the event estimated sample sizes are not met at the planned end of study.	7.9, 7.9.1	Based on feedback received from the US FDA.
2	13 Jan 2025	New publications by Boos, 2020, Gundland, 2020, Parsons, 2020, and Tenembaum, 2007 were added to the Covariates, Section 7.3.3.	7.3.3	To align with SAP
		Study timeline and milestones were updated to reflect end of data collection by June 30, 2030, and final report delivery by December 31, 2031	2, 4, 7	Based on feedback received from the US FDA

4. MILESTONES

Table 1 Milestones

Milestone	Planned Date
Start of data collection	CCI [redacted]
End of data collection	30 June 2030
Reports of inferential analyses per outcome of interest	Analyses to be conducted when required number of cases have accrued
Final report to US FDA	31 December 2031

5. RATIONALE AND BACKGROUND

RSV is an important cause of acute respiratory infections during the autumn and winter months in temperate regions and during rainy seasons in tropical regions [Obando-Pacheco, 2018]. Each season, RSV causes substantial morbidity and mortality in older adults, including lower respiratory tract disease, hospitalization, and death [Falsey, 2005; Falsey, 2014; Belongia, 2018; Shi, 2020]. In 2019, it was estimated that RSV accounted for 5.2 million cases of acute respiratory infections, 470 000 hospitalizations, and 33 000 in-hospital deaths among adults ≥60 years of age in industrialized countries [Savic, 2023]. Reduced RSV-specific T-cell responses in older adults due to immunosenescence likely contributes to the increased susceptibility to severe RSV disease in this group [Cherukuri, 2013]. Adults with certain medical conditions, including asthma, chronic obstructive pulmonary disease, cerebrovascular disease, coronary artery disease, chronic kidney disease, diabetes mellitus, heart failure, and those who are immunocompromised are at increased risk of severe lung disease from RSV infection [Waghmare, 2013; Nam, 2019; Wyffels, 2020; Branche, 2022; Kujawski, 2022]. Residents of long-term care facilities and persons classified with frailty are also at increased risk of RSV-associated hospitalization [Childs, 2019; Zheng, 2022].

To date, treatment for RSV-associated respiratory tract disease has been supportive, but vaccines represent an important prophylactic intervention for older adults [Stephens, 2021]. In May 2023, the US FDA approved the first vaccines for prevention of RSV-associated lower respiratory tract disease in adults aged ≥60 years [Melgar, 2023]. One of these products, RSVPreF3 OA (*Arexvy*, GSK), is a 1-dose (0.5 mL) adjuvanted ($AS01_E$) recombinant stabilized pre-fusion F protein (preF) vaccine. One published Phase 3 trial evaluated the efficacy of *Arexvy* against RSV-related lower respiratory tract disease in adults ≥60 years of age [Papi, 2023]. A total of 24 966 participants received one dose of *Arexvy* vaccine (intervention group; n = 12 467 participants) or saline placebo (control group; n = 12 499 participants). Over a median follow-up of 6.7 months, vaccine efficacy in preventing symptomatic, reverse transcription-polymerase chain reaction confirmed RSV-associated lower respiratory tract disease was 82.6% (95% CI, 57.9%-94.1%).

At the time of initial marketing authorization by FDA in May 2023 [Melgar, 2023], evidence regarding the safety of *Arexvy* consisted of data from 2 randomized, double-blind, placebo-controlled clinical trials, including the Phase 3 trial above [Papi, 2023] as well as a Phase 1/2 trial with 201 participants aged ≥60 years who received either *Arexvy* or saline placebo [Leroux-Roels, 2023]. Across both trials, the frequency of serious adverse events (AEs) was similar in the intervention (4.4%) and control (4.3%) groups (pooled RR=1.02; 95% CI=0.91–1.15). In addition to these trials, since the *Arexvy* marketing authorization, the safety evidence of *Arexvy* in adults ≥60 years of age has been complemented with data from other ongoing Phase 3 trials, including after administration of a second dose of *Arexvy.* The frequency of serious AEs was similar to that detailed in the previously mentioned Phase 3 and Phase 1/2 trials (3.4-4.5%) [Schwarz, 2023; Chandler, 2024; Ison, 2024]. In June 2024, the US FDA approved *Arexvy* for the prevention of RSV-associated lower respiratory tract disease in adults aged 50 to 59 years of age who are at increased risk of severe RSV lower respiratory tract disease.

The safety of *Arexvy* has been evaluated in a Phase 3 trial evaluating the safety and the non-inferiority of the immune response of *Arexvy* in adults aged 50-59 years old, including individuals with pre-defined, stable, chronic medical conditions who are at increased risk for RSV disease, compared to adults ≥60 years of age [Gerber, 2023; Ferguson, 2024]. In that trial, the frequency of serious AEs reported up to approximately 6 months post-vaccination was 3.6% and 0.5% in participants 50-59 years of age with and without the pre-defined chronic medical conditions, respectively, and 2.4% in participants ≥60 years of age.

In the pivotal efficacy Phase 3 trial, a higher number of participants in the intervention group than in the control group reported AF as an unsolicited event within the 30 days after injection (intervention: 10 events [0.1%]; control: 4 events [<0.1%]; p<0.1%), 8 of which were classified as serious AEs (intervention group: 7 events; control group: 1 event; 3 of the events corresponded to new-onset AF [intervention group: 2 events; control group: 1 event]) [Melgar, 2023]. Within 6 months after vaccination, serious events of AF were reported in 13 participants who received *Arexvy* and 15 participants who received placebo [*Arexvy*, 2023]. No imbalance in AF was observed within 30 days post-dose 2 (3 [0.06%] participants after *Arexvy* revaccination versus 5 [0.05%] after placebo, with 1 event after *Arexvy* and 2 after placebo being serious occurrences). Within 6 months post-dose 2, 11 (0.22%) participants versus 13 (0.13%) had serious occurrences of AF upon *Arexvy* and placebo administration, respectively [Ison, 2024].

In the Phase 3 trial evaluating the safety and the non-inferiority of the immune response in adults aged 50-59 years old compared to adults ≥60 years, 4 AF events were reported within 6 months post-vaccination with *Arexvy*; no AF event was reported in placebo recipients. The AF events had a time to onset spanning from 12 days up to 181 days post-vaccination and were not considered related to vaccination by the study investigator. Three of these events were reported in participants aged ≥60 years receiving *Arexvy*.

Across all GSK RSV vaccine clinical trials in older adults at the time of initial marketing authorization by FDA in May 2023, inflammatory neurologic events were reported in 3 of 17 922 participants within 42 days after receipt of *Arexvy* [Melgar, 2023]. The reported events included 1 of GBS in a participant aged 78 years from Japan with symptom onset 9 days post-vaccination in an open-label Phase 3 clinical trial, and 2 events of ADEM among participants in a randomized Phase 3 co-administration study [Melgar, 2023]. The 2 ADEM events were reported in participants each aged 71 years from the same site in South Africa after concomitant receipt of *Arexvy* and standard dose of seasonal influenzavaccine; symptom onset occurred 7- and 22-days post-vaccination, and 1 event was fatal. For both ADEM events, the diagnosis was based on symptoms and clinical findings only; diagnostic testing (including brain imaging, cerebrospinal fluid testing, and nerve conduction studies) was not performed, leading to uncertainty in the diagnoses. The reporting investigator later revised the diagnosis from ADEM to hypoglycemia and dementia for 1 participant, and to a cerebrovascular event for the other [Gerber, 2023; Melgar, 2023; Chandler, 2024]. There were no other inflammatory neurologic events reported in clinical trials after *Arexvy* vaccination.

Although no safety signals were identified in the trials, sample size and follow-up time were insufficient to monitor safety for rare inflammatory neurologic events, and the Phase 3 trials were not designed to evaluate whether *Arexvy* was associated with an elevated risk of AF after vaccination.

The US FDA conducted an analysis examining the association between RSV vaccines and GBS using data from US Medicare beneficiaries who were aged 65 years and older [Britton, 2024]. Using a self-controlled case series design with a risk interval of days 1-42 and control interval of days 43-90, the authors reported an adjusted incidence ratio for *Arexvy* and GBS of 2.30 (95% CI 0.39-13.72) among those vaccinated before October 8, 2023. However, the study relied on ascertainment of GBS cases using a claims-based algorithm and did not confirm the GBS cases via medical record review. Results from an updated analysis including vaccinations through January 28, 2024, and GBS cases that were chart-confirmed as well as those whose medical records could not be returned showed an adjusted incidence ratio of 2.46 (95% CI 1.19-5.08) for GBS following *Arexvy*. These results were presented at a meeting of the Advisory Committee on Immunization Practices [Lloyd, 2024] in October 2024 and have not yet been published in a peer-reviewed journal.

6. RESEARCH QUESTION AND OBJECTIVES

The study will address the question of whether there is an increased risk of new-onset GBS, new-onset ADEM, or new-onset AF within specified time periods after *Arexvy* vaccination among adults ≥50 years of age who are included in the study population beginning CCI [redacted], at any of 5 participating RPs (i.e., Carelon Research, CVS Health, HealthPartners, Humana, Point32Health). A SCRI design will be used to evaluate the risk of each of these outcomes separately in administrative claims data.

This overall study will include adults 50 years of age and older. *Arexvy* was approved for use in those 60 years of age and older in May 2023, and the authorization was extended to those 50 years of age and older and at high risk of severe RSV lower respiratory tract disease in June 2024. The first monitoring query covering the 2023-2024 season is expected to include only those 60 years of age and older. Subsequent monitoring queries and inferential analyses will include those 50 years of age and older.

Primary objectives

1. To assess the risk of new-onset GBS within 42 days after *Arexvy* vaccination using a SCRI design in adults ≥50 years of age in the US.
2. To assess the risk of new-onset ADEM within 42 days after *Arexvy* vaccination using a SCRI design in adults ≥50 years of age in the US.

Secondary objective

1. To assess the risk of new-onset AF within 8 days after *Arexvy* vaccination using a SCRI design in adults ≥50 years of age in the US.

7. RESEARCH METHODS

7.1. Study Design

To study the risk of acute outcomes after *Arexvy* exposure in the inferential analyses, the SCRI design will be used [Yih, 2014; Yih, 2016a; Baker, 2019]. The SCRI design is ideal for assessing transient exposures and acute outcomes. This design is a special (and simpler) case of both the case-crossover [Maclure, 1991] and the self-controlled case series [Farrington, 1995; Farrington, 1996; Petersen, 2016] designs, in which the cumulative numbers of cases in pre-specified risk and control intervals (or "windows") are compared. The unique strength of self-controlled designs is that they control for all time-fixed potential confounders, such as sex, race, ethnicity, and chronic disease status. However, potential time-varying confounders, such as seasonality, may introduce bias unless they are explicitly controlled for within the analysis. Given that adults are being studied and the relatively short time spans of the risk and control windows, confounding by age is not a concern (unlike in studies of very young children where risk of some outcomes may vary by week of age).

This study will include health plan members ≥50 years of age at the time of *Arexvy* vaccination (using codes listed in Table 2) who have ≥365 days of continuous medical and pharmacy coverage, allowing up to 45-days' gaps in coverage, prior to *Arexvy* receipt. The rationale for allowing 45-days' gap is that gaps of ≤45 days in health plan enrolment are typically considered administrative gaps (and not lapses in health plan coverage) and so are ignored [Fairbrother, 2004]. Exposure will be identified by evidence of at least one dose of *Arexvy* identified by Current Procedural Terminology (CPT) codes, National Drug Codes (NDCs), and for RPs where state immunization information system data are included the vaccination will also be identified by vaccine administered codes (CVX).

The incident outcomes will be assessed using a first-in-X-days definition of incidence, which is customary with the SCRI design to establish an equal opportunity for a case to be ascertained regardless of where in the follow-up (risk or control) period it might appear [Yih, 2014;Yih, 2016a; Baker, 2019]. The alternative to first-in-X days approach is to anchor the evaluation of the incidence criteria to the date of the vaccination.

However, such an approach introduces a potential bias toward identifying an increased risk, or a bias toward finding more cases earlier rather than later in the follow-up, as the incidence criterion becomes more stringent later in the evaluation window than it is in the earlier period of follow-up closer to the date of vaccination. The lengths of risk and control windows are defined below (Table 4) for each outcome and are based on biologic plausibility, published results, and prior vaccine safety studies [Arya, 2019; Goud, 2021; [Britton, 2024; Lloyd, 2024]. For all outcomes studied, control windows will be after risk windows rather than before the index vaccination as some individuals may delay or not get vaccinated following certain illnesses [Jackson, 2006], which would produce a bias toward identifying an increased risk if the control window were before vaccination.

The overall study will include annual, cumulative monitoring queries, a final inferential analysis evaluating new-onset AF, and a final inferential analysis evaluating GBS and ADEM. The timing of monitoring queries will depend on data availability and other factors and are expected to be annual. The data sources are described in Section 7.4 below.

During the course of the study, there will be descriptive annual monitoring queries conducted to track uptake of *Arexvy*, describe vaccinees, and assess numbers of outcomes of interest. Operationally, for the first monitoring query, *Arexvy* vaccine uptake will be assessed from CCI (the month when vaccinations began) through February 2024; subsequent queries will be cumulative from CCI. The maximum amount of time from vaccination to outcome identification is 91 days for GBS and ADEM (events will be identified through the risk window, control window, and extra days; extra days will be used to ensure that we capture potential events that had a symptom onset during the control window but a diagnosis code recorded later), and 106 days for new-onset AF definition (for new-onset AF, if the first qualifying diagnosis code occurs on Day 16, then the last possible second code would be on Day 106). See Table 4 for details of the algorithms.

Administrative claims data require time to accrue and approach completeness (approximately ≥90% complete), and the amount of time depends on care setting, with inpatient diagnoses requiring ~6 months. RP data refresh, including data quality checksthat follow the Sentinel System processes, takes approximately 1 month. The exact timing of the first monitoring query is not yet established, but this is an example of the timing for each aspect of the design and implementation using the first monitoring query for reference:

- Identify *Arexvy* vaccinees CCI – February 2024.
- Assess outcomes among vaccinees CCI through June 2024.
- Data through December 2024 will be considered adequately complete for both inpatient and ambulatory outcomes.
- Query is expected to be distributed and executed against quality-checked data in the first quarter of 2025, assuming data refresh proceeds as expected.

As part of our planned annual monitoring, counts of each of the 3 outcomes will be identified using diagnosis code-based case-finding algorithms among those vaccinated. Deaths that occur after vaccination, during follow-up, will be identified via the administrative claims data; deaths can be identified via discharge status if they occur during hospitalization or in enrolment data if they are captured administratively (see Section 7.7.1).

Concurrently, after the monitoring query results are received, chart reviews will be performed immediately for outcomes that are identified, as detailed in Section 7.3.2.

All patients identified with potential GBS and ADEM by the case-finding algorithms during the monitoring queries, and final analysis, will undergo medical record review and case adjudication using a team of clinicians, preferably neurologists, based on the approaches discussed below in Section 7.7.2.

For new-onset AF, during the early monitoring query(s), a formal validation on a sample of patients will be performed with this case-finding algorithm. A team of clinicians, preferably cardiologists, will review and adjudicate these events; further details are discussed in Section 7.3.2. The date of the final AF report is unknown at this time and will be estimated after the first few monitoring queries are conducted.

Inferential final analyses evaluating GBS and ADEM and new-onset AF will be conducted following the methods in Section 7.7.2 as well as the Statistical Analysis Plan (SAP).

7.2. Study Population and Setting

Information on the 5 participating RPs is described below in Section 7.4.

Members of participating US-based health plans ≥50 years of age will be eligible for inclusion in the evaluation of each outcome if all of the following criteria are met:

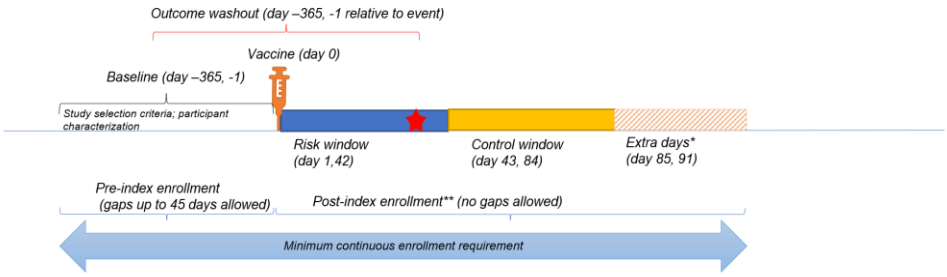
1. Evidence of receipt of a single dose *Arexvy*.
2. 365 days of continuous medical and pharmacy enrolment, allowing up to 45-days' gap, prior to *Arexvy* receipt.
3. For evaluation of GBS and ADEM cases: Continuous enrollment through the end of the respective control interval and extra days except in case of death after *Arexvy* vaccination.
4. For evaluation of AF cases: Continuous enrolment through the Day 106 post-vaccination, except in case of death after *Arexvy* vaccination.
5. For each outcome: First-in-365-days case of the outcome in the risk or control interval (i.e., definition of an incident case).
6. No evidence of a second dose of *Arexvy* during the follow-up period.
7. No evidence of administration of another medical product indicated for RSV disease prevention (i.e., vaccine from different manufacturer or a monoclonal antibody to prevent RSV lower respiratory tract disease) prior to the index *Arexvy* vaccination or during the follow-up period.

Patients will be required to be enrolled throughout the risk and control windows combined, plus an extra 7 days for GBS and ADEM analyses, and an extra 90 days for AF analysis. This study will include outcomes of interest among people who die during the full window. The number of events, if any, that were among people who died during follow-up will be quantified. See Section 7.7.2.1 for additional details regarding inclusion of those who died in the inferential analyses.

Health plan members eligible for inclusion in research activities, including chart review, will be included.

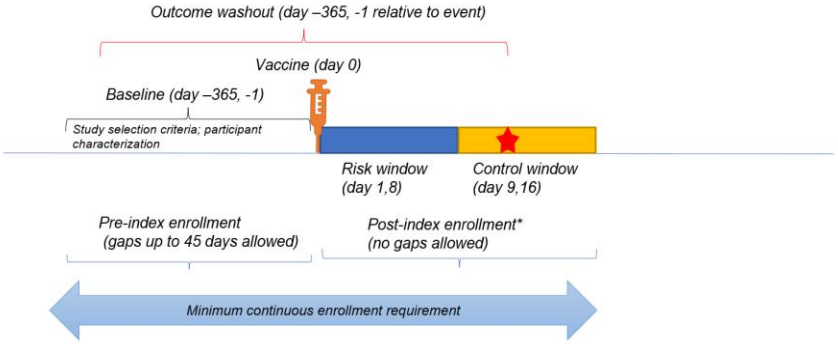
Illustrations of temporal inclusion criteria for SCRI analyses are shown Figure 1, Figure 2, and Figure 3 below. The red star in each figure indicates occurrence of an outcome of interest.

Figure 1 Illustration of SCRI study design for new-onset GBS and ADEM outcomes



*In the primary analyses, cases with symptom onset (established from chart review) in the control window may present with coded diagnoses (identified in claims data) up to 7 days after the end of the control window ('extra days').
Date of symptom onset is deemed as the date of chart confirmed events. Only events with dates of symptom onset in risk and control windows contribute to the primary analyses.
**Post-index enrolment requirement does not enforce survival through the end of all evaluation windows post-vaccination. Vaccinated cases with evidence of death in the post-index window will contribute to the analyses.

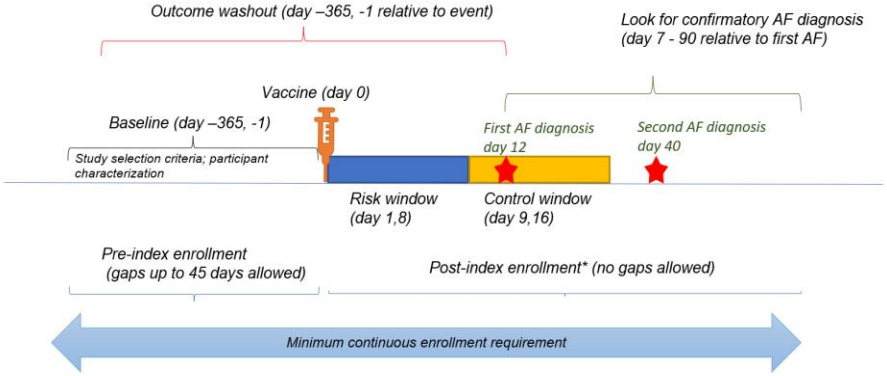
Figure 2 Illustration of SCRI design for new-onset AF† (example with 1 inpatient diagnosis code)



†Analyses will be claims-based if estimated PPV from descriptive monitoring queries is ≥80% and chart- confirmed if PPV <80%.

*Post-index enrolment requirement does not enforce survival through the end of all evaluation windows post-vaccination. Vaccinated cases with evidence of death in the post-index window will contribute to the analyses.

Figure 3 Illustration of SCRI design for new-onset AF† (example with 2 outpatient or ED diagnosis codes) ††



†Analyses will be claims-based if estimated PPV from descriptive monitoring queries is ≥80% and chart- confirmed if PPV <80%.

CCI [redacted]

* Post-index enrolment requirement does not enforce survival through the end of all evaluation windows post-vaccination. Vaccinated cases with evidence of death in the post-index window will contribute to the analyses.

Abbreviations: AF: atrial fibrillation; ED: emergency department; PPV: positive predictive value.

7.3. Variables

7.3.1. Exposure definitions

Exposure will be identified by evidence of receipt of one dose of *Arexvy* via procedure or pharmacy dispensing codes (e.g., CPT, NDC, Healthcare Common Procedure Coding System [HCPCS] codes) or if state immunization system data are available at any RP, CVX codes will be included. Duplicate codes that are expected to be erroneous (i.e., a second code for *Arexvy* within Days 0-7) will be ignored. Only a patient's first recorded dose will be included. Since the current recommendation for *Arexvy* administration is as a one-time dose, we do not anticipate many second doses, though people with evidence of a second dose during the follow-up period will be excluded (i.e., Day 8 through follow-up). If codes for both *Arexvy* and another medical product indicated for RSV disease prevention (i.e., a code for a different manufacturer's RSV vaccine or monoclonal antibody to prevent RSV lower respiratory tract disease) are identified prior to the index *Arexvy* or through follow-up, such individuals will be excluded from the study.

Table 2 Codes for Arexvy

Code Type	Code	Description
CVX	303	Respiratory syncytial virus (RSV), vaccine, recombinant, protein subunit RSV prefusion F, adjuvant reconstituted, 0.5 mL, preservative free
CPT	90679	Respiratory syncytial virus vaccine, preF, recombinant, subunit adjuvanted, for intramuscular use
NDC	58160-848-11	Respiratory syncytial virus vaccine antigen/AS01E adjuvant/PF (*Arexvy* [Pre-fusion F protein])
NDC	58160-723-03	Respiratory syncytial virus vaccine, antigen 2 of 2 (*Arexvy* Antigen Component)
NDC	58160-744-03	Vaccine adjuvant system, AS01E/PF, component vial 1 of 2 (*Arexvy* Adjuvant Component [Pre-fusion F protein])

Abbreviations: CPT: Current Procedural Terminology; CVX: Vaccine administered code; NDC; National Drug Code.

7.3.2. Outcome definitions

The 2 primary outcomes that will be evaluated are:

1. New-onset GBS, and
2. New-onset ADEM.

The 1 secondary outcome that will be evaluated is: New-onset AF.

7.3.2.1. Medical record review of primary and secondary outcomes

At each annual monitoring query, for the evaluation of primary outcomes (i.e., GBS and ADEM), screening for potential events in the administrative claims data of the RPs will be done using the case-finding algorithms described in Table 4. Once each annual monitoring query is complete, given the rarity of GBS and ADEM, we will immediately seek to obtain the medical records of all patients identified as having possible events

based on our algorithms, abstract the data necessary to confirm these diagnoses from the medical records obtained, and implement a formal adjudication process with a team of expert clinicians, preferably neurologists, to confirm these events. Only confirmed cases will be included in the final primary analyses. For those outcomes, timing of symptom onset will be discerned from medical record review and timing of the event will be classified based on expert clinician adjudication (i.e., the date of diagnosis from the claims data will not be used due to concerns with misclassification).

Since AF is a more frequent health outcome in the population of interest compared to GBS and ADEM, a conventional approach will be followed to confirm the validity of the algorithms for each of these outcomes during the initial annual monitoring queries (we anticipate that the sample sizes for each AF validation can be accrued within the first or second annual monitoring periods given the prevalence of AF in the age group of the study population, but will need to assess initial monitoring query results) [Weinstein, 2023]. For the AF outcome, we *a priori* seek to identify an algorithm that has a positive predictive value (PPV) of ≥80% to provide confidence that identified outcomes are true events. We estimate that 63 patients' charts (complete and adjudicated) would allow determination of the PPV of each case-finding algorithm with a maximum 95% CI of ±10%, assuming a PPV of 80% (Table 3).

The number of adjudicated charts needed for the AF validation will be determined based on the number of AF cases identified in the monitoring query(s). We expect to conduct the validation within 1-2 RPs, including the one RP with the most AF events identified during the initial monitoring queries.

Note that for analyses that include claims-based outcomes of interest in the inpatient setting, admission dates will be used, not discharge dates.

Table 3 Number of charts needed to obtain a 95% two-sided CI ±10% for new-onset AF validation*

Number of AF cases identified	**1 000**	**5 000**	**10 000**	**20 000**	**100 000**
Actual PPV	Number of adjudicated charts needed				
60%	86	92	93	93	94
65%	82	87	88	89	89
70%	76	81	82	82	82
75%	69	72	73	73	73
80%	59	62	63	63	63
85%	48	50	50	50	50
90%	35	36	36	36	36

Abbreviations: AF: atrial fibrillation CI: confidence interval; PPV: positive predictive value.
*The needed sample size for a 2-sided 95% CI for a binomial proportion with a 10% margin of error was calculated using a range of possible AF cases. These calculations were done in Excel.

To account for the fact that approximately 30%, or more, of hospital medical records might not be available to review, we will oversample from a random sample of the total AF cases identified according to the case-finding algorithm to ensure we obtain the target number of charts needed. Once the initial annual monitoring query, which will include new-onset AF, is complete, medical records of patients in the sample will be requested immediately. Once charts have returned, the data necessary to confirm these diagnoses from the medical records will be abstracted, implement a formal adjudication using a team of expert clinicians, preferably cardiologists, to confirm these events, and determine the PPV of the algorithm for new-onset AF.

Medical records will be obtained from participating RPs in a manner compliant with the Health Insurance Portability and Accountability Act (HIPAA) and local privacy regulations. Hospital and outpatient charts will be obtained directly through requests from RPs using identifiers obtained from administrative claims data. Designated protected health information users at each RP will link the protected health information with masked patient identification numbers, dates of birth, and provider information for the patients identified for medical record abstraction. As noted above, charts are not expected to be 100% obtainable from participating RPs and that ~30% of charts sought can be unobtainable based on prior experience. Section 7.7.2 includes description of how potential events with unobtainable charts will be handled in the analyses. Bias will not be expected based on whether charts were obtainable or unobtainable (reasons for charts being unobtainable include providers being non-responsive or providers incorrectly assuming patient authorization is required). Table 4 below summarizes the proposed diagnosis code-based case-finding algorithms and key elements of the validation of each outcome.

Table 4 Case-finding algorithms and risk and control windows for outcomes of interest

Outcome	Diagnosis code(s) to identify event	Event identification care setting and details	Risk window	Control window, Extra days	Look-back period for outcome-free window	Diagnosis code(s), care setting for outcome-free period	Published algorithm data	Chart review considerations
New- onset GBS	G61.0[a]	CCI [redacted]	Primary: 1-42 days [Sejvar, 2011; Goud, 2021; Britton, 2024 Lloyd 2024] Sensitivity: (a) 1-21 days and (b) 8-28 days	Control window: 43-84 days, Extra days: 7	-365 through -1 (day 0 is day of event), as previously conducted [Polakowski, 2013]	G61.0 or G65.0, inpatient setting (any position)	PPV from studies using Medicare data: (1) 78.57% (95% CI, 63.37%- 93.77%) [Goud, 2021] (2) 71.21% (95% CI: 63.49%-78.94%) [Arya, 2019]; (3) 68.0% (95% CI: 56.8%-77.5%) [Lloyd, 2024]	Will seek charts on all events. Final analysis will include chart-confirmed events only.

Outcome	**Diagnosis code(s) to identify event**	**Event identification care setting and details**	**Risk window**	**Control window, Extra days**	**Look-back period for outcome-free window**	**Diagnosis code(s), care setting for outcome-free period**	**Published algorithm data**	**Chart review considerations**
New- onset ADEM	G04.00, G04.01, G04.02[b]	CCI [redacted]	Primary: 1-42 days Sensitivity: a) 1-21 days and (b) 8-28 days	Control window: 43-84 days, Extra days: 7	-365 through -1 (day 0 is the day of the event)	G04.00, G04.01, or G04.02, inpatient setting (any position)	ICD-10-CM based algorithm not available	Will seek charts on all events. Final analysis will include chart-confirmed events only.

Outcome	Diagnosis code(s) to identify event	Event identification care setting and details	Risk window	Control window, Extra days	Look-back period for outcome-free window	Diagnosis code(s), care setting for outcome-free period	Published algorithm data	Chart review considerations
New- onset AF	See Table 7	CCI	Primary: 1-8 days Sensitivity (a): 1-28 days Sensitivity (b): 1-3 days	Primary: 9-16 days Sensitivity (a): 29-56 days Sensitivity (b): 4-8 days Extra days: 0	-365 through day -1 (day 0 is day of the event)	Any indicated AF diagnosis in Table 7 in any care setting	PPV for ICD-10-CM (I48) based algorithms ranged from 67.5%- 75.7% [Chamberlain, 2022]	Will aim to review charts from ~63 presumed cases from selected RPs to determine PPV.[d]

Abbreviations: AF: atrial fibrillation; ADEM: acute disseminated encephalomyelitis; ED: emergency department; GBS: Guillain-Barré syndrome; ICD-10-CM: International Classification of Diseases, tenth revision, clinical modification; PPV: positive predictive value.

a. GBS ICD-10-CM codes and descriptions:
G61.0: Guillain-Barré syndrome
G65.0: sequelae of Guillain-Barré syndrome

b. ADEM ICD-10-CM codes and descriptions:
G04.00: Acute disseminated encephalitis and encephalomyelitis, unspecified G04.01: post-infectious acute disseminated encephalitis and encephalomyelitis
G04.02: Postimmunization acute disseminated encephalitis, myelitis, and encephalomyelitis.

Note that for AF, if the first qualifying diagnosis code occurs on Day 16, then the last possible second code would be on Day 106.

c. CCI [redacted]

d. The final number of complete, adjudicated charts needed for AF will be based on the number of AF cases identified, as summarized in Table 3.

7.3.2.2. Ascertainment and confirmation of GBS events

Screening for GBS:

Within each RP's database, patients will be identified as having possible GBS within 91 days after *Arexvy* vaccination (primary analysis risk window days 1-42, control window days 43-84, and 7 extra days) if they had either: CCI [redacted]. The claims-based case date for cases will be based on the earliest diagnosis of interest. New-onset GBS will be identified by requiring that there is no evidence of GBS in the 365 days prior to the first diagnosis code of interest: no occurrence of G61.0 (GBS) or G65.0 (Sequelae of GBS) hospital discharge diagnosis (any position) in days -365 through day -1 (day 0 is the day of the event).

The primary risk window will be 42 days as several prior vaccine safety studies of post-vaccination GBS have used a 42-days window [Arya, 2019; Goud, 2021; Britton, 2024; Lloyd, 2024], and that precedent will be followed. Sensitivity analyses using risk windows of (a) days 1-21 and (b) days 8-28 will be included based on the timing of postmarketing reports of GBS, other studies of post-vaccination GBS [Klein, 2021], and the timing of the 1 reported GBS case in the *Arexvy* clinical trials [Melgar, 2023].

The control window will be days 43-84 following vaccination for both primary and sensitivity analyses' risk windows. Continuous enrolment will be required through the end of the respective control interval plus 7 extra days to ensure that diagnosis codes that are recorded after symptom onset (and potentially after the risk and comparison windows) are captured. The final analyses will include individuals with an event of interest and who die during the 91-days follow-up period.

Validation of GBS events:

Materials for medical record review (including the abstraction and adjudication forms with case classifications and standard operating procedures [SOPs]) will be developed prior to having results from the first monitoring query. Given the expected rarity of GBS events after *Arexvy* vaccination, we will attempt to obtain medical records for all vaccinees who meet the above algorithm for GBS and multiple attempts will be made for each medical record as necessary. Events of interest whose charts are unobtainable will not be included in the inferential analyses. We will review summary information from their claims data, request the hospital records of these individuals, abstract relevant data to permit confirmation of GBS, and conduct a formal adjudication to arbitrate the presence and date of onset of symptoms of the event. Inpatient medical records will be obtained from each of the RPs in a manner compliant with the HIPAA and privacy regulations. Hospital charts will be obtained directly through requests from RPs using identifiers obtained from administrative claims data. Designated protected health information users at each RP will link the protected health information with masked

patient identification numbers, dates of birth, and provider information for the patients identified for medical chart abstraction.

A trained abstractor will extract specific information from the hospital records onto a structured data abstraction form. The form will collect information from admission notes, discharge summaries, laboratory results, radiographic reports, neurologist consultation notes, inpatient progress notes, and relevant medications administered. Forms will be independently reviewed by 2 clinicians, preferably neurologists, who will use the Brighton Collaboration's case definition for GBS (Table 5) to adjudicate whether a case is confirmed, possible, or not an event [Sejvar, 2011]. Disagreements in GBS case classification will be arbitrated by a third clinician, preferably a neurologist. GBS cases identified as Brighton Level 1, 2, or 3 will be considered medical record-confirmed cases. GBS cases identified as Level 4 (lowest level of certainty) will be considered possible GBS cases. Level 5 events will not be considered cases. Abstractors and adjudicators will be blinded to vaccination date – i.e., they will not know whether the event occurred in the risk or control window.

Table 5 Brighton Collaboration GBS case classification levels of diagnostic certainty and criteria

Brighton level of diagnostic certainty	Criteria
Level 1 (Highest Level of Certainty)	Bilateral AND flaccid weakness of the limbs. Decreased or absent deep tendon reflexes in weak limbs. Monophasic illness pattern AND interval between onset and nadir of weakness between 12h and 28 days AND subsequent clinical plateau. The eventual outcome is either stabilization at nadir OR subsequent improvement OR death. Electrophysiologic findings consistent with GBS. Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μL). Absence of identified alternative diagnosis for weakness.
Level 2	Bilateral AND flaccid weakness of the limbs. Decreased or absent deep tendon reflexes in weak limbs. Monophasic illness pattern AND interval between onset and nadir of weakness between 12h and 28 days AND subsequent clinical plateau. CSF total white cell count <50 cells/μL (with or without CSF protein elevation above laboratory normal value) OR If CSF not collected or results not available, electrophysiologic studies consistent with GBS. Absence of identified alternative diagnosis for weakness.
Level 3	Bilateral AND flaccid weakness of the limbs. Decreased or absent deep tendon reflexes in weak limbs. Monophasic illness pattern AND interval between onset and nadir of weakness between 12h and 28 days AND subsequent clinical plateau. Absence of identified alternative diagnosis for weakness.
Level 4 (Lowest Level of Certainty)	A case will be classified as having "insufficient evidence" if a physician's diagnosis of GBS is made, but evidence is insufficient to classify the patient at any higher level of diagnostic certainty (i.e., the abstraction data for that case does not contradict any of the Level 3 criteria but is missing information for at least one of the Level 3 criteria). Absence of identified alternative diagnosis for weakness.

Brighton level of diagnostic certainty	Criteria
Level 5 (Not a case)	If a case does not meet the criteria necessary for classification as Brighton Level 1, 2, or 3, is not diagnosed as GBS by a physician, or has a definitive alternate diagnosis documented in the chart, the patient will be classified as “not GBS.”

Abbreviations: CSF: cerebrospinal fluid; GBS: Guillain-Barré syndrome; h: hours.

The adjudicator will record the date, or estimated date, that symptoms first appeared per information in the chart. This will be the date used in the final analyses, described in Section 7.7. The onset date is crucial to determining whether the outcome occurred during the risk or control window.

7.3.2.3. Ascertainment and confirmation of ADEM events

Ascertainment and confirmation of ADEM events will follow the same approach as GBS.

Screening for ADEM:

Within each RP's database, patients will be identified as having possible ADEM within 91 days after *Arexvy* vaccination (primary analysis risk window days 1-42, control window days 43-84, and 7 extra days) if they had either: CCI [redacted]. The claims-based case date will be based on the earliest diagnosis of interest. New-onset ADEM will be identified by requiring that there not be evidence of ADEM in the 365 days prior to the first diagnosis code of interest: no occurrence of G04.00, G04.01, or G04.02 hospital discharge diagnosis (any position) in days -365 through day – 1 (day 0 is the day of the event). We are identifying potential cases using the G04.01 diagnosis code, post-infectious acute disseminated encephalitis and encephalomyelitis, because only chart-confirmed ADEM will be included in the final analysis. The diagnosis code for post-infectious acute disseminated encephalitis will be included to ensure we identify all potential outcomes post-vaccination; a patient code be miscoded as have a post-infectious event and we are prioritizing sensitivity of the algorithm over specificity given that charts on all events identified will be obtained.

The sensitivity analyses will use risk windows of (a) 1-21 days and (b) days 8-28, both with a control window of days 43-84, to align with the GBS approach, the timing of the 2 ADEM cases reported in the clinical trial, and other studies of postvaccination ADEM [Rongxia, 2016; Klein, 2021]. Symptom onset for the 2 ADEM events reported during *Arexvy* clinical trials – which were ultimately revised to other diagnoses – was on days 7 and 22 [Melgar, 2023].

The control window will be days 43-84 following vaccination. Continuous enrolment will be required through the end of the respective control interval plus 7 extra days to ensure that diagnosis codes that are recorded after symptom onset (and potentially after the risk and comparison windows) are captured. The final analyses will include individuals who have ADEM and die during the 91-days follow-up window.

Validation of ADEM Events:

Materials for medical record review (including the abstraction and adjudication forms with case classifications and SOPs), will be developed prior to having results from the first monitoring query. Given the expected rarity of ADEM events after *Arexvy* vaccination, we will attempt to obtain medical records for all vaccinees who meet the above algorithm for ADEM, and multiple attempts will be made for each medical record as necessary. Events of interest whose charts are unobtainable will not be included in the inferential analyses. We will review summary information from their claims data, request the hospital records of these individuals, abstract relevant data to permit confirmation of ADEM, and conduct a formal adjudication to arbitrate the presence and date of onset of symptoms of the event. Inpatient medical records will be obtained from each of the RPs in a manner compliant with HIPAA and privacy regulations. Hospital charts will be obtained directly through requests from RPs using identifiers obtained from administrative claims data. Designated protected health information users at each RP will link the protected health information with masked patient identification numbers, dates of birth, and provider information for the patients identified for medical chart abstraction.

A trained abstractor will extract specific information from the hospital records onto a structured data abstraction form. The form will collect information from admission notes, discharge summaries, laboratory results, radiographic reports, neurologist consultation notes, inpatient progress notes, and relevant medications administered. Forms will be independently reviewed by 2 clinicians, preferably neurologists, to adjudicate whether a case is confirmed, possible, or not an event [Sejvar, 2007]. Disagreements in ADEM case classification will be arbitrated by a third clinician, preferably a neurologist. ADEM cases identified as Brighton Level 1, 2, or 3 will be considered medical record-confirmed cases. ADEM cases identified as Level 4 (lowest level of certainty) will be considered possible ADEM cases. Level 5 events will not be considered cases (Table 6). Abstractors and adjudicators will be blinded to vaccination date – i.e., they will not know whether the event occurred in the risk or control window.

Table 6 Brighton Collaboration ADEM case classification levels of diagnostic certainty and criteria

Brighton level of diagnostic certainty	Criteria
Level 1 (Highest Level of Certainty)	Demonstration of diffuse or multifocal areas of demyelination by histopathology. OR 2a. Focal or multifocal findings referable to the central nervous system, including one or more of the following: Encephalopathy Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness) Cranial nerve abnormality/abnormalities

Brighton level of diagnostic certainty	Criteria
	Visual field defect/defects Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex) Sensory abnormalities (either positive or negative sensory level) Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes) Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus AND 2b. Magnetic resonance imaging findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted (DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (± gadolinium enhancement on T1 sequences). AND 2c. Monophasic pattern to illness (i.e., absence of relapse within a minimum of 3 months of symptomatic nadir.
Level 2	1a. Focal or multifocal findings referable to the central nervous system, including one or more of the following: Encephalopathy Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness) Cranial nerve abnormality/abnormalities Visual field defect/defects Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex) Motor weakness (either diffuse or focal; more often focal) Sensory abnormalities (either positive or negative sensory level) Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes) Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus AND 1b. Magnetic resonance imaging findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted (DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (± gadolinium enhancement on T1 sequences). AND 1c. Insufficient follow-up time achieved to document absence of relapse within a minimum period of 3 months following symptomatic nadir.

Brighton level of diagnostic certainty	Criteria
Level 3	Focal or multifocal findings referable to the central nervous system, including one or more of the following: Encephalopathy Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness) Cranial nerve abnormality/abnormalities Visual field defect/defects Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex) Motor weakness (either diffuse or focal; more often focal) Sensory abnormalities (either positive or negative sensory level) Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes) Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus
Level 4 (Lowest Level of Certainty)	A case will be classified as having "insufficient evidence" if a physician's diagnosis of ADEM is made, but evidence is insufficient to classify the patient at any higher level of diagnostic certainty (i.e., the abstraction data for that case does not contradict any of the Level 3 criteria but is missing information for at least one of the Level 3 criteria). Absence of identified alternative diagnosis for clinical findings.
Level 5 (Not a case)	If a case does not meet the criteria necessary for classification as Brighton Level 1, 2, or 3, is not diagnosed as ADEM by a physician, or has a definitive alternate diagnosis documented in the chart, the patient will be classified as "not ADEM."

Abbreviations: ADEM: acute disseminated encephalomyelitis.

The adjudicator will record the date, or estimated date, that symptoms first appeared per information in the chart. This will be the date used in the final analyses, described in Section 7.7. The onset date is crucial to determining whether the outcome occurred during the risk or control window.

7.3.2.4. Ascertainment and Confirmation of New-Onset AF Events

Screening for New-Onset AF: Within each RP's database, patients will be identified as having new-onset AF within 16 days after *Arexvy* vaccination if they had: CCI [redacted] The primary analysis will use risk and control windows of 1-8 days and 9-16 days, respectively. This is based on

unpublished data on post-marketing adverse events reported to GSK through August 2024, which had a maximum time to onset of 8 days post-vaccination.

In one sensitivity analysis, our risk and control windows will be 1-28 days and 29-56 days respectively. This is based on: (i) the available evidence from literature on risk intervals for cardiac arrythmias after vaccination in older adults [Patone, 2022a; Patone, 2022b], and (ii) data from the Phase 3 efficacy trial which indicated that all new-onset serious AF events occurred within 28 days after vaccination (only serious reports are considered as they represent the events for which the participants were hospitalized due to their AF onset and only such reports would be captured in this study design) [GSK, 2023]. Further, using 28 days (versus, for example, 30 days) avoids potential day-of-week bias [Yih, 2016b]. In another sensitivity analysis, we will use risk and control windows of 1-3 days and 4-8 days respectively, since unpublished post-marketing reports have indicated a maximum time to onset of 3 days.

Of note, health care utilization is expected to vary by the day of the week, clustering on some days in the week compared to the others. Typically, vaccine safety studies account for potential day-of-the-week effects by using risk and control windows that are multiples of 7 [Yih, 2016b]. Our analyses with risk windows of 8 days and 3 days may be susceptible to day-of-the-week effects.

The date of the event will be the date of the first qualifying AF diagnosis if there are two outpatient codes. Continuous enrolment through Day 106 post-vaccination will be required for the primary AF inferential analysis, ensuring vaccinees have equal time to acquire a second diagnosis for AF in the outpatient/ED setting. The final analysis will include individuals who have AF and die during follow-up. We will also conduct a sensitivity analysis where continuous enrolment is required only through the control window (Day 16).

Arexvy vaccinees identified with AF via the claims-based algorithm will be assessed for a prior AF diagnosis code >365 days before the event date. The number of AF events meeting this criterion will be reported for each risk and control window combination.

Table 7 ICD-10-CM diagnosis codes for new-onset AF case-finding algorithm

Full Description	Code
Paroxysmal atrial fibrillation	I48.0
Unspecified atrial fibrillation	I48.91

Validation of New-Onset AF events: Materials for medical record review (including the abstraction and adjudication forms with case classifications and SOPs), will be developed prior to having results from the first monitoring query.

Since AF is a common health outcome among older adults, we will evaluate the PPV (95% CI) of our proposed algorithm for new-onset AF within a random sample of vaccinees who meet the algorithm. Our focus is on PPV because a sufficiently high PPV provides confidence that identified outcomes are true events.

As described in Section 7.3.2.1 above, we will identify a random sample of patients with new-onset AF across our RPs according to the algorithm developed in Table 4 and based on the number of charts needed in Table 3. If we obtain a PPV ≥80%, it will provide reassurance that majority of new-onset AF events ascertained using the algorithm are true cases and reduce concerns regarding outcome misclassification; a claims data-only analysis will be conducted, possibly including adjustment for the PPV. If, contrary to expectation, the PPV of a coding algorithm is found to be below 80%, the inferential analyses will be restricted to chart-confirmed cases only. In this situation, additional charts will be sought to obtain 69 confirmed cases. This is based on an assumption of an IR between 10 and 50 per 1000 person-years and a RR of 2.

A trained abstractor will extract specific information from the hospital records onto a structured data abstraction form. The form will collect information from hospital admission notes, hospital discharge summaries, inpatient or outpatient cardiology consultation notes, inpatient or outpatient electrocardiograms (ECG), inpatient or outpatient Holter or event monitors, inpatient or outpatient telemetry strips, and inpatient or outpatient anti-arrhythmic medications administered. Forms will be reviewed by a clinician, preferably a cardiologist. To be considered a confirmed case of AF, there must be evidence of AF on one of the following studies: 1) ECG or rhythm strip, 2) Holter monitor, event monitor, or telemetry, or 3) pacemaker interrogation [Calkins, 2017]. Possible AF will be defined as a clearly noted AF diagnosis recorded by a clinician in the chart in the absence of any arrhythmia monitoring study. Abstractors and adjudicators will be blinded to vaccination date – i.e., they will not know whether the event occurred in the risk or control window.

If an algorithm for AF is validated within the data of a participating RP at the time of study conduct and meets our performance criteria, it will be considered whether to instead apply that algorithm and the protocol and SAP will be updated accordingly.

7.3.3. Covariates

Covariates to be evaluated using descriptive statistics and curated data formatted to the Sentinel Common Data Model (SCDM) include:

- Age in years at vaccination.
- Sex.
- Race (i.e., American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiracial).
- Hispanic or Latino ethnicity (i.e., yes, no, or unknown).
- Concomitant vaccinations (e.g., influenza, COVID-19, varicella-zoster, pneumococcal vaccine) before, on the same date as, and after *Arexvy* vaccination.

- Immunocompromising conditions (defined by HPHCI: human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome, hematologic malignancy and related conditions, solid malignancy except non-melanoma skin cancer, solid organ or stem cell transplantation, rheumatological/inflammatory conditions, and immune disorders) identified via ICD-10-CM diagnosis codes; some immune disorders may be restricted to those with both diagnosis codes and evidence of treatment (e.g., multiple sclerosis and systemic lupus erythematosus).
- Other comorbidities (e.g., diabetes mellitus, chronic kidney disease, chronic pulmonary disease, stroke, heart disease) identified via ICD-10-CM diagnosis codes.
- Recent infections that might precipitate GBS, ADEM, or AF (such as respiratory infections [including for example COVID-19, and those caused by *H. influenzae*, influenza virus, *Mycoplasma pneumoniae*], gastrointestinal infections [including those caused by *Campylobacter jejuni*, hepatitis E], and others [including for example those caused by Chikungunya virus, cytomegalovirus, Epstein-Barr virus, *Escherichia coli*, herpes simplex virus, herpes zoster virus, HIV, Japanese encephalitis virus]) [Jacobs, 1998; Tenembaum, 2007; Boos, 2020; Gundland, 2020; Parsons, 2020; Anderson, 2021] identified via ICD-10-CM diagnosis codes.
- Recent health care events or conditions that might precipitate GBS, ADEM, or AF (such as solid organ or stem cell transplantation, certain surgeries, trauma, obstructive sleep apnea, hyperthyroidism, myocarditis, pneumonia, sick sinus syndrome, panic disorders, metabolic syndrome, alcohol use disorder) identified via ICD-10-CM diagnosis codes and/or procedure codes.
- Concomitant medications that are known to cause GBS, ADEM, or AF.
- Research Partner
- Geographic region (Census Bureau Regions: Northeast, Midwest, South, West, Other)
- Calendar month/year of vaccination
- Healthcare utilization in prior 365 days (e.g., ambulatory visits, hospitalizations, medication dispensings)

Note that race and ethnicity data may be incomplete, and completeness will vary by RP. Patients with immunocompromising conditions will not require to receive treatment for their condition because this would increase the likelihood of misclassification.

7.3.4. Confounders and effect modifiers

The self-controlled nature of the SCRI design means that time-fixed traits will not act as confounders. However, it is important to consider potential time-varying confounders, particularly seasonality. *Arexvy* administration will have a seasonal pattern, the outcomes of interest may have seasonal patterns [Moutzouris, 2003; Loomba, 2015; Webb, 2015; Hamdani, 2023], and the combined risk and control windows are somewhat long.

Therefore, primary analyses will be conducted unadjusted for seasonality, but sensitivity analyses will be conducted for each outcome that adjusts for seasonality (note that it will likely not be possible to adjust for seasonality for ADEM given the need for adequate reference data). Details regarding these sensitivity analyses will be included in the SAP.

7.4. Data sources

This is a non-interventional safety study based on secondary use of data previously captured from consumers or healthcare professionals for other purposes. Data to be used in this study will include medical chart reviews (including follow-up on data with healthcare professionals) and electronic healthcare records. Patients will not be administered any vaccine as part of the study. Individual case AE/adverse reaction reports will not be generated from this study.

This post-authorization safety study will be conducted using health plan administrative claims data held by 5 RPs (i.e., Carelon, CVS Health, HealthPartners, Humana, Point32Health) who are participating in the US FDA's Sentinel System [Behrman, 2011]. All RPs are expected to contribute data for each analysis. In addition to providing claims data, the RPs will provide scientific input and feedback to support this study. The 3 large RPs currently refresh their data in the Sentinel Distributed Database multiple times per year and the 2 smaller sites refresh annually. For each analysis we will leverage the most recently available data or will work with the sites to adjust their schedule. Administrative claims data require time to accrue and approach completeness (approximately ≥90% complete), and the amount of time depends on care setting, with inpatient diagnoses requiring ~6 months. RP data refreshes, including data quality checks following Sentinel System procedures, take approximately 1 month.

Each of the RP is discussed below with detail on the number of their members who are ≥50 years of age:

FDA Sentinel System RPs: The FDA Sentinel System is an active surveillance system that utilizes electronic healthcare data from a distributed data network for monitoring the safety and effectiveness of regulated medical products in the US, established under the Sentinel Initiative [Behrman, 2011; Platt, 2018; Brown, 2022]. We will leverage the technical infrastructure of the FDA's Sentinel System, including the SCDM and the Distributed Database [Curtis, 2012]. This approach allows participating organizations to retain control of their data, ensure data and patient privacy and confidentiality, and enable the identical analysis to be conducted at each site. Importantly, the data and processes developed for Sentinel includes robust data quality checks and involvement of individuals within the RP organizations who have deep expertise in the source data. The provenance of the data included in this proposal is well understood and traceable. Each of the Sentinel RPs have demonstrated capability to obtain the majority of requested original medical records for review, which would permit adjudication of outcomes when this is necessary.

The national insurer populations, CVS Health (formerly Aetna), Elevance Health (formerly Anthem; Carelon Research is a subsidiary), and Humana, currently participate

in the FDA's Sentinel System, as does the regional integrated delivery system HealthPartners. The regional insurer, Point32Health, is the home organization of the Harvard Pilgrim Health Care Institute (HPHCI) and currently participates in the Vaccine Safety Datalink, funded by the Centers for Disease Control and Prevention (CDC).

Together, these RPs provide large, representative patient populations, extensive experience with similar research, and the ability to carry out the project according to the required timeframe.

- **CVS Health** is one of the nation''s leading healthcare companies that owns Aetna, a national Health insurance company that serves over 38 million people with information and resources to help them make better-informed decisions about their health care. CVS Health became an FDA Sentinel RP in 2010 and continues to be one of the largest contributors of data for public health purposes. As of

  October 2023, there are approximately 4.4 million current members with both medical and drug coverage, who are ≥50 years of age, and are research eligible. CVS Health offers Medicare Advantage.

- **Carelon Research** is a subsidiary of Elevance Health (formerly Anthem), the largest health benefits company in terms of medical membership in the US. Elevance Health is an independent Blue Cross and Blue Shield Association licensee. Carelon Research is the health services research entity for Elevance Health that integrates the public health, pharmacoepidemiologic, health outcomes, and pharmacoeconomic concerns of these companies and their clients to conduct outcomes analyses. Carelon Research includes approximately 68.4 million current members with medical and prescription drug coverage who are research eligible. As of December 2023, there are approximately 7 million current members with both medical and drug coverage, who are ≥50 years of age and are research eligible. Health plan members span the US, specifically, the Northeastern, Mid-Atlantic, Southeastern, Midwestern, Central, and Western regions.

- **HealthPartners** is an active collaborator and RP in the FDA Sentinel System. HealthPartners is the largest consumer-governed non-profit health care organization in the country, providing care, coverage, research, and education to improve health and well-being in partnership with its members, patients and community. Included under HealthPartners' umbrella are Regions Hospital, HealthPartners Care Group, HealthPartners Center for Memory & Aging, Park Nicollet Methodist Hospital and HealthPartners Institute. HealthPartners has formal relationships with hospitals and clinics throughout Minnesota and western Wisconsin, including Westfields Hospital (New Richmond, WI), Lakeview Hospital (Stillwater, MN), Hudson Hospitals and Clinics (Hudson, WI), Amery Hospital and Clinic (Amery, WI), St Francis Regional Medical Center (Shakopee, MN), Hutchinson Health (Hutchinson, MN), TRIA Orthopedic Center, and Physicians Neck and Back Clinic. Founded in 1957, the HealthPartners family of care serves more than 1.8 million medical and dental health plan members. As of September 2023, there are approximately 247 000 current members with both medical and drug coverage, who are ≥50 years of age, and are research eligible. HealthPartners is one of the top-ranked commercial health plans in

Minnesota and is also one of the highest rated plans in the nation, according to the National Committee for Quality Assurance's Health Insurance Plan Rankings 2021-2022.

- **Humana** is an active collaborator and RP in the FDA Sentinel System, the Patient-Centered Outcomes Research Institute's National Patient-Centered Clinical Research Network (PCORnet), and several distributed research network initiatives for vaccine safety. As of September 2023, Humana includes about 6.13 million members actively enrolled with both medical and prescription insurance coverage and who are research eligible. Among them, approximately 5.56 million are ≥50 years of age. Humana includes members throughout the US, with highest concentration of members in the South region.
- **Point32Health** is the second largest New England based health plan. It provides care to 2.2 million individuals under the names, Harvard Pilgrim Health Care and Tufts Health Plan. Harvard Pilgrim Health Care participated in the Sentinel System and Point32Health is currently a site for the CDCs Vaccine Safety Datalink. As of September 2023, there are approximately 248 000 current members with both medical and drug coverage, who are ≥50 years of age, and are research eligible. Although Point32Health is smaller than the other RPs, it has the important advantages of being the institutional home of HPHCI. HPHCI personnel have direct access to Point32Health's data, providing the ability to work directly with source data to understand apparent anomalies in any analyses performed within this distributed data network.

Specific information in the SCDM includes, but is not limited to, the following data:

- **Enrolment data:** One record per covered individual per unique enrolment span is included in the SCDM. Individuals are assigned a unique identifier by their insurer, which is linkable to all other data in the SCDM. Due to changes in employment status, individuals may be enrolled multiple times with the same insurer, and the length of each given enrolment span may vary substantially. Each record in the enrolment file indicates the patient identifier, enrolment start and end dates, and whether the patient was enrolled in medical coverage, pharmacy coverage, or both during that range.
- **Demographic data**, including birth date, sex, race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or Multiracial), Hispanic ethnicity, and zonal improvement plan (ZIP) code of their most recently recorded primary residence.
- **Immunization data** are primarily captured via NDC and procedure codes in administrative claims data. We expect claims data to be a sufficiently complete source of exposure information for this *Arexvy* vaccine safety study since we expect its administration to be billed to payers and the SCRI design alleviates concerns about exposure misclassification. However, some of the participating RPs may link to state-based immunization information systems with varying levels of completeness and timeliness. Data from immunization registries will be included if available and permissible.

- **Pharmacy dispensing data**, including the date and NDC identifier for each dispensed prescription, the nominal days' supply, and the number of individual units (pills, tables, vials, etc.) dispensed. Products purchased out-of-pocket (i.e., not billed to insurance) are not captured.
- **Medical encounter data**, including the healthcare provider identified with the encounter as well as the facility in which the encounter occurred and its ZIP code. Admission and discharge dates (if applicable) are also included, as is the encounter type (either an ambulatory visit, an ED visit, an inpatient hospital stay, a non-acute inpatient stay, or an otherwise unspecified ambulatory visit). Discharge disposition (alive, expired, or unknown) as well as discharge status (where a patient was discharged) are also included for inpatient hospital stays and non-acute inpatient stays.
- **Laboratory data**, both tests and their results, are available for some laboratory tests. Depending on the need for laboratory test result data in the analyses, we will work with the RPs to assess completeness and quality of the tests.
- **Diagnosis data**, including the date of diagnosis, its associated encounter identifier, admission date, provider identifier, and encounter type. Diagnoses are recorded using (ICD-10-CM) diagnosis codes. For hospital and non-acute inpatient stay encounters, the SCDM includes both primary and non-primary (secondary or unknown) discharge diagnoses. Health outcomes and covariates are typically identified using ICD-10-CM codes alone or in combination with other elements, as appropriate, including dispensing date and laboratory test results.
- **Procedure data**, including the procedure date, its associated encounter identifier, admission date, provider identifier, and encounter type, are available. Procedures may be coded as: ICD-10 Procedure Coding System procedure codes; CPT categories II, III, or IV codes; revenue codes; or HCPCS levels II and III codes.

7.5. Study size

The sample size and power calculations are estimated for the primary outcomes of the study, GBS and ADEM, and the primary risk (days 1-42) and control (days 43-84) windows. In the US, background rates of GBS reported in the literature range from 1.6 to 6.3 per 100 000 person-years in the overall population. In those ≥60 years of age, the IRs vary from 2.4 to 4.7 per 100 000 person-years in studies conducted over several years between 1935 and 1987 [Law, 2021]. More recent publications are reporting IR ≥ 4 GBS cases per 100.000 person-years in older adults. A study conducted in the US on background rates of adverse events of special interest reported a GBS IR of 4.6 per 100.000 person-years in adults ≥ 65 years of age [Moll, 2023]. The background rate in the analysis conducted by [Lloyd, 2024] was 4.4 per 100,000 person-years (unpublished). Background rates of ADEM range from 0.3 to 0.6 per 100 000 person-years in the overall population [Pohl, 2016].

The estimated number of vaccinated individuals needed to detect an association between *Arexvy* and the outcomes, assuming 80% statistical power, a two-sided alpha = 0.05, and an equal duration of 42 days for the risk window and 42 days for the control window, are

reported in Table 8 for GBS and ADEM for a range of RRs to be detected and a range of IR for the outcomes. Table 9 is for AF and is based on risk and control windows of 8 days.

Using a background rate for GBS of4.5 cases per 100 000 person-years (taken as the average from [Lloyd, 2024] (4.4) and Moll, 2023 (4.6)), a total number of 69 cases in the combined risk and control intervals provides 80% power to reject the null hypothesis of no association when the true RR is ≥2.0. Approximately 4.4 million vaccinated patients are needed to accrue the number of cases of GBS (Table 8).

Using a background rate for ADEM cases of 0.45 per 100 000 person-years, a total number of 12 cases in the combined risk and control intervals provides 80% power to reject the null hypothesis of no association when the true RR is ≥7.0. Approximately 3.9 million vaccinated patients are needed to accrue the number of cases of ADEM (Table 8).

In the US, an IR of 16.6 cases per 1000 person-years has been reported for AF in 2018 for those 55 years and older, with a range of 6.9 to 52.5 cases per 1000 person-years for those aged 55-64 and ≥85 years of age, respectively [Williams, 2020]. For this secondary outcome, to detect a RR of ≥2, 69 cases will be needed (Table 9).

Table 8 Estimated number of cases and vaccinated health plan members needed to detect an association between RSV vaccination and GBS or ADEM using a SCRI design, with 80% power, a two-sided alpha = 0.05, under different scenarios for relative risk and background incidence rate: 42-day risk and control window

Relative risk	Total number of cases (control and risk periods) *	Number of cases in control period	0.3 per 100 000 PY	0.45 per 100 000 PY	0.6 per 100 000 PY	2 per 100 000 PY	3 per 100 000 PY	4 per 100 000 PY	4.5 per 100 000 PY	5 per 100 000 PY	6 per 100 000 PY
1.25	634	282	817464286	544976191	408732143	122619643	81746429	61309822	54497620	49047858	40873215
1.50	194	78	226107143	150738096	113053572	33916072	22610715	16958036	15073810	13566429	11305358
2.00	69	23	66672620	44448413	33336310	10000893	6667262	5000447	4444842	4000358	3333631
2.50	41	12	34785715	23190477	17392858	5217858	3478572	2608929	2319048	2087143	1739286
3.00	29	8	23190477	15460318	11595239	3478572	2319048	1739286	1546032	1391429	1159524
4.00	20	4	11595239	7730159	5797620	1739286	1159524	869643	773016	695715	579762
5.00	15	3	8696429	5797620	4348215	1304465	869643	652233	579762	521786	434822
6.00	13	2	5797620	3865080	2898810	869643	579762	434822	386508	347858	289881
7.00	12	2	5797620	3865080	2898810	869643	579762	434822	386508	347858	289881

*Total number of cases was calculated using the method described by Musonda et al. [Musonda, 2006], assuming that the length of the risk period is the same as the length of the control period.

Table 9 Estimated number of cases and vaccinated health plan members needed to detect an association between RSV vaccination and AF using a SCRI design, with 80% power, a two-sided alpha = 0.05, under different scenarios for relative risk and background incidence rate (8-day risk and control windows)

Relative risk	Total number of cases (control and risk periods)*	Number of cases in control period	1 per 1000 PY	2 per 1000 PY	5 per 1000 PY	10 per 1000 PY	50 per 1000 PY
1.25	634	282	12875063	6437532	2575013	1287507	257502
1.50	194	78	3561188	1780594	712238	356119	71224
2.00	69	23	1050094	525047	210019	105010	21002
2.50	41	12	547876	273938	109575	54788	10958
3.00	29	8	365251	182626	73050	36525	7305
4.00	20	4	182626	91313	36525	18263	3653
5.00	15	3	136969	68485	27394	13697	2740
6.00	13	2	91313	45657	18263	9132	1827
7.00	12	2	91313	45657	18263	9132	1827

*Total number of cases was calculated using the method described by Musonda et al. [Musonda, 2006], assuming that the length of the risk period is the same as the length of the control period.
PY=person-years

7.6. Data management

7.6.1. Data handling conventions

HPHCI will serve as the Coordinating Center for the proposed study. HPHCI staff or contractors will be responsible for writing and distributing Statistical Analysis System (SAS) programs that evaluate data from the administrative claims databases at participating RPs. The distributed network will allow RPs to maintain physical and operational control of their data while allowing use of the data to meet the study needs. HPHCI will maintain a secure distributed querying web-based portal to enable secure distribution of analytic queries, data transfer and document storage. The system will meet all required State and Federal security guidelines for health data.

7.6.2. Resourcing needs

HPHCI brings expertise in conducting multi-site evaluations using disparate electronic healthcare data systems, including extensive work with the Health Care Systems Research Network, the Vaccine Safety Datalink, FDA Sentinel, the National Institutes of Health, and PCORnet. HPHCI will oversee all project activities, including scientific leadership, management of the partnership, coordination of activities with the RPs and other patients, oversight of the project plan and budgets, establishment of secure

infrastructure used for collaboration, and training related to use of the SCDM and associated querying tools. The RPs will establish and maintain the administrative, hardware, and software capabilities and capacity to respond to data requests in a timely manner. They will also provide data science support during review of results.

7.7. Data analysis

Whenever possible, publicly available analytic tools created for the FDA's Sentinel System will be used. These are the same tools used by the FDA. Modifications to the tools may be needed to meet study objectives, in which case Sentinel's SAS programming data quality assurance (QA) SOPs will be followed. All the statistical analyses will be done in SAS 9.4 or higher.

Descriptive monitoring analyses, described in Section 7.7.1 below, will be conducted annually. Inferential analyses will be conducted following the methods in Section 7.7.2 as well as the SAP that will be developed and finalized prior to conducting the analyses.

For each outcome, the final inferential analysis will be performed once the number of events needed has accrued. For GBS and ADEM, depending on the accrual pace, separate analyses will be done (e.g., if GBS events accrue faster than ADEM), otherwise analysis of both primary outcomes will be combined in a single final analysis at study end. For new-onset AF, since these events are relatively more common, the final analysis will be conducted earlier than the GBS and ADEM final analyses (Table 10).

Table 10 Sequence of analysis

Outcome	Target risk to detect	Analysis sequence
AF	RR ≥2	Phase 1
GBS	RR ≥2	Phase 2
ADEM	RR ≥7	Phase 3

ADEM: acute disseminated encephalomyelitis; AF: atrial fibrillation; GBS: Guillain-Barré syndrome; RR: relative risk

7.7.1. Descriptive analyses and annual monitoring

On an annual basis, among our RPs, we will conduct descriptive monitoring queries to assess uptake of *Arexvy* and describe the demographic and clinical characteristics of recipients of *Arexvy*, overall, within subgroups of interest, and by risk/control window per the claims data. Assessment of baseline pre-existing conditions of interest (e.g., recent prior infections), receipt of concomitant vaccines (e.g., influenza, COVID-19, shingles, pneumococcal), and general healthcare utilization will be done. Baseline characteristics of vaccinees will be described using tabular and graphical methods to assess temporal patterns by year-month.

As part of our planned annual monitoring, we will also identify counts of each of the individual outcomes in the risk and control windows based on diagnosis code-based case-finding algorithms (only) among those vaccinated. Concurrently, after the outcomes have

been identified by the case-finding algorithms, chart reviews will be performed immediately.

Deaths that occur after vaccination during follow-up among those with an outcome of interest will be counted if they are recorded in the data. Deaths are captured via discharge status (for in-hospital deaths) and via enrolment data (for both in-hospital and out-of-hospital deaths). The death data are expected to be incomplete due to the nature of administrative claims data in the US and the time lag in the identification of out-of-hospital deaths in these data sources.

7.7.2. Primary analysis

7.7.2.1. Main analytical approach

SCRI-based analyses of primary and secondary objectives will include the *Arexvy* vaccinees with an event of interest in the risk window, control window, or the extra days after the control. In these analyses, each individual serves as their own control. IRRs of the outcomes will be estimated with 95% CIs using conditional Poisson regression models. All SCRI-based analyses will use conditional Poisson regression. A forthcoming SAP will be finalized prior to conducting the inferential analyses.

Analysis of the primary GBS and ADEM outcomes will be based on chart-confirmed cases as has been previously done [Arya, 2019]. For those outcomes, onset of symptoms will be discerned from medical record review and date of the event will be classified based on expert clinician adjudication. Identification of all events in days 1 through 91 after vaccination will be included in the medical record review but which window (risk, control, extra days) the events are counted in for the analysis will be determined based on the symptom onset date from the medical record. Events identified in the claims data with unobtainable charts will be excluded from the primary analyses due to concerns about misclassification of the outcome and timing of onset of symptoms.

As previously noted, events among people who die during the follow-up window (risk window, control window, or during the extra days) will be included. The number of events will be quantified, if any, that were among people who died during follow-up. The final analyses will include individuals who die during the risk or control intervals.

Follow-up time will be artificially continued until the last day of the control interval, which will avoid including fatal cases that occurred in the control interval over fatal cases that occurred in the risk interval. If a fatal event occurs during the risk window, all the remaining days in the risk window and all the days that would have occurred in the control window will be included in the analyses.

7.7.2.2. Data handling conventions

Exposure to *Arexvy* will be identified via CPT, NDC, HCPCS, and CVX codes, as described in Section 7.3.1 (Table 2). Individuals with evidence of both Arexvy and another medical product indicated for RSV disease prevention (i.e., vaccine from a

different manufacturer or monoclonal antibody to prevent RSV lower respiratory tract disease) will be excluded. Outcomes will be identified using the algorithms in Table 4. Covariates will be identified by the presence of diagnosis codes and/or medications of interest; the absence of such evidence is interpreted to mean the individual has not been diagnosed or received the treatment of interest. As previously described, enrolment through the end of follow-up- will be required, unless an eligible member has an event and dies, in which case they will be included in the analysis. Only individuals with complete dates of birth will be included.

7.7.2.3. Sensitivity analyses

Sensitivity analyses will be conducted to assess whether results are robust after addressing concerns related to misclassification or other biases. The analyses are summarized in the protocol and will be detailed in the SAP.

As summarized in Table 4, there will be sensitivity analyses for GBS, ADEM and AF with different risk and control windows.

The primary inferential analyses for GBS and ADEM will be restricted to those cases that are adjudicated as "confirmed" during medical record review. As a sensitivity analysis the same analyses will be conducted but will include cases adjudicated as confirmed or possible based on medical record review. In addition, if charts are not obtainable for all events identified via the claims-based algorithms, a sensitivity analysis will be conducted including chart-confirmed cases plus those patients identified with an outcome of interest whose charts were unobtainable (and excluding those adjudicated as not cases).

As described in Section 7.3.4, there is a potential for confounding due to seasonal trends in both *Arexvy* vaccination and the outcomes of interest. For the GBS and AF inferential analyses, adjustment will be made for seasonality.

For GBS and ADEM, a sensitivity analysis will be conducted excluding patients with evidence of an immunocompromising condition.

For AF, the PPV for the algorithm will be calculated using confirmed cases only as the primary analysis. A sensitivity analysis will also be conducted where both confirmed and possible cases are included in the calculation. In addition, a sensitivity analysis will be conducted where the post-vaccination enrolment requirement is through the control window (Day 16); this is compared to the primary AF analysis where enrolment is required through Day 106, the last day an AF diagnosis code may occur for the algorithm criterium that requires 2 diagnosis codes in the outpatient or ED setting.

For all outcomes, if there are an adequate number of events with evidence of concomitant vaccination, infection, or medication (where concomitant is defined as before, on the same day as, or after *Arexvy* administration), additional analytic possibilities beyond descriptive statistics will be considered.

Any additional analyses will be described in detail in the SAP.

7.7.3. Secondary analysis/Exploratory analysis

The analysis of new-onset AF, a secondary outcome, will be conducted using the same analytic approach as the primary outcomes described above in Section 7.7.2.1 in terms of the SCRI design as well as identification of fatal events. However, as explained in detail in Section 7.3.2.4, all claims-identified cases will be included for new-onset AF assuming the PPV for the diagnostic coding algorithm is ≥80%.

7.8. Quality control and Quality assurance

As described above, the distributed network utilizes the SCDM, enabling data standardization across RPs. Furthermore, each of the participating RPs has experience with this data model given its role as an active participant in the FDA's Sentinel System. This study is expected to use the same data quality assurance procedures as the Sentinel System. The quality assurance approach assesses consistency with the SCDM, evaluates adherence to data model requirements and definitions, evaluates logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across RPs. Full quality assurance processes and details on the Sentinel data curation approach are documented on the Sentinel website. The data curation approach is consistent with guidance set forth by the FDA in its current recommendations for data quality assurance published in May 2013 [FDA, 2013].

In addition to quality assurance of data elements, HPHCI adopts standard SAS programming quality assurance and quality control processes used by the Sentinel System to check SAS programs and deliverables.

Study records should be retained by HPHCI, or the RP, according to local regulations or as specified in the research agreement with GSK, whichever is longer. HPHCI, or the RP, must ensure that the records continue to be stored securely for so long as they are retained. For RPs that will be retaining study records, records must be kept for a maximum of 12 years from the issue date of the protocol or study report/summary or equivalent, unless HPHCI, the RPs, and GSK have expressly agreed to a different period of retention via a separate written agreement.

The investigators agree to be responsible for implementing and maintaining a quality management system with written development procedures and functional area SOPs to ensure that studies are conducted, and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical and Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

7.9. Limitations of the research methods

There are potential scientific risks and limitations as well as logistical risks to consider.

Sample Size: Adequate sample size will be difficult to achieve if uptake of *Arexvy* is low, since the primary outcomes are rare. To minimize this likelihood, it is proposed to evaluate vaccinees within data from large national RPs.

Confounding*:* The use of the SCRI design for acute outcomes guards against confounding by many of the covariates that can confound other designs, including chronic disease status. Nonetheless, seasonality can confound SCRI analyses. Assessment of whether there is evidence of seasonality will be done and if so, a sensitivity analysis will be conducted that explicitly adjusts for seasonality. In addition, specifying the optimal risk window can be a challenge and misclassification is possible with respect to timing of the event. To address this, for the primary outcomes of GBS and ADEM, the final inferential analyses will be restricted to chart-confirmed cases using information and the timing of the event (i.e., risk vs control window) will be based on information from the medical record.

Misclassification bias*:* As in any study that includes administrative claims data, case ascertainment algorithms are rarely perfectly sensitive and specific. As such, we may not identify all potential outcomes of interest and some outcomes will not be true events.GBS and ADEM will be ascertained using full case adjudication. If records are unable to be retrieved for event confirmation, those patients will not be included in the primary analysis. New-onset AF will be ascertained using an algorithm with ≥80% PPV. We may perform quantitative bias analyses to assess the impact of outcome misclassification to understand the effect of imperfect specificity and sensitivity on observed effect sizes.

In addition, the death data are expected to be incomplete due to the nature of administrative claims data in the US. There is a time lag in the identification of out-of-hospital deaths in these data sources.

Day-of-the-week effects: Health care utilization is expected to vary by the day of the week, clustering on some days in the week compared to the others. Typically, vaccine safety studies account for potential day-of-the-week effects by using risk and control windows that are multiples of 7 [Yih, 2016b]. Our analyses with risk windows of 8 days and 3 days maybe susceptible to day-of-the-week effects.

Administration of concomitant vaccines*:* Concomitant vaccination may make it difficult to separate out the effect of *Arexvy* from other vaccines. The concomitant administration of other vaccines will be described during all analyses and will consider appropriate analytic options if there are adequate numbers of events with concomitant vaccination.

Change in some health plans' policies regarding ability to retrieve records: If this occurs, the focus will be on records from organizations that continue to permit retrieval and then extrapolate to the full population.

Incomplete ascertainment of charts: We expect that <100% of charts we seek to obtain will be retrievable. For GBS and ADEM, where the outcomes are rare and misclassification of the outcomes is a major concern, a sensitivity analysis will be conducted (as noted in Section 7.7.2.3) that includes chart-confirmed cases as well as

events among those whose charts were unobtainable. It is expected that there will be enough AF events identified via the claims-based algorithm to ensure that the minimum number of charts required for adjudication is met (see Table 3).

7.9.1. Study closure

Data collection is planned to end in June 2030 or once the number of cases needed to power the study with adequate precision have been accrued.

7.10. Other aspects

Not applicable.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

As the Coordinating Center for the current study, HPHCI has the responsibility to obtain approval of the study protocol, protocol amendments, and other relevant documents, from an Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Participating RPs can either cede IRB review to HPHCI or seek approval from their local IRB. All correspondence with the IRB/IEC will be retained in the Investigator File.

All parties will ensure protection of patients' personal data in compliance with HIPAA and will not include patient identifiers on any sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, high standards of confidentiality and protection of patient personal data will be maintained.

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. Study results will be in tabular form and aggregate results will omit subject identification.

Therefore, informed consent, ethics committee, and IRB approval are not required. Any publications and reports will not include subject identifiers.

The study will be conducted with a waiver of informed consent. This study will involve numerous individuals from multiple health plans and delivery systems. Thus, it could not be practically conducted without a waiver of informed consent. The proposed study has minimal risk; potential breaches of privacy and confidentiality are the primary study risks, and these risks will be minimized by ensuring that rigorous security procedures are applied to data collection, management, and transfer. Some of these procedures include using a study identification number in place of direct patient identifiers; transferring data using secure, encrypted websites; and ensuring that appropriate data transfer agreements are in place between institutions prior to data sharing. Additionally, only trained and authorized study staff will be allowed to access study data, and secure data storage methods, such as password protected electronic files and locked paper files, will be used by all participating RPs and the data Coordinating Center.

8.2. Subject confidentiality

All parties will ensure protection of patients' personal data in compliance with HIPAA and will not include patient identifiers on any sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, high standards of confidentiality and protection of patient personal data will be maintained.

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 will it comply with any specified prohibitions of use.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study has safety objectives.

Study type 5: Secondary data collection studies including unstructured data with human review with safety objectives. An example is human review of verbatim text in a medical record as part of a chart review study.	*These studies can identify solicited events in aggregate at study end but cannot identify spontaneous events*

Definitions of Solicited and Spontaneous Events

Solicited events are defined as those AEs related to the GSK product under evaluation and identified for collection in the study database as per study objectives.

Solicited events must be collected in the study database and reported to GSK for entry into the GSK Safety database. Onward reporting to regulators, in the form of Individual Case Safety Reporting (ICSRs), is only applicable for primary data collection studies (further information below). For secondary data collection studies, information on solicited events will be contained in the study report.

Spontaneous events are defined as:

- Those unsolicited AEs observed related to the GSK product under evaluation but exempted from collection, as justified in the protocol. (Only applicable to studies capturing solicited events).
- Those AEs observed related to any GSK/ViiV product not under evaluation in the study.

- Any Adverse Drug Reactions (ADRs) observed related to non-GSK product(s), for which the ADRs should be reported to the appropriate marketing authorization application of the product(s) or Health Authority per local regulations.

  Spontaneous events are not collected in the study database BUT are still reported to GSK for entry in the GSK Safety database.

Collection of adverse events/reactions (Solicited Events)

The purpose of the study is to monitor exposure to *Arexvy* and to evaluate the risk of new-onset GBS, new-onset ADEM, and new-onset AF. For *Arexvy*, pre-defined safety events of interest GBS, ADEM and AF, will be systematically recorded in aggregate. These will be summarized in final study reports. This study is based on secondary use of existing health data and as such ICSRs to regulatory agencies is not required.

Reporting of adverse events/reactions (Spontaneous Events)

This study is based on data previously collected for other purposes, e.g., routine healthcare encounters. As such, there is no requirement for the collection and reporting of Individual Case Safety Reports (ICSRs). Although the study is based on human review of unstructured data, the nature of the secondary data protocol driven data collection and analysis does not allow for reporting of serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK/ViiV product during the conduct of this research. In addition, the minimum criteria of identifiable patient, reporter, exposure, and event needed to report individual case safety reports may not be present in the information reviewed within the context of the study. The data also may lack an identifiable patient and reporter and may be insufficient to establish attribution between a potential safety event and an individual patient using a GSK/ViiV product.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study information from this protocol will be posted on publicly available registers following finalization of the protocol. The results of these studies will be published in a peer-reviewed scientific literature. Manuscripts will be submitted within 18 months of completion of the analysis. Any publications will follow formal reporting guidelines, including those for authorship (e.g., guidelines established by the International Committee of Medical Journal Editors, 2018) and for reporting of observational studies in epidemiology [von Elm, 2007].

12. REFERENCES

Anderson T C, Leung JW, Harpaz R, et al. Risk of Guillain-Barre syndrome following herpes zoster, United States, 2010-2018. Hum Vaccin Immunother. 2021;*17*(12):5304-5310. https://doi.org/10.1080/21645515.2021.1985890

Arexvy (respiratory syncytial virus vaccine, adjuvanted) Product Information. May, 2023.

Arya DP, Said MA, Izurieta HS, et al. Surveillance for Guillain-Barre syndrome after 2015-2016 and 2016-2017 influenza vaccination of Medicare beneficiaries. Vaccine. 2019;37(43):6543-6549. https://doi.org/10.1016/j.vaccine.2019.08.045

Baker MA, Baer B, Kulldorff M, et al. Kawasaki disease and 13-valent pneumococcal conjugate vaccination among young children: A self-controlled risk interval and cohort study with null results. PLoS Med. 2019;16(7):e1002844. https://doi.org/10.1371/journal.pmed.1002844

Behrman RE, Benner JS, Brown JS, et al. Developing the Sentinel System-a national resource for evidence development. N Engl J Med. 2011;364(6):498-499. https://doi.org/10.1056/NEJMp1014427

Belongia EA, King JP, Kieke BA, et al. Clinical Features, Severity, and Incidence of RSV Illness During 12 Consecutive Seasons in a Community Cohort of Adults >/=60 Years Old. Open Forum Infect Dis. 2018;5(12):ofy316. https://doi.org/10.1093/ofid/ofy316

Boos CJ. Infection and atrial fibrillation: inflammation begets AF. Eur Heart J. 2020;41(10):1120-1122. https://doi.org/10.1093/eurheartj/ehz953

Branche AR, Saiman L, Walsh EE, et al. Incidence of Respiratory Syncytial Virus Infection Among Hospitalized Adults, 2017-2020. Clin Infect Dis. 2022;74(6):1004-1011. https://doi.org/10.1093/cid/ciab595

Britton A, Roper LE, Kotton CN, et al. Use of Respiratory Syncytial Virus Vaccines in Adults Aged ≥60 years: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2024;73(32):696-702. http://dx.doi.org/10.15585/mmwr.mm7332e1

Brown JS, Mendelsohn AB, Nam YH, et al. The US Food and Drug Administration Sentinel System: a national resource for a learning health system. J Am Med Inform Assoc, 2022;29(12):2191-2200. https://doi.org/10.1093/jamia/ocac153

Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2017;14(10):e275-e444. https://doi.org/10.1016/j.hrthm.2017.05.012

Chamberlain AM, Roger VL, Noseworthy PA, et al. Identification of incident atrial fibrillation from electronic medical records. J Am Heart Assoc. 2022;11(7):e023237. https://doi.org/10.1161/JAHA.121.023237

Chandler R, Montenegro N, Llorach C, et al. Immunogenicity, reactogenicity, and safety of AS01E-adjuvanted RSV prefusion F protein-based candidate vaccine (RSVPreF3 OA) when co-administered with a seasonal quadrivalent influenza vaccine in older adults: Results of a phase 3, open-label, randomized controlled trial. Clin Infect Dis. 2024. https://doi.org/10.1093/cid/ciad786

Cherukuri A, Patton K, Gasser RA, et al. (2013, Feb). Adults 65 years old and older have reduced numbers of functional memory T cells to respiratory syncytial virus fusion protein. Clin Vaccine Immunol. 2013;20(2):239-247. https://doi.org/10.1128/CVI.00580-12

Childs A, Zullo AR, Joyce NR, et al. The burden of respiratory infections among older adults in long-term care: a systematic review. BMC Geriatr. 2019;19(1):210. https://doi.org/10.1186/s12877-019-1236-6

Curtis LH, Weiner MG, Boudreau DM, et al. Design considerations, architecture, and use of the Mini-Sentinel distributed data system. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 1:23-31. https://doi.org/10.1002/pds.2336

Fairbrother G, Park HL, Haivderv A. Center for Health Care Strategies, Inc. Policies and Practices that Lead to Short Tenures in Medicaid Managed Care – 2004. 2004. Accessed 3 January 2024. https://www.chcs.org/media/churning.pdf.

Falsey AR, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. 2005;352(17):1749-1759. https://doi.org/10.1056/NEJMoa043951

Falsey AR, McElhaney JE, Beran J, et al. Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness. J Infect Dis. 2014;209(12):1873-1881. https://doi.org/10.1093/infdis/jit839

Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. Biometrics. 1995;51(1):228-235. https://www.ncbi.nlm.nih.gov/pubmed/7766778

Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. American journal of epidemiology. 1996;143(11):1165-1173. https://doi.org/10.1093/oxfordjournals.aje.a008695

Food and Drug Administration (FDA). Guidance for industry and FDA staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data. Rockville, MD; 2013. Accessed 27 July 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-

practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic.

Ferguson M. Respiratory syncytial virus Prefusion F Protein vaccine (RSVPREF3 OA) is immunogenic and well-tolerated in adults 50-59 years, including adults at increased risk for RSV disease [Abstract 115]. 8th ReSViNEt Conference. Mumbai, India. 2024. Accessed 13 March 2024. https://resvinet.org/wp-content/uploads/2024/02/Abstract-Booklet-09Feb24.2.pdf.

Gerber, S. (2023). GSK's RSVPreF3 + AS01E Vaccine (AREXVY). Meeting of the Advisory Committee on Immunization Practices - October 25, 2023. Accessed 14 March 2023. Accessed at https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-10-25-26/02-gerber- adult-RSV-508.pdf

GlaxoSmithKline (GSK). FDA Briefing Document: Respiratory Syncytial Virus Vaccine Recombinant, Adjuvanted (Proposed Trade Name: *Arexvy*. Vaccines and Related Biological Products Advisory Committee Meeting - March 1, 2023. 2023. Accessed 14 March 2024. https://www.fda.gov/media/165622/download.

Goud R, Lufkin B, Duffy J, et al. Risk of Guillain-Barre Syndrome Following Recombinant Zoster Vaccine in Medicare Beneficiaries. JAMA Intern Med. 2021;181(12):1623-1630. https://doi.org/10.1001/jamainternmed.2021.6227

Gundland A, Bjerring Olesen J, Butt JH, et al. One-year outcomes in atrial fibrillation presenting during infections: a nationwide registry-based study. Eur Heart J. 2020;41(10):1112-1119. https://doi.org/10.1093/eurheartj/ehz873

Hamdani AG, Thibault D, Willis AW. Seasonal variation in neurologic hospitalizations in the United States. Ann Neurol. 2023;93(4):743-751. https://doi.org/10.1002/ana.26579

Ison MG, Papi A, Athan E, et al. Efficacy and safety of respiratory syncytial virus prefusion F protein vaccine (RSVPreF3 OA) in older adults over 2 RSV seasons. Clin Infect Dis. 2024. https://doi.org/10.1093/cid/ciae010.

Jackson LA, Nelson JC, Benson P, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. Int J Epidemiol. 2006;35(2):345-352. https://doi.org/10.1093/ije/dyi275

Jacobs BC, Rothbarth PH, van der Meche FG, et al. The spectrum of antecedent infections in Guillain-Barre syndrome: a case-control study. Neurology.1998;51(4):1110-1115. https://doi.org/10.1212/wnl.51.4.1110

Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA. 2021;326(14):1390-1399. doi:10.1001/jama.2021.15072

Kujawski SA, Whitaker M, Ritchey MD, et al. Rates of respiratory syncytial virus (RSV)-associated hospitalization among adults with congestive heart failure-United

States, 2015-2017. PLoS One. 2022;17(3):e0264890. https://doi.org/10.1371/journal.pone.0264890

Law B. Safety Platform for Emergency Vaccines (SPEAC). AESI Case Definition Companion Guide for 1st Tier AESI: Guillain Barré and Miller Fisher Syndromes. V1.0 – February 9, 2021. 2021. Accessed on 17 January 2024. https://brightoncollaboration.org/wp-content/uploads/2023/06/SPEAC_D2.5.2.1-GBS-Case-Definition-Companion-Guide_V1.0_format12062-1-1.pdf.

Leroux-Roels I, Davis MG, Steenackers K, et al. Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F (RSVPreF3) Candidate Vaccine in Older Adults: Phase 1/2 Randomized Clinical Trial. J Infect Dis. 2023;227(6):761-772. https://doi.org/10.1093/infdis/jiac327

Lloyd DP. Evaluation of Guillain-Barré Syndrome (GBS) following Respiratory Syncytial Virus (RSV) Vaccination Among Adults 65 Years and Older. Presented at: Meeting of the Advisory Committee on Immunization Practices (ACIP); October 24, 2024; Atlanta, Georgia, United States. https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/05-RSV-Adult-Lloyd-508.pdf

Loomba RS. Seasonal Variation in Paroxysmal Atrial Fibrillation: A Systematic Review. J Atr Fibrillation. 2015;7(5):1201. https://doi.org/10.4022/jafib.1201

Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. American journal of epidemiology. 1991;133(2):144-153. https://doi.org/10.1093/oxfordjournals.aje.a115853

Melgar M, Britton A, Roper LE, et al. Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices - United States, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(29):793-801. https://doi.org/10.15585/mmwr.mm7229a4

Moll K, Lufkin B, Fingar KR, et al. Background rates of adverse events of special interest for COVID-19 vaccine safety monitoring in the United States, 2019–2020. Vaccine. 2023;41(2):333-353. doi:10.1016/j.vaccine.2022.11.003

Moutzouris DA, Hassid VJ. Seasonal variation of atrial fibrillation: further supportive evidence. Epidemiology. 2003;14(1):127. https://doi.org/10.1097/00001648-200301000-00032

Musonda P, Farrington CP, Whitaker HJ. Sample sizes for self-controlled case series studies. Stat Med. 2006;25(15):2618-2631. https://doi.org/10.1002/sim.2477

Nam HH, Ison MG. Respiratory syncytial virus infection in adults. BMJ. 2019;366:l5021. https://doi.org/10.1136/bmj.l5021

Obando-Pacheco P, Justicia-Grande AJ, Rivero-Calle I, et al. Respiratory Syncytial Virus Seasonality: A Global Overview. J Infect Dis. 2018;217(9):1356-1364. https://doi.org/10.1093/infdis/jiy056

Papi A, Ison MG, Langley JM, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. N Engl J Med. 2023;388(7):595-608. https://doi.org/10.1056/NEJMoa2209604

Parsons T, Banks S, Bae C, Gelber J, et al. COVID-19-associated acute disseminated encephalomyelitis (ADEM). J Neurol. 2020;267(10):2799-2802. https://doi.org/10.1007/s00415-020-09951-9

Patone M, Mei XW, Handunnetthi L, et al. Risk of Myocarditis After Sequential Doses of COVID-19 Vaccine and SARS-CoV-2 Infection by Age and Sex. Circulation. 2022a;146(10):743-754. https://doi.org/10.1161/CIRCULATIONAHA.122.059970

Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med. (2022b;28(2):410-422. https://doi.org/10.1038/s41591-021-01630-0

Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016;354:i4515. https://doi.org/10.1136/bmj.i4515

Platt R, Brown JS, Robb M, et al. The FDA Sentinel Initiative - An Evolving National Resource. N Engl J Med. 2018;379(22):2091-2093. https://doi.org/10.1056/NEJMp1809643

Pohl D, Alper G, Van Haren K, et al. (2016, Aug 30). Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. Neurology. 2016;87(9 Suppl 2):S38-45.

Polakowski LL, Sandhu SK, Martin DB, et al. Chart-confirmed Guillain-Barre Syndrome after 2009 H1N1 influenza vaccination among the Medicare population, 2009-2010. American journal of epidemiology. 2013;178(6):962-973. https://doi.org/10.1093/aje/kwt051

Rongxia L, Stewart B, McNeil MM, et al. Post Licensure Surveillance of Influenza Vaccines in the Vaccine Safety Datalink in the 2013-2014 and 2014-2015 Seasons. Pharmacoepidemiol Drug Saf. 2016;25(8):928-934.

Savic M, Penders Y, Shi T, et al. Respiratory syncytial virus disease burden in adults aged 60 years and older in high-income countries: A systematic literature review and meta-analysis. Influenza Other Respir Viruses. 2023;17(1):e13031. https://doi.org/10.1111/irv.13031

Schwarz TF, Hwang SJ, Ylisastigui P, et al. Immunogenicity and safety following one dose of AS01E-adjuvanted respiratory syncytial virus prefusion F protein vaccine in older adults: a phase 3 trial. J Infect Dis. 2023. https://doi.org/10.1093/infdis/jiad546

Sejvar JJ, Kohl KS, Bilynsky R, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5771-5792. https://doi.org/10.1016/j.vaccine.2007.04.060

Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612. https://doi.org/10.1016/j.vaccine.2010.06.003

Shi T, Denouel A, Tietjen AK, et al. Global Disease Burden Estimates of Respiratory Syncytial Virus-Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. J Infect Dis. 2020;222(Suppl 7):S577-S583. https://doi.org/10.1093/infdis/jiz059

Stephens LM, Varga SM. Considerations for a Respiratory Syncytial Virus Vaccine Targeting an Elderly Population. Vaccines (Basel). 2021;9(6). https://doi.org/10.3390/vaccines9060624

Tenembaum S, Chitnis T, Ness J, et al. Acute disseminated encephalomyelitis. Neurology. 2007;68(16 Suppl 2):S23-36. https://doi.org/10.1212/01.wnl.0000259404.51352.7f

von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-1457. https://doi.org/10.1016/S0140-6736(07)61602-X

Waghmare A, Campbell AP, Xie H, et al. Respiratory syncytial virus lower respiratory disease in hematopoietic cell transplant recipients: viral RNA detection in blood, antiviral treatment, and clinical outcomes. Clin Infect Dis. 2013;57(12):1731-1741. https://doi.org/10.1093/cid/cit639

Webb AJ, Brain SA, Wood R, et al. Seasonal variation in Guillain-Barre syndrome: a systematic review, meta-analysis and Oxfordshire cohort study. J Neurol Neurosurg Psychiatry. 2015;86(11):1196-1201. https://doi.org/10.1136/jnnp-2014-309056

Weinstein EJ, Ritchey ME, Lo Re V. Core concepts in pharmacoepidemiology: Validation of health outcomes of interest within real-world healthcare databases. Pharmacoepidemiol Drug Saf. 2023;32(1):1-8. https://doi.org/10.1002/pds.5537

Williams BA, Chamberlain AM, Blankenship JC, et al. Trends in Atrial Fibrillation Incidence Rates Within an Integrated Health Care Delivery System, 2006 to 2018. JAMA

Network Open. 2020;3(8):e2014874.
https://doi.org/10.1001/jamanetworkopen.2020.14874

Wyffels V, Kariburyo F, Gavart S, et al. (2020, Mar). A Real-World Analysis of Patient Characteristics and Predictors of Hospitalization Among US Medicare Beneficiaries with Respiratory Syncytial Virus Infection. Adv Ther. 2020;37(3):1203-1217.
https://doi.org/10.1007/s12325-020-01230-3

Yih WK, Lieu TA, Kulldorff M, et al. Intussusception risk after rotavirus vaccination in U.S. infants. N Engl J Med. 2014;370(6):503-512.
https://doi.org/10.1056/NEJMoa1303164.

Yih WK, Greene SK, Zichittella L, et al. Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females. Vaccine. 2016a;34(1):172-178. https://doi.org/10.1016/j.vaccine.2015.09.087

Yih WK, Kulldorff M, Sandhu SK, et al. Prospective influenza vaccine safety surveillance using fresh data in the Sentinel System. Pharmacoepidemiol Drug Saf. 2016b;25(5):481-492. https://doi.org/10.1002/pds.3908.

Zheng Z, Warren JL, Shapiro ED, et al. Estimated incidence of respiratory hospitalizations attributable to RSV infections across age and socioeconomic groups. Pneumonia (Nathan). 2022;14(1):6. https://doi.org/10.1186/s41479-022-00098-x

Annex 1 LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference No	Date	Title
1.	Annex 1 (220149)	25 Apr 2024	List of stand-alone documents
2.	Annex 2 (220149)	25 Apr 2024	List of investigators
3.	Annex 3 (220149)	25 Apr 2024	Codelists
4.	Annex 4 (220149)	25 Apr 2024	ENCePP checklist for study protocols

Annex 2 List of Investigators

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

Annex 3 CODELISTS

Code type	Code	Description
***Arexvy* identification**		
CVX	303	Respiratory syncytial virus (RSV), vaccine, recombinant, protein subunit RSV prefusion F, adjuvant reconstituted, 0.5 mL, preservative free
CPT	90679	Respiratory syncytial virus vaccine, preF, recombinant, subunit adjuvanted, for intramuscular use
NDC	58160-848-11	Respiratory syncytial virus vaccine antigen/AS01E adjuvant/PF (*Arexvy* [Pre-fusion F protein])
NDC	58160-723-03	Respiratory syncytial virus vaccine, antigen 2 of 2 (*Arexvy* Antigen Component)
NDC	58160-744-03	Vaccine adjuvant system, AS01E/PF, component vial 1 of 2 (*Arexvy* Adjuvant Component [Pre-fusion F protein])
GBS event identification		
ICD-10-CM	G61.0	Guillain-Barré syndrome
ADEM event identification		
ICD-10-CM	G04.00	Acute disseminated encephalitis and encephalomyelitis, unspecified
ICD-10-CM	G04.01	Post-infectious acute disseminated encephalitis and encephalomyelitis
ICD-10-CM	G04.02	Postimmunization acute disseminated encephalitis, myelitis, and encephalomyelitis
AF event identification		
ICD-10-CM	I48.0	Paroxysmal atrial fibrillation
ICD-10-CM	I48.91	Unspecified atrial fibrillation

Abbreviations: ADEM: acute disseminated encephalomyelitis; AF: atrial fibrillation; CPT: Current Procedural Terminology; CVX: Vaccine administered code; GBS: Guillain-Barré syndrome; ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification; NDC; National Drug Code.

Annex 4 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 collection2	☒	☐	☐	4
End of data collection3	☐	☐	☒	4
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:

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
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)	☒	☐	☐	6, 7.2
Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	2, 7.5
If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

2 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.

3 Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g., cohort, case-control, cross- sectional, other design)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	6, 7.1, 7.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7.7
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
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:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	7.4
4.2 Is the planned study population defined in terms of:				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
Study time period	☒			4, 7.2
Age and sex				7.2
Country of origin	☒			7.2
Disease/indication	☒			7.1, 7.2
Duration of follow-up	☒	☐	☐	7.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	7.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	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
5.3 Is exposure categorized according to time windows?	☒			7.3.2
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?	☒	☐	☐	7.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	6
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, PPV, 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)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	7.3.3, 7.9
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	7.1
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.3.2, 7.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	7.7.2.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7.3.1, 7.7.2.2
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
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	7.3.1, 7.7.2.2
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.3.2
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3
9.3 Is a coding system described for:				

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
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒ ☐	☐ ☐	☒	

Comments:

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
10.2 Is study size and/or statistical precision estimated?	☒			7.5
10.3 Are descriptive analyses included?				7.7.1
10.4 Are stratified analyses included?				
10.5 Does the plan describe methods for analytic control of confounding?	☒ ☒	☐ ☐	☐ ☐	7.3.3, 7.9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒☐	☐☐ ☐	☐☒ ☐	7.3.2
10.7 Does the plan describe methods for handling missing data?	☐			
10.8 Are relevant sensitivity analyses described?	☒	☒ ☐	☐ ☐	7.7.2.3

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	7.6

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
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:

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?	☒	☐	☐	7.1
12.1.2 Information bias?	☒ ☒	☐ ☐	☐ ☐	7.3.2, 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).				7.3.3, 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, 7.9

Comments:

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

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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Reason for signing: Approved	Name: PPD Role: A Date of signature: 13-Jan-2025 14:16:48 GMT+0000

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