NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Epidemiology of Guillain-Barré Syndrome and Risk Associated with Exposure to ABRYSVO™ Among Vaccinees 18-59 Years of Age in the United States
Protocol number	C3671072
Protocol version identifier	3.0
Date	27 May 2025
EU Post Authorization Study (PAS) register number	To be registered prior to the start of data collection
Active substance	Bivalent respiratory syncytial virus (RSV) stabilized prefusion F subunit vaccine (RSVpreF), J07BX05
Medicinal product	ABRYSVO™

Research questions and objectives	**Research Question 1:** What is the epidemiology and natural history of Guillain-Barré Syndrome (GBS) in the United States for adults ≥18 years of age between 2017 and 2024?
	
	• **GBS Epidemiology and Incidence -** Objectives:
	    • Estimate the incidence of GBS overall and in subgroups of interest (e.g., age, sex, comorbidities, region) over time.
	    • Describe individuals with GBS with respect to demographics, clinical characteristics, risk factors, treatment, and outcomes.
	
	• **GBS Etiology -** Objectives:
	    • Conduct a detailed medical record review of a sample of GBS cases to validate a claims-based algorithm and to identify potential causes of GBS.
	    • Perform an exploratory data mining-based signal detection analysis to identify specific vaccines, drugs, and infections potentially associated with GBS.

	Research Question 2: What is the risk of GBS after exposure to ABRYSVO among non-pregnant recipients 18-59 years of age at increased risk of lower respiratory tract disease caused by RSV (RSV-LRTD)? • **Objectives:** • Signal Detection: Among non-pregnant individuals 18-59 years at increased risk of RSV-LRTD, compare observed GBS case counts after ABRYSVO vaccination against expected GBS case counts via rapid cycle analysis (RCA). • Signal Evaluation: Among non-pregnant individuals 18-59 years of age, assess risk of GBS in the 21 days or 42 days (depending on length of risk window) following ABRYSVO vaccination using a self-controlled risk interval (SCRI) design.
Country of study	United States
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CPT	Current Procedural Terminology
CVX	Vaccine administered code
DCT	Data collection tool
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
HIPAA	Health Insurance Portability and Accountability Act
HPHCI	Harvard Pilgrim Health Care Institute
HPV	Human papillomavirus
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IIS	Immunization information systems
LRTD	Lower respiratory tract disease
MMRV	Measles, mumps, rubella, and varicella vaccine
mRNA	Messenger ribonucleic acid
NDC	National Drug Code
PASS	Post-authorization safety study
PEPR	Patient Episode Profile and Retrieval
PmaxSPRT	Poisson maximized sequential probability ratio testing
PMR	Postmarketing requirement
PPV	Positive predictive value
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
QC	Quality control
QA	Quality assurance
RCA	Rapid cycle analysis
RP	Research Partner
RSV	Respiratory syncytial virus
RSV-LRTD	Respiratory syncytial virus-associated lower respiratory tract disease
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SCDM	Sentinel Common Data Model
SCRI	Self-controlled risk interval
SGLT2	Sodium-Glucose Cotransporter-2
SOP	Standard operating procedure
Tdap	Tetanus, diphtheria, and acellular pertussis vaccine
US	United States
VSD	Vaccine Safety Datalink

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: Epidemiology of Guillain-Barré Syndrome and Risk Associated with Exposure to ABRYSVO™ Among Vaccinees 18-59 Years of Age in the United States

Version and date: Version 3.0, 27 May 2025

Main authors: Jenny Sun, PhD, Safety Surveillance Research, Pfizer, Inc.; Scott Kelly, PhD, Global Medical Epidemiology, Pfizer, Inc.; Noelle Cocoros, DSc, MPH, Harvard Medical School & Harvard Pilgrim Health Care Institute; Elizabeth J. Bell, PhD, MPH, Harvard Medical School & Harvard Pilgrim Health Care Institute

Rationale and background: ABRYSVO™ is a bivalent, adjuvanted RSVpreF vaccine that has been approved for use in the United States (US) in adults 18-59 years of age at increased risk of respiratory syncytial virus-associated lower respiratory tract disease (RSV-LRTD), pregnant individuals at 32-36 weeks gestational age of pregnancy for the prevention of RSV-LRTD in infants, and in adults ≥60 years of age. This protocol complements ABRYSVO's clinical development program, which observed no GBS events among ABRYSVO-vaccinated adults 18-59 years of age. This is a post-authorization safety study (PASS) to monitor the incidence of GBS in ABRYVSO-vaccinated adults 18-59 years of age at increased risk of RSV-LRTD. This protocol additionally complements studies C3671031 and C3671054 with analyses of the epidemiology and natural history of GBS in the US. A better understanding of the epidemiology of GBS in the US, including preceding risk factors and contemporaneous background rates, is important to contextualize the risk of GBS after vaccinations and can inform vaccine safety studies of GBS risk.

Research questions and objectives:

Research Question 1: What is the epidemiology and natural history of GBS in the US for adults ≥18 years of age between 2017 and 2024?

- *GBS epidemiology and incidence* – Objectives:
    - Estimate the incidence of GBS overall and in subgroups of interest (e.g., age, sex, comorbidities, region) over time.
    - Describe individuals with GBS with respect to demographics, clinical characteristics, risk factors, treatment, and outcomes.
- *GBS etiology* – Objectives:
    - Conduct a detailed medical record review of a sample of GBS cases to validate a claims-based algorithm for GBS and to identify potential causes of GBS.
    - Perform an exploratory data mining-based signal detection analysis to identify specific vaccines, drugs, and infections potentially associated with GBS.

Research Question 2: What is the risk of GBS after exposure to ABRYSVO among non-pregnant recipients 18-59 years of age at increased risk of RSV-LRTD?

- Objectives:

  - *Signal Detection:* Among non-pregnant individuals 18-59 years at increased risk of RSV-LRTD, compare observed GBS case counts after ABRYSVO vaccination against expected GBS case counts via RCA.

  - *Signal Evaluation:* Among non-pregnant individuals 18-59 years of age, assess risk of GBS in the 21 days or 42 days (depending on length of risk window) following ABRYSVO vaccination using a SCRI design.

Research Question 1

Study design (Research Question 1)

- *GBS epidemiology and incidence* – Cases of incident, hospitalized GBS will be identified in administrative claims data, or equivalent, in 2017 through 2024, among adults 18 years and older. Incidence rates of GBS will be estimated overall and among subgroups of interest (e.g., age group, sex, comorbidities including underlying conditions that increase risk of RSV-LRTD, and region). Among the cohort identified with GBS, demographic and clinical characteristics will be summarized, including underlying conditions and antecedent health events that are potential risk factors for GBS, such as infections. Care, treatment, and sequelae captured in claims data will be described.

- *GBS etiology: Medical record review* – This study will validate an algorithm for incident GBS among adults 18 and older based on work by Goud and colleagues,[1] which identified GBS via the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code G61.0 in the primary position of an inpatient encounter. A detailed medical record review will be performed for ~300 cases in total, sampled based on factors such as age, antecedent vaccination of any kind, certain risk factors (e.g., those associated with RSV-LRTD or recent infection), and calendar time. Cases will be adjudicated as confirmed, possible, or not GBS based on the Brighton Collaboration criteria.[1,2] The positive predictive value (PPV) and corresponding 95% confidence interval (CI) of the GBS algorithm will be calculated overall and within key subgroups. Among confirmed and possible GBS cases in the validation activity, the potential cause of GBS, pre-existing conditions, and preceding events will be summarized from information in the medical record.

- *GBS etiology: Exploratory data mining-based signal detection* – Tree-based scan statistics will be used to search for potential risk factors of GBS. Statistically significant clusters of exposures (i.e., vaccines, drugs, infections) that have been organized into a "tree" based on coding hierarchies will be scanned for associations with GBS. A modified case-crossover design will be implemented.

Setting (Research Question 1)

- *GBS epidemiology and incidence* - The source population will be members of multiple large national health plans; members from 1 or more regional integrated delivery systems or other data sources may also be included. Individuals will meet eligibility criteria if they are ≥18 years of age with ≥365 days of medical and pharmacy coverage preceding cohort entry between 2017 and 2024.

- *GBS etiology: Medical record review* – The source population will be health plan members from regional integrated delivery systems with linked electronic health records (EHR) and administrative billing data. Individuals will meet eligibility criteria if they are ≥18 years of age with ≥365 days of medical and pharmacy coverage preceding cohort entry. Inpatient GBS diagnoses in the primary position will be identified via billed ICD-10-CM diagnosis codes in 2017 through 2024. Medical record review will be primarily conducted via direct access to the EHR, but charts may be requested as needed. To ensure the subgroups of interest (e.g., adults 18-59 years of age at increased risk of RSV-LRTD; adults with recent vaccination) are included in the medical record review, stratified random sampling of eligible cases identified in the billing data will be conducted, though oversampling of more recent GBS diagnoses may be needed.

- *GBS etiology: Exploratory data mining-based signal detection* – The source population will be health plan members. Individuals will meet eligibility criteria if they are ≥18 years of age with ≥365 days of medical and pharmacy coverage preceding date of the incident GBS diagnosis between 2017 and 2024.

Variables (Research Question 1)

For all objectives, incident GBS will be identified via a GBS diagnosis code (G61.0) in the primary position in the inpatient setting or incident GBS in any setting and any position with a hospitalization within 7 days, again with GBS as the primary diagnosis. Incidence will be defined using a 365-day washout for G61.0 or G65.0 (sequelae of GBS) in any care setting. Additional demographic, clinical characteristics, treatment, vaccines, medications, and outcome variables will be ascertained for some objectives.

- *Variables for GBS epidemiology and incidence* – Subgroups of interest will include age group (e.g., 18-59 years; ≥60 years), sex, presence of underlying conditions that increase the risk of RSV-LRTD, evidence of certain antecedent infections that have been associated with GBS (e.g., respiratory viruses, gastrointestinal infections), recent vaccination, and region. Characteristics of those identified with GBS will be described with respect to demographics, underlying conditions (e.g., chronic conditions, evidence of concurrent pregnancy), antecedent infections, recent vaccinations, care and testing received in relation to GBS, and symptoms and sequelae of GBS, to the extent they are captured in the data sources.

- *Variables for GBS etiology: Medical record review* – Based on the available information in the medical records, GBS cases will be adjudicated by clinicians and, among confirmed and possible cases, potential causes of GBS (e.g., infection, vaccination) will be identified.

- *Variables for GBS etiology: Exploratory data mining-based signal detection* – One exposure tree will be developed with top-level categories of 1) vaccines, 2) drugs, and 3) infections.

Data sources (Research Question 1)

- *GBS epidemiology and incidence* - This study will be conducted using health plan administrative claims data from up to 3 national health plans; other RPs may be added as appropriate.

- *GBS etiology: Medical record review*: This study will be conducted using administrative billing data, or equivalent, from approximately 3 regional integrated delivery systems, or other appropriate data sources, with geographic diversity. Potential GBS cases will be identified via billing data; EHRs from within each RP will be used for abstraction, review, and adjudication of the cases, as well as assessment of the potential cause of GBS.

- *GBS etiology: Exploratory data mining-based signal detection* – This study will be conducted using health plan administrative claims data held by up to 3 national health plans; other RPs may be added as appropriate.

Study size (Research Question 1)

Data on all individuals meeting the applicable eligibility and inclusion/exclusion criteria within the contributing RPs will be analyzed, except for the medical record review objective, which will be conducted on approximately 300 cases. It is estimated that there will be approximately 2,000 GBS cases in the analyses for the epidemiology and incidence objective.

Data analysis (Research Question 1)

- *GBS epidemiology and incidence* –The annual incidence rates and corresponding 95% CIs for GBS will be estimated overall and for subgroups (e.g., age, sex, comorbidities, and region), showing how and to what degree incidence rates vary across groups and over the study period. Descriptive statistics of adults who meet the GBS algorithm will be reported regarding their demographics, clinical characteristics, risk factors, treatment, and outcomes.

- *GBS etiology: Medical record review* – Demographic and baseline clinical characteristics (e.g., recent vaccination, antecedent infection, and underlying conditions) of those who meet the GBS algorithm and are included in the sample will be summarized from the medical record and reported via descriptive statistics. The PPV for all confirmed GBS cases, and separately for all confirmed or possible GBS, will be calculated with corresponding 95% CIs. PPVs will also be calculated by age group, evidence of antecedent infection, evidence of recent vaccination, and presence of conditions putting individuals at increased risk of RSV-LRTD.

- *GBS etiology: Exploratory data mining-based signal detection* – The tree-based scan statistics use log-likelihood ratio tests to detect elevated frequencies of codes that have been grouped into a hierarchical tree structure and automatically adjusts for multiple overlapping scenarios inherent to data mining. The test statistic is computed via Monte Carlo hypothesis testing. Under the alternative hypothesis, there is at least 1 exposure, or group of exposures, for which there is a temporal cluster of GBS cases during some time interval in the observation window. The observation window (e.g., 84 days), whether the risk window will be fixed or varying, and the specific scan statistic used (i.e., conditional or unconditional) will be specified in the SAP.

Research Question 2

Study design (Research Question 2)

This PASS will implement a stepwise active safety surveillance approach for approximately 4 RSV seasons in non-pregnant individuals aged 18-59 years at increased risk of RSV-LRTD. Approximately 1 RCA will be conducted on the accumulating data per season for each of the 2 RCA study designs (historical comparator and concurrent comparator). If an RCA detects a statistically significant positive association between risk of GBS and ABRYSVO vaccination, or if 4 RSV vaccination seasons have completed without an RCA detecting a statistically significant finding of higher risk, a SCRI study will be conducted to allow for a more comprehensive assessment of the association of ABRYSVO exposure and GBS. If the RCA does not detect a statistically significant finding or reach a pre-specified number of GBS cases by the end of 4 RSV seasons, inclusion of additional RPs or extending the length of the RCA study period will be considered. The SCRI study will use all data available at that time, which could include multiple RSV seasons.

- *Historical Comparator RCA* – The rate of GBS among non-pregnant ABRYSVO vaccinees 18-59 years of age at increased risk of RSV-LRTD will be compared to a background rate estimated from a historical vaccine-exposed group. The historical comparator group will consist of non-pregnant individuals 18-59 years of age at increased risk of RSV-LRTD who received a comparator vaccine between 01 January 2017 and 30 September 2024 (for analyses with a 21-day risk window) or 09 September 2024 (for analyses with a 42-day risk window). These vaccine capture end dates are 21 and 42 days, respectively, before the US Food and Drug Administration (FDA) approved ABRYSVO for adults 18-59 years at increased risk of RSV-LRTD. Comparator vaccines will be mRNA COVID-19 and seasonal influenza vaccines because these are vaccines that cause no to minimal increased risk of GBS (i.e., 0-2 attributable cases per million doses).

- *Concurrent Comparator RCA* – Because the historical comparator group could be subject to secular trends in GBS, a second RCA design will use a concurrent comparator design amongst all non-pregnant ABRYSVO-vaccinees 18-59 years of age. The concurrent comparator RCA will compare GBS rates during risk intervals for individuals recently vaccinated with ABRYSVO to rates during comparison intervals for those less recently vaccinated with ABRYSVO.

- *SCRI study* – The SCRI analysis will compare incidence of GBS during a primary risk window of 1-42 days after ABRYSVO vaccination with incidence of GBS during a primary control window of 43-84 days after ABRYSVO. A secondary risk window of 1-21 days and secondary control window of 43-84 days will also be studied. If the SCRI analysis is triggered due to a statistically significant positive association between risk of GBS and ABRYSVO vaccination in any RCA, GBS diagnoses will be confirmed via medical record review as part of the signal refinement process. If the SCRI analysis commences after 4 RCA seasons in the absence of a statistically significant higher risk, the SCRI analysis will employ PPV-adjustment of the claims-identified GBS cases.

Setting (Research Question 2)

The source population for both the RCA and SCRI studies will be members from up to 3 national health plans.

- *Historical Comparator RCA* – The exposed group will include non-pregnant individuals 18-59 years of age at increased risk of RSV-LRTD and administered ABRYSVO between 22 October 2024 and 21 or 42 days prior (depending on length of risk window for analyses) to the most recent data available at the time of study commencement. The historical comparator group will be non-pregnant individuals 18-59 years of age at increased risk of RSV-LRTD who received a comparator vaccine between 01 January 2017 and 30 September 2024 (for analyses with a 21-day risk window) or 09 September 2024 (for analyses with a 42-day risk window). Increased risk will be defined by an algorithm that will be designed to match the Centers for Disease Control and Prevention's (CDC's) definition for increased risk of RSV-LRTD in individuals 18-59 years as closely as possible.

- *Concurrent Comparator RCA and SCRI study* – The study population will be non-pregnant individuals 18-59 years of age who received an ABYRSVO vaccination between 22 October 2024 and the most recent data available at the time of study commencement. The primary analysis for the SCRI study and the concurrent comparator RCA will not require vaccinees to meet the algorithm definition for increased risk of RSV-LRTD due to concerns with misclassification (i.e., not everyone with one of these conditions will be identified as such via the claims-based algorithm), but vaccinees will be presumed to be at increased risk of RSV-LRTD because this is the indication for ABRYSVO and a secondary analysis for the SCRI study will require the algorithm definition for increased risk be met. If the indications for ABRYSVO change over the course of the study, the protocol and SAP will be amended.

- Variables (Research Question 2)

- *Exposure* – Exposure to ABRYSVO will be identified in claims data and, as available, state-based immunization information systems (IIS) data.

- *Outcome for RCA* – Incident GBS will be identified using the same algorithm as Research Question 1, which is based on Goud and colleagues work: a GBS diagnosis (G61.0) in the primary position in the inpatient setting or, incident GBS in any setting and any position, with a hospitalization within 7 days, again with GBS as the primary diagnosis.[1] Incidence will be defined using a 365-day washout for G61.0 or G65.0 in any care setting. GBS cases will not be confirmed via medical record review for any RCA, although a statistically significant positive association between risk of GBS and ABRYSVO vaccination from an RCA would trigger medical record review for the subsequent SCRI study.

- *Outcome for SCRI design study* – If the SCRI study commences due to a statistically significant positive association between risk of GBS and ABRYSVO vaccination from one of the RCAs, medical record confirmation of GBS cases in the SCRI study will be conducted as part of the signal evaluation. The medical record associated with the inpatient encounter where GBS was diagnosed will be requested. The record for the first subsequent ambulatory encounter with a neurologist, if applicable, will also be requested. If the SCRI study commences after 4 seasons of the RCA in the absence of a statistically significant finding of increased risk, GBS cases will not be confirmed via medical record review, but rather results will be adjusted based on the PPVs from Research Question 1.

<u>Data sources (Research Question 2)</u>

The RCA and SCRI studies will be conducted using health plan administrative claims data from up to 3 national health plans. Additional RPs may be included, as appropriate.

<u>Study size (Research Question 2)</u>

- *Historical Comparator RCA* – Assuming 10 events in the historical comparator group and targeting an attributable risk of 10 excess cases per million doses (corresponding to a relative risk of 9.7), 3 GBS cases will need to be observed in the ABRYSVO-exposed group to have 80% power (alpha = 0.05, 1-sided) to reject the null hypothesis of no association in a conditional Poisson maximized sequential probability ratio testing (PmaxSPRT) analysis with a Wald-type alpha spending plan and a continuous monitoring scheme. Under the assumption that each ABRYSVO vaccine contributes 21 days of follow-up time, 2.6 million ABRYSVO vaccinees are needed.

- *Concurrent comparator RCA* – Targeting an attributable risk of 10 excess cases per million doses (corresponding to a relative risk of 9.7), 8 GBS cases will need to be observed to have 80% power (alpha = 0.05, 1-sided) to reject the null hypothesis of no association. Under the assumption that each ABRYSVO vaccine contributes 63 days of follow-up time, 2.3 million ABRYSVO vaccinees are needed.

- *SCRI design study* – A total number of 7 GBS cases in the combined risk and control intervals provides 80% power (alpha = 0.05, 1-sided) to reject the null hypothesis of no association between ABRYSVO vaccination and GBS when the true attributable risk in excess cases per million doses is 10 (which corresponds to a relative risk of 9.7). Assuming a conservative background rate of 2 cases of GBS per 100,000 person-years,[3] 7 GBS cases will need to be observed amongst 2.0 million ABRYSVO vaccinees.

<u>Data analysis (Research Question 2)</u>

- *Historical Comparator RCA* – Observed ABRYSVO-exposed GBS counts will be compared against expected GBS counts using sequential hypothesis testing, adjusting for secular trends in GBS in the historical comparator group, if secular trends are observed. The conditional PmaxSPRT will be used to generate the test statistic (i.e., a log-likelihood ratio) which will be measured against a critical value. The critical value will be dynamic over the course of the analysis, as data accrue.

- *Concurrent Comparator RCA* – Observed ABRYSVO-exposed GBS cases will be compared against expected GBS counts using sequential hypothesis testing. The binomial maximized sequential probability ratio testing (BmaxSPRT) will be used to generate the test statistic (i.e., a log-likelihood ratio) which will be measured against a dynamic critical value.

- *Data analysis for SCRI design study* – Case-centered logistic regression will be used for analysis (Fireman, 2009). Incidence rate ratios with 95% CIs (to estimate relative risk) and attributable risk with 95% CIs per 100,000 doses and 100,000 person-years (to estimate absolute risk) will be calculated.

Milestones

The anticipated start of data collection (defined as first date of data extraction) is 01 July 2025, and the end of data collection (defined as last date of data extraction) is anticipated to be no later than 28 February 2029. A final study report is planned for no later than 31 January 2030.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
3.0	27 May 2025	Substantial	4, 8, 9.2	Research questions and objectives: In the signal evaluation section, revised the risk window described in this objective to include “or 42	This revision was made to address the FDA’s comment received on 27 May 2025 and to align with

				days (depending on length of risk window)”.	the remainder of the protocol.
		Substantial	4, 9.2.1.2	Study design (Research Question 2): Revised the SCRI analysis primary risk window to 1-42 days after ABRYSVO vaccination, and the secondary risk window to 1-21 days.	This revision was made to address the FDA’s comment received on 27 May 2025.
		Administrative	3, 4	Modified the Pfizer investigator/author list.	Change in Pfizer Principal Investigator
2.0	24 April 2025	Substantial	4, 9.2.1.1.1., 9.2.2.1.1.2.	Added the word “seasonal” to the description of the influenza vaccine throughout the protocol for clarity.	This revision was made to address FDA comment #1 on Research Question 2, received on 03 April 2025.
			9.2.2.1.1.2.	For clarity, added the rationale for an eligibility criterion for the historical comparator group, as well as limiting this exclusion to the Janssen vaccine.	This revision was made to address FDA comment #2 on Research Question 2, received on 03 April 2025.
			9.2.1.1., 9.2.3.2.1.1., 9.2.7.1.	Added text related to new risk window of 1–42 days for all RCAs.	This revision was made to address FDA comment #5 on Research Question 2, received on 03 April 2025.
			4, 9.1.3.1.	Added antecedent vaccination to abstract, Table 2, and paragraph text surrounding Table 2.	This revision was made to address FDA comment #1 on Research Questions 1 and 2, received on 03 April 2025.

			4, 9.2.1.1.1, 9.2.2.1.1, 9.2.2.1.1.1., 9.2.2.1.1.2.	Modification of vaccine capture end dates for historical comparator RCA to allow for the full 21 days of follow-up (or 42 days for the 42-day risk window analyses) prior to either FDA approval of ABRYSVO for adults 18-59 years (for historical comparator) or most recent available data (for ABRYSVO exposed). This ensures the two groups are comparable in the scenario that GBS events are not evenly distributed throughout the risk window and restricts follow-up for historical comparator to a pre-ABRSVO timeframe.	Additional change
			6	The anticipated start of data collection (defined as first date of data extraction) is now 01 July 2025, based on the expected date of SAP finalization.	Additional change
			9.2.1.1.	Modified the RCAs to not require adjustment for incomplete data. When we thought about this again, we realized that it would be better to wait the 6-months to obtain data completeness than to wait only 3-months and introduce the assumption that comes with adjustment for incomplete data. The assumption with only waiting 3 months and adjusting is that we have correctly specified the curve of when data comes in and is complete and, if this curve is mis-specified, could bias our results. Dates of delivery of RCAs to the FDA remain unchanged.	Additional change
			9.2.2.	Added GBS washout criterion throughout safety studies so that everyone was at risk of	Additional change

				GBS (per our algorithm) on day 1 of follow-up. Take, for example, the criterion for the ABRYSVO-exposed group: "No code for GBS or its sequalae, in any setting or position, in the 365 days prior to and including ABRYSVO vaccination."	

6. MILESTONES

Below is the anticipated schedule of milestones, based on the anticipated data lags and timing of data availability for the planned data sources.

Milestone	Planned Dates
Registration in the HMA-EMA Catalogues of RWD studies	Prior to start of data collection
Start of data collection[1]	01 July 2025
End of data collection[2]	28 February 2029
GBS Epidemiology and Natural History Final Report (Research Question 1)	30 September 2026
RCA Report 1 (2024/2025 and 2025/2026 RSV seasons)[3]	30 September 2027
RCA Report 2 (2026/2027 RSV season)	30 September 2028
RCA Report 3 (2027/2028 RSV season)	30 September 2029
Final study report (will include SCRI analysis[4])	31 January 2030

1 Estimated date for when data are extracted for first GBS Epidemiology and Natural History report. Start of data collection will occur after submission of final protocol and SAP finalization, which may be adjusted should there be any further feedback from the FDA.
2 Reflects final dataset extracted for analysis (includes data lag time and potential medical chart review).
3 RCA reports will provide a high-level summary of cumulative safety monitoring results.
4 The SCRI analysis may be triggered at an earlier date due to a statistically significant finding in the RCA. In this scenario, the final study report with the SCRI analysis and chart-confirmed GBS cases will be delivered to the FDA approximately 12 months, dependent on chart retrieval, after the statistically significant finding from the RCA is reported.

7. RATIONALE AND BACKGROUND

ABRYSVO™ is a bivalent, adjuvanted RSVpreF vaccine that was approved in the US on 31 May 2023 for the prevention of RSV-LRTD in people ≥60 years of age, and on 21 August 2023 for the prevention of RSV-LRTD in infants from birth up to 6 months of age by immunization of pregnant individuals at 32 through 36 weeks gestational age of pregnancy. Pfizer is currently conducting multiple PASS in the US to evaluate the risk of GBS among individuals aged ≥60 years of age who are vaccinated with ABRYSVO (Studies C3671031 and C3671054) and among pregnant individuals who are vaccinated with ABRYSVO (Studies C3671026, C3671027, C3671041, C3671042). The US FDA approved ABRYSVO use in adults 18-59 years of age at increased risk of RSV-LRTD on 22 October 2024; recommendations from the Advisory Committee on Immunization Practices (ACIP) on use in this age group are pending as of January 2025.

The epidemiology of GBS may be changing, with evidence of increasing prevalence globally. In North America, a 41.2% increase in the age-standardized prevalence of GBS per 100,000 population was observed between 1990 and 2019.[4] Causes for the change are unknown but may be due to factors including increasing rates of infections and better surveillance for GBS.[5] While many have published on the epidemiology of GBS,[6–10] important questions remain unanswered. For example, there is concern that long-term sequelae from COVID-19 may impact GBS risk and, thus, may have changed the distribution of preceding risk factors.[11,12] Further, the background incidence rate of GBS has been reported in recent years,[1,3,12–14] but not for important subgroups, such as those with certain underlying conditions. A better understanding of the epidemiology of GBS in the US, including preceding risk factors and contemporaneous background rates, is important to contextualize the risk of GBS after vaccinations and can inform vaccine safety studies of GBS risk.

This protocol complements ABRYSVO's clinical development program, which observed no GBS events among ABRYSVO-vaccinated adults 18-59 years of age. This is a PASS to monitor the incidence of GBS in ABRYVSO-vaccinated adults 18-59 years of age at increased risk of RSV-LRTD. This protocol additionally complements Studies C3671031 and C3671054 with analyses of the epidemiology and natural history of GBS in the US.

This noninterventional study is designated as a PASS and is a commitment to the US FDA as a postmarketing requirement (PMR).

8. RESEARCH QUESTION AND OBJECTIVES

This study has 2 research questions, each with multiple objectives.

Research Question 1: What is the epidemiology and natural history of GBS in the US for adults ≥18 years of age between 2017 and 2024?

<u>GBS epidemiology and incidence</u>

Objectives:

- Estimate the incidence of GBS overall and in subgroups of interest (e.g., age, sex, comorbidities, region) over time.
- Describe individuals with GBS with respect to demographics, clinical characteristics, risk factors, treatment, and outcomes.

<u>GBS etiology</u>

Objectives:

- Conduct a detailed medical record review of a sample of GBS cases to validate a claims-based algorithm and to identify potential causes of GBS.

- Perform an exploratory data mining-based signal detection analysis to identify specific vaccines, drugs, and infections potentially associated with GBS.

Research Question 2: What is the risk of GBS after exposure to ABRYSVO among non-pregnant recipients 18-59 years of age at increased risk of RSV-LRTD?

Objectives:

- Signal Detection: Among non-pregnant individuals 18-59 years at increased risk of RSV-LRTD, compare observed GBS case counts after ABRYSVO vaccination against expected GBS case counts via RCA.

- Signal Evaluation: Among non-pregnant individuals 18-59 years of age, assess risk of GBS in the 21 days or 42 days (depending on length of risk window) following ABRYSVO vaccination using a SCRI design.

9. RESEARCH METHODS

9.1. Research Methods for Research Question 1

Research Question 1: What is the epidemiology and natural history of GBS in the US for adults ≥18 years of age between 2017 and 2024?

<u>GBS epidemiology and incidence</u>

Objectives:

- Estimate the incidence of GBS overall and in subgroups of interest (e.g., age, sex, comorbidities, region) over time.

- Describe individuals with GBS with respect to demographics, clinical characteristics, risk factors, treatment, and outcomes.

- <u>GBS etiology</u>

- Objectives:

- Conduct a detailed medical record review of a sample of GBS cases to validate a claims-based algorithm and to identify potential causes of GBS.

- Perform an exploratory data mining-based signal detection analysis to identify specific vaccines, drugs, and infections potentially associated with GBS.

9.1.1. Study Design for Research Question 1

9.1.1.1. Study Design for GBS epidemiology and incidence

To understand the epidemiology of GBS in the US in recent years, descriptive analyses of incident, hospitalized GBS cases will be conducted. Cases will be identified in closed administrative claims data, or equivalent (i.e., billed diagnosis codes in EHR data), from 2017 through 2024, among adults 18 years and older. This timeframe is restricted to the ICD-10-CM diagnosis code era, removing any potential variability across ICD revisions.

Incidence rates of GBS will be estimated overall and among subgroups of interest. Incidence will be calculated by age group, sex, presence of underlying conditions or events that increase risk of RSV-LRTD, and evidence of certain antecedent infections (e.g., respiratory and gastrointestinal infections, including COVID-19),[15–17] amongst other characteristics. Incidence rates will be calculated annually for the study period to assess whether the risk of GBS has changed for certain populations, such as those who received a vaccine, had evidence of certain infections, or had certain underlying conditions of interest. Incidence of GBS will also be reported by broad factors, including geographic region and season.

Among the cohort identified with GBS, demographic and clinical characteristics will be summarized, including age, sex, underlying conditions (e.g., chronic conditions, evidence of concurrent pregnancy), and antecedent health events that are potential risk factors for GBS (e.g., infections). Patterns in care and treatment received, as well as outcomes such as length of hospitalization, subsequent healthcare utilization, sequelae of GBS, and death will also be assessed.

9.1.1.2. Study Design for GBS etiology: Medical record review

The ICD-10-CM diagnosis code for GBS, G61.0, has been used to identify potential GBS cases in numerous vaccine safety studies, and medical record review has often been performed to adjudicate the diagnosis. Medical record review of cases with G61.0 in the inpatient setting, in the primary position, has yielded PPVs of 79.5% (95% CI 67.6-91.5%),[18] 78.6% (95% CI 63.4-93.8%),[1] and 71.2% (95% CI 63.5-78.9%)[19] for Medicare beneficiaries. Other studies have reported a range of PPVs for GBS, from 24% to 82%, with differences in algorithm, ICD-CM revision era, age, and whether the study was for vaccine safety versus descriptive epidemiology[18,20–22] It is not clear whether the PPV for the GBS diagnosis code varies by important characteristics, such as underlying conditions or antecedent events associated with GBS (e.g., vaccination versus infection). Given that PPVs are impacted by the prevalence of the condition under study,[23] it is important to assess whether the ICD-10-CM diagnosis code for GBS is reliable in identifying true GBS in different populations. Further, PPVs are often utilized for adjustment in vaccine safety studies, such as the SCRI study described in Section 9.2.

This study will validate incident, inpatient GBS diagnosis via ICD-10-CM in the primary position among adults 18 and older (see Table 1 for the algorithm details). A detailed medical record review will be performed for approximately 300 cases in total, sampled based on factors such as age, antecedent vaccination of any kind, certain risk factors (e.g., those associated with RSV-LRTD, recent infection), and calendar time. See Section 9.1.2 for details on sampling for the medical record review.

Abstraction and adjudication forms, as well as standard operating procedures (SOP), will be developed prior to conduct of the medical record review. The medical records from the applicable inpatient encounter and the first post-discharge ambulatory encounter with a neurologist will be reviewed. If no appointment with a neurologist occurs within approximately 60 days, the first ambulatory encounter post hospitalization will be included in the review. Trained abstractors, or the adjudicators themselves, at each participating RP will extract information from the applicable inpatient and ambulatory records into a structured form or database equivalent (e.g., REDCap). Information will be collected from medical record elements / sections including admission notes, discharge summaries, laboratory test results, radiographic reports, specialist consultation notes, progress notes, and applicable treatments administered. The abstracted information and corresponding records will be reviewed by a clinician, preferably a neurologist, within each RP who will use the study's case definitions for GBS to adjudicate whether a case is confirmed, possible, or not GBS.[1,2] If a neurologist is unavailable, an alternative clinician will conduct the adjudication; training in the adjudication of GBS by a neurologist will be provided if possible. Adjudicators will be asked to assess what they think the cause of GBS was (e.g., infection, vaccination) based on the available information. The database used for abstraction and adjudication will be maintained by each RP and only deidentified data (e.g., relativized dates) will be shared with the Harvard Pilgrim Health Care Institute (HPHCI) for analysis. Aggregate data will be shared externally, including with Pfizer and FDA.

The PPVs and corresponding 95% confidence intervals of the GBS algorithm will be calculated overall and within subgroups for confirmed cases only, and for confirmed and possible cases combined.

Descriptive information will be summarized for diagnoses and care received during hospitalization. The potential cause of GBS, pre-existing conditions, and preceding events will also be summarized for confirmed and possible cases. Where records from preceding ambulatory care are available, information on diagnostic testing and results for antecedent infection, for example, will be reported.

9.1.1.3. Study Design for GBS etiology: Exploratory data mining-based signal detection

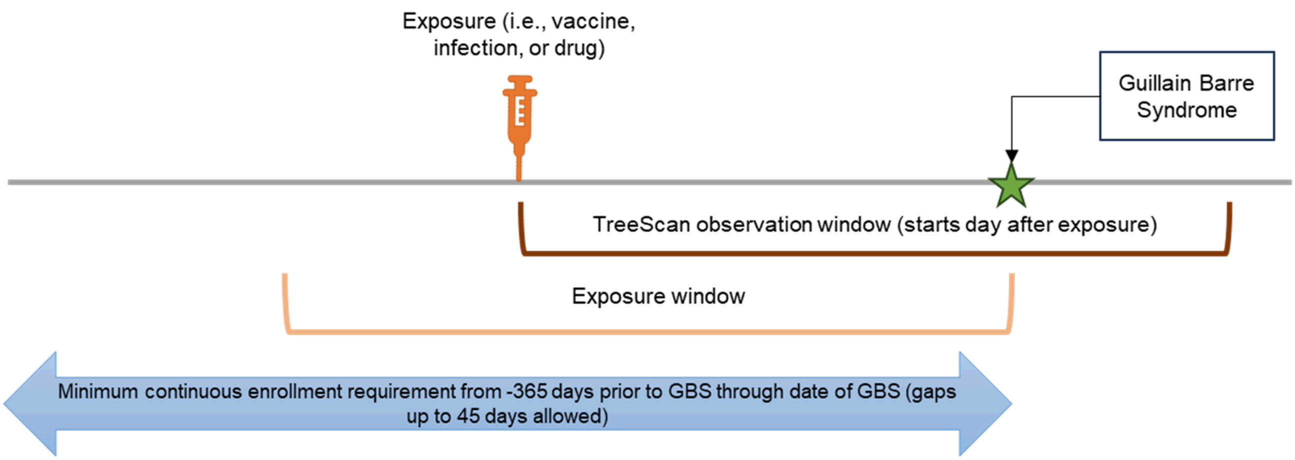
The study design and research approach for this objective was taken largely from Maro et al.,[24] with adaptations. This signal detection analysis will use tree-based scan statistics to broadly search for vaccines, drugs, and infections that may be potential risk factors for GBS.

The method was originally designed and used to detect the association between a specific product (drug or vaccine) and a broad, unspecified range of health outcomes organized in a hierarchical "tree" structure based on their diagnosis codes. For a medical product of interest—influenza vaccine, for example—vaccinees' diagnoses recorded during *post-vaccination* follow-up time are scanned to look for statistically unusual clustering of diagnoses. This method has been used for drugs as well as vaccines.[24–31]

In this project's application of the method, the analysis will be anchored on the outcome of interest (i.e., GBS) and the software will scan for statistically significant clusters of exposures (i.e., infection diagnoses, vaccines, and drugs) in a pre-specified number of days (e.g., 84) *prior* to the occurrence of the outcome. The hierarchical organization of exposures enables detection of, not only product-specific effects, but also class- or type-wide effects (e.g., mRNA vaccines).

A case-crossover design, which minimizes bias by automatically adjusting for time-invariant confounding, will be implemented (see Figure 1). First, incident cases of GBS will be identified using the ICD-10-CM diagnosis code based algorithm, as described in the below Table 1. Incident exposures (i.e., infection diagnoses, vaccines, and drugs) in the exposure assessment window (to be defined in the SAP) preceding each GBS case will then be identified. Exposures and GBS will not be permitted on the same day because of the inability to distinguish the sequence of events within the same day in administrative claims data. The time-to-event from the exposure to the GBS diagnosis date will be identified. The analysis assesses when a greater than expected frequency of precipitating events occurs that puts the GBS outcome in the risk window. Log-likelihood ratios and Monte Carlo hypothesis testing are used to scan the tree for a potential signal. Further details on this data mining technique are in Section 9.1.7.3.

Figure 1. Example design diagram for the self-controlled case crossover design for GBS.



9.1.2. Setting for Research Question 1

GBS will be identified, for all objectives in this protocol, using an algorithm based on Goud and colleagues (2021), which is very similar to other algorithms.[18,19] GBS will be defined as incident primary GBS diagnosis (G61.0) in the inpatient setting, or incident GBS in any setting and any position, with a hospitalization within 7 days where GBS is the primary diagnosis. Incidence is defined using 365-day washout for G61.0 or G65.0 in any care setting.

Table 1. Algorithm for incident GBS

ICD-10-CM code	Setting of code	Definition of "incident"	Performance
G61.0 (Guillain-Barré syndrome)	1) G61.0 as primary hospital discharge diagnosis or 2) G61.0 in any position, any setting, followed by a hospitalization within the 7 subsequent days	No evidence of GBS (G61.0 [GBS] or G65.0 [Sequelae of GBS], any setting, any position) in the 365 days	PPV from study using Medicare data: 79%

	for which G61.0 was the primary hospital discharge diagnosis. *The date of GBS onset will be considered the date of the first eligible G61.0 code in any setting.*	prior to the first diagnosis code of interest.	(95% CI, 64% - 94%)[1]

9.1.2.1. Setting for GBS epidemiology and incidence

The source population for the GBS epidemiology and incidence objectives will be members from up to 3 national health plans; members from 1 or more regional integrated delivery systems or other data sources may also be included. The participation of specific RPs will be noted in the final SAP.

Individuals must meet all of the following inclusion criteria to be eligible for inclusion in this analysis:

- Research eligible at the participating RP;
- ≥18 years of age during the study period, January 2017 – December 2024;
- Have ≥365 days of medical and pharmacy coverage preceding cohort entry, with gaps of ≤45 days permitted (they are considered administrative gaps, not lapses in health plan coverage); and
- Meet the algorithm for incident GBS (outlined in Table 1).

- There are no exclusion criteria for this analysis.

9.1.2.2. Setting for GBS etiology: Medical record review

The source population for the GBS etiology medical record review objective will be health plan members from approximately 3 regional integrated delivery systems. These systems have access to linked EHR and administrative billing data. The participation of the specific RPs, selected based in part on geographic representation, will be noted in the final SAP.

Individuals must meet all of the following inclusion criteria to be eligible for inclusion in this analysis:

- Research eligible at the participating RP;
- ≥18 years of age during the study period, January 2017 – December 2024;
- Have ≥365 days of medical and pharmacy coverage preceding cohort entry, with gaps of ≤45 days permitted; and
- Meet the algorithm for incident GBS (outlined in Table 1).

- There are no exclusion criteria for this analysis.

- Diagnoses will be identified via billed ICD-10-CM diagnosis codes within the source data. Medical record review will be conducted via direct EHR access or medical records will be requested if necessary.

To ensure the subgroups of interest are included in the medical record review, there will be stratified random sampling within subgroups of eligible cases identified in the billing data. It is expected that all GBS cases with evidence of antecedent vaccination of any type (e.g., within 42 days) will be included in the medical record review as they are typically a minority of GBS cases. The balance of GBS cases without recent vaccination, which is expected to be the majority, will be randomly sampled to ensure adults <60 years of age with underlying conditions of interest (e.g., conditions associated with increased risk of RSV-LRTD) are included. Oversampling of more recent cases in 2023-2024 may be necessary. The number of charts sampled per subgroup will be decided upon after review of the distribution of the subgroups among GBS cases in the source population.

9.1.2.3. Setting for GBS etiology: Exploratory data mining-based signal detection

The source population for the data mining-based signal detection objective will be members from up to 3 national health plans. The participation of specific RPs will be noted in the final SAP.

Individuals must meet all of the following inclusion criteria to be eligible for inclusion in this analysis:

- Research eligible at the participating RP;
- ≥18 years of age during the study period, January 2017 – December 2024;
- Have ≥365 days of medical and pharmacy coverage preceding cohort entry, with gaps of ≤45 days permitted; and
- Meet the algorithm for incident GBS (outlined in Table 1).

- There are no exclusion criteria for this analysis.

9.1.3. Variables for Research Question 1

9.1.3.1. Variables for GBS epidemiology and incidence

Subgroups of interest will include age (e.g., 18-59 years; ≥60 years), sex, comorbidities, recent vaccination, and region.

For the second objective in Research Question 1 – *Describe individuals with GBS with respect to demographics, clinical characteristics, risk factors, treatment, and outcomes* – variables of interest are listed in Table 2. The presence of underlying conditions that increase the risk of RSV-LRTD will be assessed, as well as evidence of certain antecedent infections that have been associated with GBS, such as COVID-19, influenza, other upper or lower respiratory tract infection, unspecified viral infection, gastrointestinal infections, and urinary tract infections.[9,15,17,32]. Recent antibiotic use, recent vaccination, or other preceding events that are risk factors for GBS may also be described. [9,10] Diagnostic testing for GBS (e.g., lumbar puncture, imaging) and treatment (e.g., intravenous immunoglobulin and plasma exchange) that is captured via codes in the data sources will be described.[21,33] Documentation of ICD-10-CM diagnosis code G65.0, sequelae of GBS, will be examined, as well as other diagnoses (e.g., muscle weakness), though common symptoms associated with GBS may not be coded.

Table 2. Variables expected to be included in descriptive analysis of incident, inpatient GBS cases

Variable	Notes
Demographics	
Age, age group	In years
Sex[a]	Male, Female, Ambiguous, Unknown
Race[a]	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiracial, Unknown
Hispanic ethnicity[a]	Yes, No, Unknown
Region	e.g., Census Bureau
Month-year of event	Dichotomous per month-year
Underlying conditions in 1-year prior to GBS diagnosis (days -365 to -1)	
Combined comorbidity index	Mean, standard deviation Categories (0, 1, 2, ≥3)
Cardiovascular disease (e.g., heart failure, coronary artery disease, or congenital heart disease [excluding isolated hypertension])	Dichotomous
Chronic lung or respiratory disease (e.g., chronic obstructive pulmonary disease, emphysema, asthma, interstitial lung disease, or cystic fibrosis)	Dichotomous
End-stage renal disease or dependence on hemodialysis or other renal replacement therapy	Dichotomous
Diabetes	Dichotomous
Diabetes mellitus complicated by chronic kidney disease, neuropathy, retinopathy, or other end-organ damage, or requiring treatment with insulin or sodium-glucose cotransporter-2 inhibitor	Dichotomous
Neurologic or neuromuscular conditions causing impaired airway clearance or respiratory muscle weakness (e.g., poststroke dysphagia, amyotrophic lateral sclerosis, or muscular dystrophy [excluding history of stroke without impaired airway clearance])	Dichotomous
Chronic liver disease (e.g., cirrhosis)	Dichotomous
Chronic hematologic conditions (e.g., sickle cell disease or thalassemia)	Dichotomous
Severe obesity (body mass index ≥40kg/m^2)	Dichotomous; Based on diagnosis codes, not measured height and weight
Moderate or severe immune compromise	Dichotomous; Based on diagnosis codes for specific conditions

Table 2. Variables expected to be included in descriptive analysis of incident, inpatient GBS cases

Variable	Notes
Frailty score	Based on Kim,[34] will be assessed in those 65 and older
Antecedent infections in 60 days prior to GBS diagnosis	
Respiratory infections	Dichotomous; e.g., COVID-19, influenza, otitis media, pneumonia, upper and lower respiratory tract infections
Gastrointestinal infections	Dichotomous; e.g., Campylobacter jejuni
Urinary tract infections	Dichotomous
Other infections	Dichotomous; e.g., Epstein-Barr virus, Zika virus, septicemia
Unspecified viral infections	Dichotomous; e.g., B34.9
Vaccination within 42 days prior to GBS diagnosis[b]	
COVID-19 vaccination	Dichotomous
Influenza vaccination	Dichotomous
Meningococcal vaccination	Dichotomous
Pneumococcal vaccination	Dichotomous
RSV vaccination	Dichotomous
Tetanus-containing vaccination	Dichotomous
Zoster vaccination	Dichotomous
Other vaccinations	Dichotomous
Concurrent use of medication associated with GBS	Dichotomous; e.g., antibiotics, anti-tumor necrosis factor alpha
Symptoms / sequelae of GBS during hospitalization or in the 90 days after diagnosis	
Sequelae of GBS (G65.0)	Dichotomous
ICU admission	Dichotomous; Based on diagnosis, procedure, and/or revenue codes, which may under-capture this care
Ventilation	Dichotomous; Based on diagnosis and/or procedure codes, which may under-capture this care
History of GBS >365 days prior to current diagnosis	Yes/No; Ever in day -365 or earlier, based on available enrollment
Evidence of concurrent pregnancy	Dichotomous
Care and testing received related to GBS during hospitalization	
Intravenous immunoglobulin	Dichotomous
Plasmapheresis	Dichotomous
Lumbar puncture	Dichotomous
Imaging (e.g., MRI)	Dichotomous

a. These are defined based on the Sentinel Common Data Model.
b. Variables for vaccination within 21 days prior to GBS diagnosis will also be created.

Note that nursing home residence, which is a factor associated with increased risk of severe RSV,[32] is not reliably identifiable in claims data.

The final variables will be specified in the SAP. Code lists for the variables listed above will be developed during SAP finalization. Some of the variables may be under-captured and therefore misclassified due to the nature of claims data.

9.1.3.2. Variables for GBS etiology: Medical record review

Abstraction and adjudication forms will be developed and finalized prior to medical record review start and variables to be collected during the review will be included in the SAP. In brief, date of symptom onset, diagnostic testing, symptoms, underlying conditions (e.g., those associated with increased risk of RSV-LRTD), antecedent infections, and other information needed for adjudication against the Brighton Collaboration case classifications will be recorded based on review of available records; see Table 3 for the classifications and criteria, as applied by Goud.[1] Adjudicators will also assess the potential etiology of GBS among confirmed and possible cases per the Brighton Collaboration criteria based on the information available in the medical records.

9.1.3.3. Variables for GBS etiology: Exploratory data mining-based signal detection

9.1.3.3.1. Exposure for GBS etiology: Exploratory data mining-based signal detection

One exposure tree will be developed with top-level categories of vaccines, drugs, and infections. This tree, with hierarchal branches, will allow for the detection of potential associations with GBS on both a specific and group level.

Individuals will be permitted to have multiple exposures if the exposure incidence criteria are met. Rules to define an incident exposure will be included in the SAP. If an individual receives multiple exposures within the same branch of the tree on the same day, then only one of those exposures will be included in the analysis. In this situation, the exposure with the smallest count of unique users over the study period will be retained to increase numbers for the rarer exposures.

9.1.3.3.2. Outcome for GBS etiology: Exploratory data mining-based signal detection

GBS will be identified in claims data using the algorithm detailed in Table 1. Alternative case-finding algorithms may be used in sensitivity analyses, which will be specified in the SAP.

9.1.4. Data Sources for Research Question 1

9.1.4.1. Data Sources for GBS epidemiology and incidence

These analyses will be conducted using health plan administrative claims data held by up to 3 national health plans (e.g., Carelon, Humana, and CVS Health). These RPs participate in the US FDA's Sentinel System.[35,36] Other RPs may be included and final participating sites will be specified in the SAP.

The FDA Sentinel System, established under the Sentinel Initiative,[35–37] uses electronic healthcare data from a distributed data network for monitoring the safety of regulated medical products in the US. Sentinel RPs use the Sentinel Common Data Model (SCDM) to standardize demographic and clinical data elements.[38,39]

In addition to providing claims data for the analysis, the RPs will provide scientific input and feedback to support this study. For this analysis, the most recently available data refreshed for the Sentinel System will be leveraged if possible, or sites will create a study-specific refresh as needed.

9.1.4.2. Data Sources for GBS etiology: Medical record review

The GBS etiology medical record review objective will be conducted using administrative billing data from approximately 3 regional integrated delivery systems, or other appropriate data sources, with geographic diversity. Where applicable, administrative billing data that has been converted into the SCDM will be used for this objective. EHRs from within each RP will primarily be used for abstraction, review, and adjudication of the identified cases; if cases are seen at hospitals outside of the RP, charts may be requested.

9.1.4.3. Data Sources for GBS etiology: Exploratory data mining-based signal detection

The GBS etiology data mining-based signal detection objective will be conducted using health plan administrative claims data held by up to 3 national health plans (e.g., Carelon, Humana, and CVS Health). These RPs participate in the US FDA's Sentinel System.[35,36] In addition to providing claims data in the SCDM, the RPs will provide scientific input and feedback to support this study.

9.1.5. Study Size for Research Question 1

Data on all individuals meeting the applicable eligibility criteria within the contributing RPs will be analyzed for the GBS epidemiology and incidence objectives, and the data mining-based signal detection objective.

For the first 2 objectives, where we will estimate the incidence of GBS and describe individuals with GBS, the national health plans expected to participate in these analyses have provided preliminary counts of inpatient, incident GBS: ≥1,000 GBS cases among those 18-59 years of age and ≥2,000 among those 60 and older.

The medical record review objective will be conducted on approximately 300 cases.

9.1.6. Data Management for Research Question 1

Please see Section 9.2.6 for Data Management details for the full study.

9.1.7. Data Analysis for Research Question 1

Detailed methodology for summary and statistical analyses will be documented in the SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

When appropriate, publicly available Sentinel analytic tools will be used for analyses. Modifications to the tools, when used, may be needed to meet study objectives, in which case the SAS programming data quality assurance (QA) standard operating procedures will be followed (see Figure 3). All statistical calculations will be performed using SAS 9.4 or higher.

9.1.7.1. Data Analysis for GBS epidemiology and incidence

Descriptive statistics of adults 18 and older with GBS in 2017 through 2024 will be reported via frequencies and percentages for discrete variables and, for continuous variables, either means and standard deviations or medians and interquartile ranges. The incidence rate of GBS, and corresponding 95% CIs, will be estimated overall and for several subgroups, as described in Section 9.1.1.1, showing how and to what degree incidence rates vary across groups and whether there have been changes in rates during the study period.

9.1.7.2. Data Analysis for GBS etiology: Medical record review

Demographic and clinical characteristics of members with algorithm-defined GBS will be summarized using descriptive statistics (e.g., means and standard deviations or medians and interquartile ranges for continuous variables and frequencies and percentages for discrete variables).

Once all medical records are reviewed and adjudicated, the data will be combined across RPs and the PPV for GBS will be calculated as:

$$PPV = \frac{\text{members with chart-confirmed GBS, among those with algorithm-defined GBS}}{\text{members with algorithm-defined GBS with complete charts}} * 100$$

The PPV of confirmed and possible GBS cases combined will also be calculated.

PPVs will be calculated by age group (e.g., 18-59 and ≥60 years), evidence of antecedent infection, evidence of recent vaccination, and presence of conditions putting individuals at increased risk of RSV-LRTD. Ninety-five percent CIs for PPVs will be calculated.

9.1.7.3. Data Analysis for GBS etiology: Exploratory data mining-based signal detection

The statistical methods for this activity are described briefly below. Greater detail will be provided in the SAP.

9.1.7.3.1. Data mining analyses and statistical methods

TreeScan™ software (www.treescan.org) will be used to analyze data via a self-controlled case-crossover design. In brief, the tree-based scan statistics use log-likelihood ratio tests to detect elevated frequencies of codes in electronic health data that have been grouped into a hierarchical tree structure and automatically adjusts for multiple overlapping scenarios inherent to data mining.[24,25] The test statistic is computed via Monte Carlo hypothesis testing. Under the alternative hypothesis, there is at least 1 exposure, or group of exposures, for which there is a temporal cluster of GBS cases during some time interval in the observation window.

The important analytic information in the self-controlled case-crossover design using TreeScan is the time from the exposure to the outcome, within the prespecified observation window. The observation window for analysis (e.g., 84 days) is divided into a risk window and a comparison window. Both "fixed risk window" and "varying risk window" approaches are possible. In a fixed risk window analysis using TreeScan, these values are defined *a* *priori* (e.g., days -21 through -1 prior to GBS diagnosis as the risk window; days -84 through -43 as the comparison window). In a varying risk window analysis, the risk window is allowed to move within the overall observation window, while the comparison window varies accordingly and consists of all the days that are not in the risk window being evaluated. Exposure and GBS will not be permitted on the same day (day 0) because of the inability to distinguish the sequence of events within the same day in administrative claims data.

The self-controlled case-crossover design is compatible with the following 4 tree-based scan statistics: conditional and unconditional Bernoulli tree-based scan statistics for fixed risk window analyses, and conditional and unconditional tree-temporal analyses for varying risk window analyses. The specific statistic(s) that will be used will be specified in the final SAP.

Analyses will be performed with a threshold for statistical significance of $p = 0.05$ (1-sided).

9.1.7.3.2. Statistical signal investigation

The TreeScan based analyses may find a statistical signal, suggesting a possible association between an exposure or group of exposures and GBS. However, false alarms are possible, and any statistical signal arising from these data mining analyses must be investigated with appropriately designed and controlled epidemiologic studies (outside the scope of this current protocol) rather than viewed, in and of itself, as evidence of causality. Where statistical signals cannot be ruled out (e.g., on the basis of obvious temporal confounding) or determined to be consistent with known associations, there may be an investigation using data summarized via the Patient Episode Profile and Retrieval (PEPR) tool.[40] PEPR summarizes information including diagnoses, procedures, and vaccines from administrative claims data for a specific window of time around an anchor of interest (e.g., GBS diagnosis). Signal investigation, if any, will be further described in the SAP.

9.1.8. Quality Control

Please see Section 9.2.8 for quality control details for the full study.

9.1.9. Limitations of the Research Methods for Research Question 1

9.1.9.1. Limitations of GBS epidemiology and incidence

For this specific objective, the limitations are related to the nature of the data sources in general. Any study that utilizes administrative claims data is subject to misclassification. The GBS algorithm described in Table 1, which has been validated by others,[1] is expected to have a PPV of ~80%, meaning some of the incident GBS “cases” will not be GBS. Covariates of interest, such as certain antecedent and underlying conditions, may be misclassified due to under-capture of these conditions if they are not medically attended, diagnosed, and/or billed. Treatment of GBS in the hospital setting may be under-captured in claims data due to bundling of care. Vaccination status may be under-captured as participating national health plans do not have complete linkage with IIS sources and some IIS data may not be permissible to use for this project due to governance rules within the health plans. In addition, the COVID-19 pandemic affected healthcare utilization, and may have impacted rates of GBS.[12]

9.1.9.2. Limitations of GBS etiology: Medical record review

There are potential limitations of the research methodology and data sources for this objective. First, members within the RPs, which are expected to be integrated delivery systems, may not be representative of the general population and findings from their data may not be representative of patient care in other settings.

PPVs will be calculated for the GBS algorithm overall and within important subgroups. Because stratified sampling will be done to ensure representation of the groups of interest, the PPV estimates may have wide 95% CIs. In addition, this study is not designed to calculate sensitivity or specificity of the algorithms.

Identification of the etiology of GBS, among those identified as confirmed or possible cases, may be challenging. Identifying antecedent infections or other preceding events requires documentation in the medical record, and diagnostic testing for many infections is uncommon. Clinician adjudicators may not have the information available to make the case and/or the etiologic determination.

9.1.9.3. Limitations of GBS etiology: Exploratory data mining-based scan statistics

Tree-based data mining is hypothesis generating and exploratory. Therefore, causation cannot be determined. Further, a tree organized around 1 characteristic (e.g., vaccine manufacturing platform or antigen content) may perform poorly if the outcome of interest is driven by a different characteristic (e.g., a specific adjuvant).

Like some other self-controlled methods, including the self-controlled case-crossover design, the method can be subject to time-varying confounding, including potentially by seasonality.

As noted above in Sections 9.1.9.1 and 9.1.9.2, vaccination status and antecedent infections may be under-captured. Another situation that may lead to a variable being under-captured is in the tie breaker scenario of multiple exposures within the same branch of the tree occurring on the same day (noted in Section 9.1.3.3.1). In this scenario, only the rarer exposure will be counted to give the rarer exposure more power. However, in practice, the tie breaker situation is rarely invoked. If it is invoked commonly in the conduct of this objective, a secondary analysis could select an exposure randomly as a sensitivity analysis.

9.1.10. Other Aspects for Research Question 1

Not applicable.

9.2. RESEARCH METHODS FOR RESEARCH QUESTION 2

Research Question 2: What is the risk of GBS after exposure to ABRYSVO among non-pregnant recipients 18-59 years of age at increased risk of RSV-LRTD?

Objectives:

- Signal detection: Among non-pregnant individuals 18-59 years at increased risk of RSV-LRTD, compare observed GBS case counts after ABRYSVO vaccination against expected GBS case counts via RCA.

- Signal evaluation: Among non-pregnant individuals 18-59 years of age, assess risk of GBS in the 21 or 42 days (depending on length of risk window) following ABRYSVO vaccination using a SCRI design.

9.2.1. Study Design for Research Question 2

This PASS will implement a stepwise active safety surveillance approach for 4 RSV seasons in non-pregnant individuals 18-59 years at increased risk of RSV-LRTD. During initial stages of vaccination roll-out, an RCA using sequential surveillance methods will be the primary method for signal detection. Approximately 1 RCA will be conducted on the accumulating data per season for each of the 2 RCA study designs. If an RCA detects a statistically significant positive association between risk of GBS and ABRYSVO vaccination, or if 4 RSV vaccination seasons have completed without an RCA detecting a statistically significant finding of higher risk, a SCRI study will be conducted to allow for a more comprehensive assessment of the association of ABRYSVO exposure and GBS. If the RCA does not detect a statistically significant finding or reach a pre-specified number of GBS cases (to be specified in the SAP) by the end of 4 RSV seasons, inclusion of additional RPs or extending the length of the RCA study period will be considered. Once commenced, the SCRI study will use all data available at that time, which could include multiple RSV seasons.

9.2.1.1. Study Design for RCA

RCA is a method used to conduct population-based active surveillance of vaccine-related potential adverse events using electronic health data.[41] Since 2005, it has been used by the CDC’s Vaccine Safety Datalink (VSD) to monitor the safety of tetanus, diphtheria, pertussis (Tdap), measles, mumps, rubella, and varicella (MMRV), rotavirus, human papillomavirus (HPV), influenza, and coronavirus disease 2019 (COVID-19) vaccines.[42,43] With this method, hypothesized exposure-outcome associations are evaluated using sequential methods under the null hypothesis that the vaccine does not increase the risk of the outcome. Sequential statistical analyses account for multiple testing of accumulating data.[44] The goal of RCA is to detect potential safety problems as soon as possible while minimizing false positive signals.

Each RCA will be conducted on the accumulating data using 2 study designs, a historical comparator RCA and a concurrent comparator RCA. The first RCA will identify ABRYSVO vaccinees from October 2024 through October 2025; the subsequent 2 RCAs will be cumulative, using data starting from October 2024. Specifically, the second RCA will identify ABRYSVO vaccinees from October 2024 through October 2026, and the third RCA will identify ABRYSVO vaccinees from October 2024 through January 2028. GBS will be identified in the 21 days post-ABRYSVO vaccination, e.g., through November 2025 for the first RCA. GBS will also be identified 42 days post-ABRYSVO vaccination, but, for simplicity, an example timeline for 21-days post is presented below. Administrative claims data require time to accrue and approach completeness. Typically, it takes up to 6 months for ≥90% completeness in the inpatient setting. RP data refreshes with data quality checks that follow the Sentinel System processes take approximately 2 additional months. Below is an example of the anticipated timing for the first RCA:

- Identify ABRYSVO vaccinees from October 2024 – October 2025
- Assess outcomes through November 2025
- Data through the end of November will have attained the 6-month lag at the beginning of June 2026. Thus, in June, RPs can begin building their datasets for data quality checks.
- RPs conduct data analysis on quality-checked data and provide results to HPHCI by early September 2026.

9.2.1.1.1. Study Design for Historical Comparator RCA

For the ABRYSVO-exposed group, ABRYSVO vaccinations from 22 October 2024 (the date of FDA approval of ABRYSVO for adults 18-59 years at increased risk of RSV-LRTD) through 21 days (for analyses using a risk window of 21 days) or 42 days (for analyses using a risk window of 42 days) prior to the most recent data available at the time of each RCA commencement will be included. Notably, although ABRYSVO has been FDA approved, insurance companies will likely not cover ABRYSVO for adults 18-59 years at increased risk of RSV-LRTD until after an ACIP recommendation, which is pending as of January 2025. Thus, ABRYSVO vaccinations in claims data will begin after the date of ACIP recommendation, not the date of FDA approval. However, for comprehensiveness and because IIS data may be available, ABRYSVO vaccinations will be included from the date of FDA approval onward.

For the comparator group, a background rate estimated from a historical vaccine-exposed group will be obtained. Historical comparators are routinely used in RCAs when evaluating rare outcomes because the expected outcome rates in the comparator can be generated using multiple years of prior data.[45] The historical comparator group will consist of non-pregnant individuals 18-59 years of age at increased risk of RSV-LRTD who receive a comparator vaccine (mRNA COVID-19 or seasonal influenza vaccines) between 01 January 2017 and 30 September 2024 (for analyses using a risk window of 21 days) or 09 September 2024 (for analyses using a risk window of 42 days). These vaccine capture end dates are 21 and 42 days, respectively, prior to the US Food and Drug Administration (FDA) approval of ABRYSVO for adults 18-59 years at increased risk of RSV-LRTD. mRNA COVID-19 and seasonal influenza vaccines were selected as the comparator vaccines because these are adult vaccines that either do not or minimally increase risk of GBS (i.e., 0-2 attributable cases per million doses).[46]

GBS will be identified from claims in all eligible individuals, using the algorithm specified in Table 1 during the specified follow-up time (follow-up time is defined in Section 9.2.3.2.1).

Confounding will be handled by using historical background incidence rates stratified by select covariates (described in Section 9.2.3.3.1 and 9.2.7.1.2).

9.2.1.1.2. Study Design for Concurrent Comparator RCA

Because the historical comparator group could be subject to secular trends in GBS, a concurrent comparator RCA will be performed among ABRYSVO-vaccinated individuals.

Using pre-defined risk and control windows (one analysis will use 1-21 days for risk and 43-84 days for control and another will use 1-42 days for risk and 43-84 for control; this timing is justified in Section 9.2.1.2) following ABRYSVO vaccination, and a time-based stratification approach, the risk of GBS will be evaluated based on the proportion of vaccinated individuals that are in the risk window at the time of the GBS event.[43] A binomial variant of the maxSPRT will be used with a case-centered logistic regression approach. Additional advantages of this approach are that it does not need to restrict to a study population who meets the algorithm for increased risk of RSV-LRTD because these ABRYSVO-vaccinated individuals will be presumed to meet the indication, and it inherently adjusts for any seasonality trends.

9.2.1.2. Study Design for SCRI

There are 2 scenarios in which the SCRI study may be initiated: 1) if a statistically significant positive association between risk of GBS and ABRYSVO vaccination arises from any RCA, or 2) after 4 RCA seasons, if there was no risk detected. In the former scenario, the SCRI study will serve as refinement of the RCA finding, given the improved control of confounding with the SCRI design, to determine whether a true association exists.

The SCRI design is ideal for studying acute events (e.g., GBS) with well-defined risk periods after a transient exposure.[47–49] The incidence of events within a risk window is compared to the incidence of events within a control window. A strength of this design is its ability to control for time-invariant confounders, such as race and age. Time-varying confounders such as seasonality are not controlled unless explicitly accounted for in analyses.

The study population (detailed in Section 9.2.2.2) will be comprised of non-pregnant adults 18-59 years who received an ABYRSVO vaccination from 22 October 2024 (the date of FDA approval of ABRYSVO for adults 18-59 years at increased risk of RSV-LRTD) through the most recent data available at the time of the study commencement, which could include multiple RSV seasons.

The SCRI will compare incidence of GBS during a primary risk window of 1-42 days after ABRYSVO vaccination (day 0 is vaccination) with incidence of GBS during the primary control window 43-84 days after ABRYSVO. The 42-day risk window after vaccine administration for GBS is based upon recent studies that have found days 1-42 post-vaccination to contain the time of increased risk.[1,43,50] A secondary risk window of 1-21 days and secondary control window of 43-84 days will also be studied in a sensitivity analysis.

GBS will be identified from claims in all eligible individuals using the algorithm specified in Table 1 during risk and control windows. If the SCRI study is triggered due to a statistically significant finding in the RCA, the GBS cases identified in claims will be confirmed via medical record review as part of the signal refinement process. If the SCRI study commences after 4 seasons without a signal in an RCA, the SCRI study will employ PPV-adjustment of the claims-identified GBS cases.[51]

9.2.2. Setting for Research Question 2

The source population for both the RCA and SCRI studies will be members from up to 3 national health plans; members from other appropriate data sources may be included. The participation of specific RPs will be noted in the final SAP.

9.2.2.1. Setting for RCA

9.2.2.1.1. Setting for Historical Comparator RCA

For the historical comparator RCA, the exposed group will include non-pregnant individuals 18-59 years of age at increased risk of RSV-LRTD and administered ABRYSVO between 22 October 2024 and 21 or 42 (depending on length of risk window) days prior to the most recent data available at study commencement. The historical comparator group will consist of non-pregnant individuals 18-59 years of age at increased risk of RSV-LRTD who receive a comparator vaccine between 01 January 2017 and 30 September 2024 (for analyses with a 21-day risk window) or 09 September 2024 (for analyses with a 42-day risk window).

9.2.2.1.1.1. ABRYSVO™-Exposed Group

Individuals in the ABRYSVO-exposed group must meet all of the following inclusion criteria to be eligible for inclusion in the historical comparator RCA:

1. ABRYSVO vaccination (exposure ascertainment further described in Section 9.2.3.1) between 22 October 2024 and 21 or 42 days (depending on length of risk window) prior to the last date of available data.

2. Individuals aged 18 to 59 years old at ABRYSVO vaccination.

3. At least 365 days of continuous enrollment in medical and pharmacy claims prior to and including the day of ABRYSVO vaccination, with gaps of up to 45 days in coverage permitted. The required pre-vaccination continuous enrollment will allow identification of individuals at increased risk of RSV-LRTD.

4. Individuals must meet the algorithm definition (i.e., ≥ 1 underlying condition) for increased risk of RSV-LRTD (Table 3).

Table 3. Criteria for identifying individuals at increased risk of RSV-LRTD[a]

Individuals meeting ≥1 of the following criteria[b] in the 365 days prior to and including the day of vaccination may be considered at increased risk of RSV-LRTD:
• Chronic cardiovascular disease • Chronic lung or respiratory disease • End-stage renal disease or dependence on hemodialysis or other renal replacement therapy • Diabetes mellitus complicated by chronic kidney disease, neuropathy, retinopathy, or other end-organ damage, or requiring treatment with insulin or sodium-glucose cotransporter-2 (SGLT2) inhibitor • Neurologic or neuromuscular conditions causing impaired airway clearance or respiratory muscle weakness (e.g., amyotrophic lateral sclerosis) • Chronic liver disease

Table 3. Criteria for identifying individuals at increased risk of RSV-LRTD[a]

• Chronic hematologic conditions • Severe obesity (body mass index ≥40 kg/m^2) • Moderate or severe immune compromise • Frail[34]

a. Based on CDC guidance[32]

b. The full algorithm, including code lists and number of codes required to fulfill a criterion, will be detailed in the SAP. Criteria may be modified during SAP development to match the CDC's definition for increased risk of RSV-LRTD in individuals 18-59 years as closely as possible.

This algorithm will only be able to ascertain conditions to the extent that they are recorded in claims data. This is noted in the limitations (Section 9.2.9) and the concurrent comparator RCA will address this limitation.

5. Not pregnant, defined as no diagnosis or procedure codes for a pregnancy marker in the 42 weeks prior to ABRYSVO vaccination through and including the day of ABRYSVO vaccination AND no diagnosis or procedure codes for a pregnancy outcome on the day of ABRYSVO vaccination through up to the 42 weeks (as data is available) after ABRYSVO vaccination.

6. No receipt of AREXVY (RSV vaccine, adjuvanted) or other non-Pfizer RSV vaccine in the 365 days prior to and including ABRYSVO vaccination through the 21 days (as data is available) post-vaccination.

7. No code for GBS or its sequalae, in any setting or position, in the 365 days prior to and including ABRYSVO vaccination.

There are no exclusion criteria for ABRYSVO-exposed group. All eligible ABRYSVO-exposed individuals will be followed for GBS, as described in Section 9.2.3.2.1.

9.2.2.1.1.2. Historical Comparator Group

Individuals in the historical comparator group must meet all of the following inclusion criteria to be eligible for inclusion in the historical comparator RCA:

1. Comparator vaccination between 01 January 2017 and 30 September 2024 (for analyses with a 21-day risk window) or 09 September 2024 (for analyses with a 42-day risk window). Comparator vaccines will be mRNA COVID-19 and seasonal influenza vaccines, which are adult vaccines that either do not or have minimally increased risk for GBS (i.e., 0-2 attributable cases per million doses).[46]

2. No Janssen COVID-19 vaccination within the 42 days previous to the comparator vaccination. This criterion will prevent the comparator group from systematically being in the risk window for a Janssen COVID-19 vaccine during primary series vaccine

administration. Although the Janssen primary series is typically one dose, immunocompromised were advised to additionally receive an mRNA vaccine.

3. Individuals aged 18 to 59 years old at comparator vaccination.

4. At least 365 days of continuous enrollment in medical and pharmacy claims prior to and including the day of comparator vaccination, with gaps of up to 45 days in coverage permitted.

5. Individuals must meet the algorithm definition for increased risk of RSV-LRTD (Table 3).

6. Not pregnant, defined as no diagnosis or procedure codes for a pregnancy marker in the 42 weeks prior to the comparator vaccination through and including the day of comparator vaccination AND no diagnosis or procedure codes for a pregnancy outcome on the day of comparator vaccination through up to the 42 weeks (as data is available) after comparator vaccination.

7. No comparator vaccination within the previous 42 days. To allow re-entry into the comparator cohort, an individual who meets all other criteria may re-enter the cohort with a subsequent eligible comparator vaccination, given that there is no comparator vaccination within the 42 days previous to the vaccination of interest. Concomitant (same-day) vaccinations will be allowed and described.

8. No code for GBS or its sequalae, in any setting or position, in the 365 days prior to and including ABRYSVO vaccination.

There are no exclusion criteria for historical comparator group. All eligible comparator individuals will be followed for GBS, as described in Section 9.2.3.2.1.

9.2.2.1.2. Setting for Concurrent Comparator RCA

Individuals must meet all of the following inclusion criteria to be eligible for inclusion in the concurrent comparator RCA study:

1. ABRYSVO vaccination (exposure ascertainment further described in Section 9.2.3.1) from 22 October 2024 through the most recent data available at study commencement.

2. Individuals aged 18 to 59 years old at ABRYSVO vaccination.

3. At least 365 days of continuous enrollment in medical and pharmacy claims prior to and including the day of ABRYSVO vaccination, with gaps of up to 45 days in coverage permitted.

4. Not pregnant, defined as no diagnosis or procedure codes for a pregnancy marker in the 42 weeks prior to ABRYSVO vaccination through and including the day of ABRYSVO vaccination AND no diagnosis or procedure codes for a pregnancy outcome on the day of

ABRYSVO vaccination through up to the 42 weeks (as data is available) after ABRYSVO vaccination.

5. No receipt of AREXVY (RSV vaccine, adjuvanted) or other non-Pfizer RSV vaccine during the 365 days pre- or 84 days (as data is available) post-vaccination.

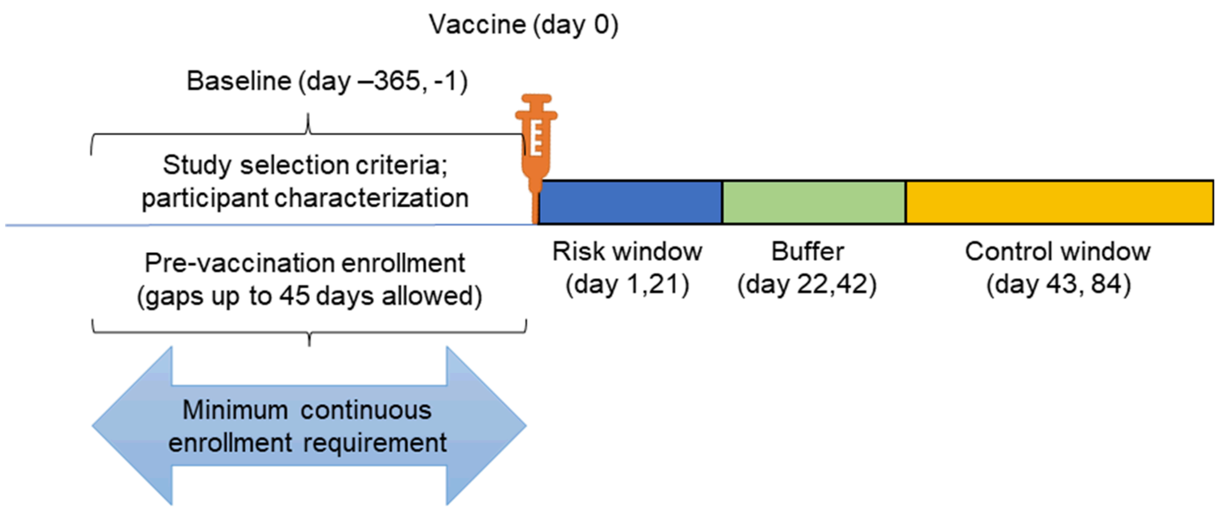
6. No code for GBS or its sequalae, in any setting or position, in the 365 days prior to and including ABRYSVO vaccination.

There are no exclusion criteria for this analysis.

9.2.2.2. Setting for SCRI

The study population for the SCRI study will be non-pregnant individuals 18-59 years who received an ABYRSVO vaccination from 22 October 2024 through the most recent data available at the time of the study commencement (Figure 2). The primary analysis for the SCRI study will not require vaccinees to meet the algorithm definition for increased risk of RSV-LRTD due to concerns with misclassification (i.e., not everyone with one of these conditions will be identified as such via the claims-based algorithm), but vaccinees will be presumed to be at increased risk of RSV-LRTD because this is the indication for ABRYSVO. A secondary analysis (Section 9.2.7.2) will restrict to the population who meet the algorithm definition (Table 3).

Figure 2. SCRI study design



Individuals must meet all of the following inclusion criteria to be eligible for inclusion in the SCRI study:

1. ABRYSVO vaccination (exposure ascertainment further described in Section 9.2.3.1) from 22 October 2024 through the most recent data available at the time of the study commencement.

2. Individuals aged 18 to 59 years old at ABRYSVO vaccination.

3. At least 365 days of continuous enrollment in medical and pharmacy claims prior to and including the day of ABRYSVO vaccination, with gaps of up to 45 days in coverage permitted.

4. Not pregnant, defined as no diagnosis or procedure codes for a pregnancy marker in the 42 weeks prior to ABRYSVO vaccination through and including the day of ABRYSVO vaccination AND no diagnosis or procedure codes for a pregnancy outcome on the day of ABRYSVO vaccination through up to the 42 weeks (as data is available) after ABRYSVO vaccination.

5. No receipt of AREXVY (RSV vaccine, adjuvanted) or other non-Pfizer RSV vaccine during the 365 days pre- or 84 days (as data is available) post-vaccination.

6. No code for GBS or its sequalae, in any setting or position, in the 365 days prior to and including ABRYSVO vaccination

There are no exclusion criteria for this analysis.

9.2.3. Variables for Research Question 2

Information about ABRYSVO exposure, GBS, and covariates will be collected from claims data and, as available, state-based IIS data.

9.2.3.1. Exposure for Both RCA and SCRI

Exposure to ABRYSVO between 22 October 2024 and the most recent data available at the time of study commencement will be identified in claims data and, as available, state-based IIS data. Receipt of ABRYSVO will be identified using Current Procedural Terminology (CPT) code 90678, vaccine administered code CVX 305, and National Drug Code (NDC) codes 00069-0207-01, 00069-0344-01, and 00069-0344-05. Additional codes for identification of ABRYSVO will be included if relevant codes become available in the future.

9.2.3.2. Outcome

Outcome for RCA

GBS will be identified in claims data using the algorithm detailed in Table 1. GBS cases will not be confirmed via medical record review for the RCA.

9.2.3.2.1.1. Outcome for Historical Comparator RCA

Follow-up time for GBS in the ABRYSVO-exposed group will start the day after ABRYSVO vaccination and end at the earliest of the following: date of GBS case, 21 days after vaccination, death, or disenrollment.

Follow-up time for GBS in the historical comparator group will start the day after the comparator vaccination and end at the earliest of the following: date of GBS case, 21 days after vaccination, death, or disenrollment.

A second historical comparator RCA will modify the criterion of "21 days after vaccination" for the ABRYSVO-exposed and historical comparator group to "42 days after vaccination."

9.2.3.2.1.2. Outcome for Concurrent Comparator RCA

Follow-up time for GBS in the concurrent comparator RCA will start the day after ABRYSVO vaccination and end at the earliest of the following: date of GBS case, 84 days after vaccination, death, or disenrollment.

9.2.3.2.2. Outcome for SCRI

GBS will be identified in claims data using the algorithm detailed in Table 1. This study will include GBS cases during the risk and control windows among people who die during follow-up. Deaths will be captured via enrollment data (for both in-hospital and out-of-hospital deaths) and hospital discharge status (for hospital deaths); death capture is expected to be incomplete, as is typically the case with death data from administrative claims data in the US. Follow-up time will artificially *not* be censored at the time of death. In other words, an eligible individual who has a GBS case during the risk or control windows and dies will still contribute to the full risk and control windows.

If the SCRI study commences due to completion of 4 RSV seasons with no statistically significant positive association between ABRYSVO and GBS from the RCA, GBS cases will not be confirmed via medical record review, but rather results will be adjusted using the PPV of the GBS algorithm produced in Research Question 1.[51] If the SCRI study commences due to a statistically significant finding from an RCA, medical record review of GBS cases in the SCRI study will be conducted as part of the signal evaluation. However, a limitation of medical record review is that not all medical records will be retrievable. For the GBS cases where medical records cannot be retrieved, results will be adjusted using the PPV of the GBS algorithm. For example, if medical records cannot be retrieved for 10 GBS cases and the PPV for the GBS algorithm is 80%, this will be readjusted to 8 GBS cases.

9.2.3.2.2.1. Medical Record Review of Outcome for SCRI

In the scenario of medical record review of GBS cases identified via the SCRI analysis, GBS during the 84 days after ABRYSVO vaccination will be validated, the date of symptom onset identified, and key clinical information abstracted for analysis. The general approach to abstraction and GBS case adjudication outlined in the sections describing the GBS etiology sub-activity of medical record review (Section 9) will be used. Briefly, the medical record associated with the inpatient encounter where GBS was diagnosed will be requested and will serve as the primary focus for adjudication. The record for the first subsequent ambulatory encounter with a neurologist, if applicable, will also be requested. Trained abstractors, or the adjudicators, will extract information from the inpatient and ambulatory records into a database (e.g., REDCap). Information will be collected from sections including admission notes, discharge summaries, laboratory test results, radiographic reports, specialist consultation notes, progress notes, and applicable treatments administered. The abstracted information and corresponding records will be reviewed by a clinician, preferably a neurologist, using study case definitions based on the Brighton Collaboration case definitions for confirmed, possible, and not GBS.[1,2] The clinician adjudicator will also record the estimated date that symptoms first appeared per information in the medical record, and this date will be the date used in the final analysis. The GBS onset date is crucial to determining whether the outcome occurred during the risk or control window. Abstractors and adjudicators will be blinded, to the extent possible by redaction, to whether the GBS case occurred in the vaccination risk or control window. Only deidentified data (e.g., relativized dates) will be shared with HPHCI for the analyses. Only aggregate data will be shared externally, including with Pfizer and FDA. Individual-level data will not be shared between RPs or with the study sponsor. 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 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.

Notably, medical records will not be 100% obtainable from participating RPs. Section 9.2.7.2. includes a description of how potential events with unobtainable medical records will be handled in the analyses.

9.2.3.3. Other Variables

Descriptive variables, such as concomitant vaccinations, will be detailed in the SAP.

9.2.3.3.1. Other Variables for RCA

Covariates used for confounding control will be detailed in the SAP and may include age at vaccination, sex, an indicator variable for in and out of season vaccinations, an indicator variable for concomitant vaccinations, and a comorbidity score.

9.2.3.3.2. Other Variables for SCRI

Due to the self-controlled nature of the SCRI design, time-invariant covariates will not be confounding variables. Regarding potential time-varying confounding variables, increasing age is not expected to significantly change one's risk of GBS over the course of a few months. Thus, no covariates will be used for confounding control.

9.2.4. Data Sources for Research Question 2

This study will be conducted using health plan administrative claims data held by up to 3 national health plans (e.g., Carelon Research, Humana, and CVS Health). These RPs participate in the US FDA's Sentinel System.[35,36] Additional RPs may be included and will be specified in the SAP. In addition to providing claims data in the SCDM, the RPs will provide scientific input and feedback to support this study. For Research Question 2, the most recently available data refreshed for the Sentinel System will be leveraged if possible, or the RPs will provide a study-specific refresh, as needed.

9.2.5. Study Size for Research Question 2

9.2.5.1. Study Size for RCA

9.2.5.1.1. Study Size for Historical Comparator RCA

The conditional PmaxSPRT will be used for the historical comparator RCA and requires specification of the number of GBS cases that have accrued in the historical comparator group, which, at this point, is unknown. Assuming between 10 and 20 GBS cases in the historical comparator group (for 10 GBS cases to be observed, approximately 8.8 million comparator vaccinations will need to be included in the RCA; for 20 GBS cases to be observed, approximately 17.5 million comparator vaccinations will need to be included in the RCA), Table 4 contains sample size calculations for the conditional PmaxSPRT analysis when a Wald-type alpha spending plan is specified and a continuous monitoring scheme. Note: the built-in sample size functionality is only available for a continuous monitoring scheme. The statistical signaling criteria might be higher than what is observed in the actual study, where data are expected to arrive in irregular increments over the 3 interim studies.

Assuming 10 events in the historical comparator group and targeting an attributable risk of 10 excess cases per million doses (corresponding to a relative risk of 9.7), 3 GBS cases will need to be observed in the ABRYSVO-exposed group to have 80% power (alpha = 0.05, 1-sided) to reject the null hypothesis of no association. Under the assumption that each ABRYSVO vaccine contributes 21 days of follow-up time, 2.6 million ABRYSVO vaccinees are needed.

Table 4. Sample size calculations for the conditional PmaxSPRT with a Wald-style alpha spending function, no minimum events required to signal

Target attributable risk in excess cases per million doses	Equivalent relative risk	Target power	Type 1 error	GBS cases needed in the ABRYSVO-exposed group[a]	Assumed number of GBS cases in the historical comparator group[b]	ABRYSVO vaccinees needed in millions[b]
2	2.7	0.8	0.05	75	10	65.2
3	3.6	0.8	0.05	15	10	13.0
4	4.5	0.8	0.05	9	10	7.8
5	5.4	0.8	0.05	6	10	5.2
8	8.0	0.8	0.05	4	10	3.5
10	9.7	0.8	0.05	3	10	2.6
2	2.7	0.8	0.05	27	15	23.5
3	3.6	0.8	0.05	11	15	9.6
4	4.5	0.8	0.05	8	15	7.0
5	5.4	0.8	0.05	6	15	5.2
8	8.0	0.8	0.05	4	15	3.5
10	9.7	0.8	0.05	3	15	2.6
2	2.7	0.8	0.05	21	20	18.3
3	3.6	0.8	0.05	10	20	8.7
4	4.5	0.8	0.05	7	20	6.1

5	5.4	0.8	0.05	5	20	4.3
8	8.0	0.8	0.05	4	20	3.5
10	9.7	0.8	0.05	3	20	2.6

a. GBS cases needed was calculated using the R sequential package.
b. Assuming a conservative background rate of 2 cases of GBS per 100,000 person-years[3] in individuals 18-59 years at increased risk of RSV-LRTD and that each vaccinee contributes 21 days of follow-up.

9.2.5.1.2. Study Size for Concurrent Comparator RCA

For the concurrent comparator RCA, a binomial variant of the maxSPRT will be used. Sample size calculations were performed (Table 5), again with a Wald-type alpha spending plan and a continuous monitoring scheme.

Targeting an attributable risk of 10 excess cases per million doses (corresponding to a relative risk of 9.7), 8 GBS cases will need to be observed to have 80% power (alpha = 0.05, 1-sided) to reject the null hypothesis of no association. Under the assumption that each ABRYSVO vaccine contributes 63 days of follow-up time, 2.3 million ABRYSVO vaccinees are needed.

Table 5. Sample size calculations for the binomial maxSPRT with a Wald-style alpha spending function, assuming data are evenly spaced over 3 interim tests

Target attributable risk in excess cases per million doses	Equivalent relative risk	Target power	Type 1 error	Total GBS cases neededa	Risk window length, control window length (days)	ABRYSVO vaccinees needed in millionsb
2	2.7	0.8	0.05	31	21, 42	9.0
3	3.6	0.8	0.05	19	21, 42	5.5
4	4.5	0.8	0.05	16	21, 42	4.6
5	5.4	0.8	0.05	12	21, 42	3.5
8	8.0	0.8	0.05	9	21,42	2.6
10	9.7	0.8	0.05	8	21,42	2.3

a. GBS cases needed was calculated using the R sequential package.
b. Assuming a conservative background rate of 2 cases of GBS per 100,000 person-years[3] in individuals 18-59 years at increased risk of RSV-LRTD and that each vaccinee contributes 63 days of follow-up.

9.2.5.2. Study Size for SCRI

A total number of 7 GBS cases in the combined risk and control intervals provides 80% power (alpha = 0.05, 1-sided) to reject the null hypothesis of no association between ABRYSVO vaccination and GBS when the true attributable risk in excess cases per million doses is 10 (which corresponds to a relative risk of 9.7; Table 6). Assuming a conservative background rate of 2 cases of GBS per 100,000 person-years,[3] 7 GBS cases will be observed amongst 2.0 million ABRYSVO vaccinees. The number of ABRYSVO vaccinations needed for this SCRI study may be revised upon a better understanding of the incidence of GBS in individuals 18-59 years at increased risk of RSV-LRTD from Research Question 1.

Table 6. Sample size calculations for the SCRI design

Target attributable risk in excess cases per million doses	Equivalent relative risk	Target power	Type 1 error	Total GBS cases needed[a]	Risk window length, control window length (days)	ABRYSVO vaccinees needed in millions[b]
2	2.7	0.8	0.05	29	21, 42	8.4
3	3.6	0.8	0.05	16	21, 42	4.6
4	4.5	0.8	0.05	15	21, 42	4.3
5	5.4	0.8	0.05	11	21, 42	3.2
8	8.0	0.8	0.05	8	21,42	2.3
10	9.7	0.8	0.05	7	21,42	2.0

a. GBS cases needed was calculated using the R sequential package.
b. Assuming a conservative background rate of 2 cases of GBS per 100,000 person-years[3] in individuals 18-59 years at increased risk of RSV-LRTD and that each vaccinee contributes 63 days of follow-up.

9.2.6. Data Management for Research Questions 1 and 2

Data management for both Research Questions 1 and 2 are detailed in this section.

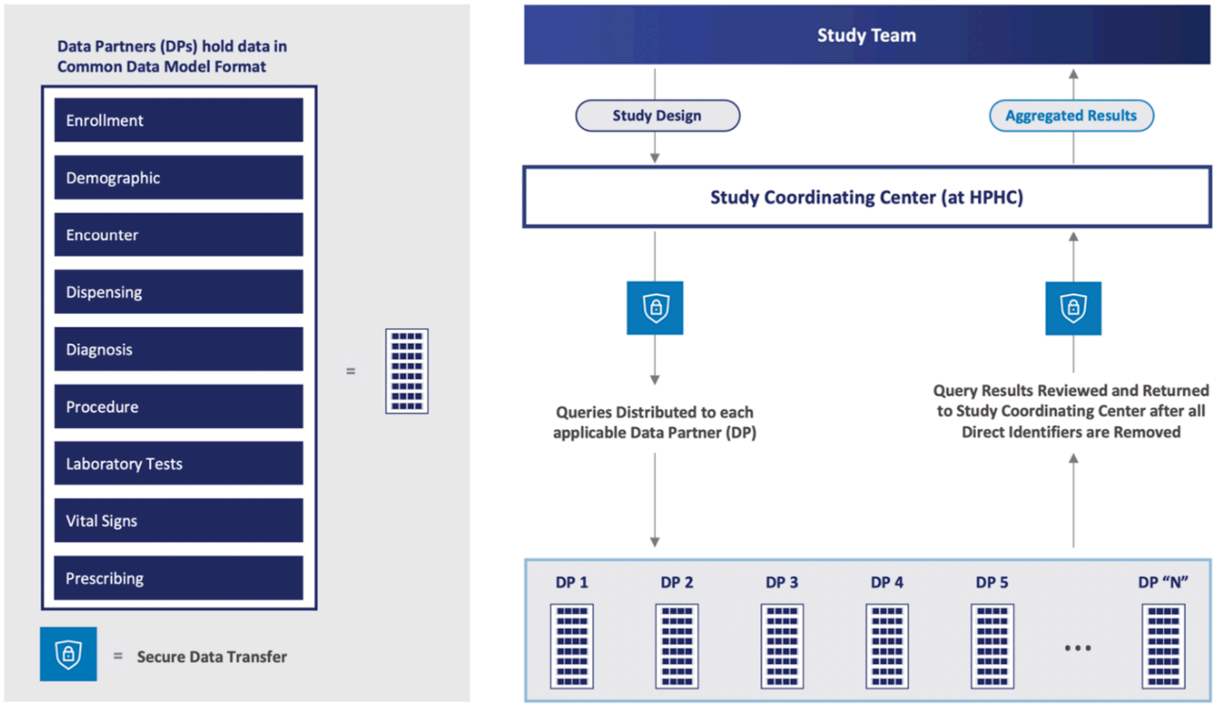
HPHCI, located in Boston, Massachusetts, will serve as the coordinating center for all activities and objectives in the study. For all objectives except perhaps the medical record review objective in Research Question 1, HPHCI staff or contractors will be responsible for writing and distributing SAS-based programs to participating RPs. The distributed network developed for the Sentinel System will be leveraged wherever possible. In all aspects of the project, RPs will 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 national health plans that will participate in the study, as well as some of the IDS partners, will have data in the SCDM. One of the IDS partners participating in the medical record review objective may not have their data in the SCDM.

The RPs will establish and maintain the administrative, hardware, and software capabilities and capacity to respond to data requests in a timely manner. RPs will also provide data science support with epidemiologic review.

The general analytic workflow is depicted in Figure 3, below. For all objectives except the medical record review in Research Question 1, HPHCI will submit a computer program designed to meet the needs of the study to each participating RP via a secure portal. Next, the participating RPs will receive and run the computer program behind their firewalls, using data formatted to the SCDM. Then, the RPs will review the analysis results and return them to the study coordinating center through a secure portal. The study coordinating center will review and aggregate the results across the RPs. As a final step, the aggregated results will then be transferred to the study team, including the study sponsor.

Figure 3. General analytic workflow



If the medical record review objective in Research Question 1 does not use the distributed approach, a "common protocol" approach will be taken where HPHCI provides the RP(s) with detailed specifications to identify the cohort of interest and generate the aggregated data necessary for analysis.

9.2.6.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As the analyses will be based on secondary data, the only data collection tool (DCT) that may be applicable will be data abstraction forms that will be developed for the purpose of validation / adjudication and review of select outcomes. Details of how data will be handled will be described in a validation plan that will be developed prior to implementing validation.

As used in this protocol, the term DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A DCT is required and should be completed for each included individual. The completed original DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the DCTs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator (HPHCI or RPs) has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCTs must be signed by the investigator or by an authorized staff member to attest that the data contained on the DCTs are true. Any corrections to entries made in the DCTs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the DCTs must match those charts.

In some cases, the DCT may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the DCT, and for which the DCT will stand as the source document.

9.2.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator (HPHCI as the coordinating center, or RPs who are retaining their own study records) agrees to keep records, including the identity of all participating individuals (sufficient information to link records, e.g., DCTs and hospital records), copies of all DCTs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by investigator according to local regulations or as specified in the research agreement, whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. For RPs that will be retaining study records, no records will be transferred to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless HPHCI, the RPs, and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.2.7. Data Analysis for Research Question 2

Detailed methodology for statistical analyses of data collected in this study will be documented in the SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

When appropriate, publicly available Sentinel analytic tools will be used for the analyses; these are the same tools used by FDA for similar analyses of distributed databases. Modifications to the tools may be needed to meet study objectives, in which case the SAS programming data QA Standard Operating Procedures will be followed (see Section 9.2.8).

9.2.7.1. Data Analysis for RCA

Each RCA round, the historical comparator RCA and concurrent RCA will be completed twice: once using a 1-21 day risk window and 43-84 day control and again using a 1-42 day risk window and 43-84 day control. Once an RCA has reached a stopping boundary, sequential monitoring may continue but hypothesis testing will be completed. If there is a statistically significant positive association between risk of GBS and ABRYSVO vaccination, an SCRI analysis will be conducted as refinement of this finding (described throughout Section 9).

9.2.7.1.1. Descriptive Analysis

In each RCA study, descriptive analysis of characteristics of eligible ABRYSVO vaccinees and comparators will be performed. Counts of GBS cases will be reported during post-vaccination follow-up.

9.2.7.1.2. Sequential Statistical Analysis for Historical Comparator RCA

Background incidence estimates of GBS will be calculated within strata of both RP and pre-defined covariates to control for confounding. Observed ABRYSVO-exposed GBS case counts will be compared against expected GBS case counts using sequential hypothesis testing. The conditional PmaxSPRT will be utilized to generate the test statistic (i.e., a log-likelihood ratio), which will be measured against a critical value.[44] The critical value is dynamic over the course of the analysis as data accrue. Log-likelihood ratios are analogous to relative risks but on a different scale. They are calculated as point estimates without confidence intervals to determine presence or absence of a statistically significant finding. Adjustment for secular trends in GBS in the historical comparator group will be conducted, if secular trends are observed. Adjusted thresholds have been used in prior vaccine safety monitoring studies to prevent a statistically significant finding due to an artifact of secular trends, independent of the exposure of interest.[52]

9.2.7.1.3. Sequential Statistical Analysis for Concurrent Comparator RCA

Because the historical comparator group could be subject to secular trends in GBS, a concurrent comparator RCA will also be performed among ABRYSVO-vaccinated individuals. Using a pre-defined risk and control interval following ABRYSVO vaccination, and a time-based stratification approach, the risk of GBS will be evaluated based on the proportion of vaccinated individuals that are in the risk window at the time of the GBS event. More specifically, for each calendar day, the numerator is calculated as the number of ABRYSVO vaccinees in a specific stratum (e.g., age group, sex, RP) who were in the risk interval on that day, and the denominator is calculated as the number of ABRYSVO vaccinees in the same stratum who were in either the risk or control window on that calendar day. This proportion determines the expected number of GBS events in the risk window which is compared to the observed number of GBS cases in the risk window on that day. This calculation is performed for all GBS cases. A GBS case is only informative if there are vaccinees in both windows (e.g., positivity assumption). A binomial variant of the maxSPRT will be used to analyze the data. An additional advantage of this approach is that it does not need to restrict to a study population who meets the algorithm for increased risk of RSV-LRTD because these ABRYSVO-vaccinated individuals will be presumed to meet the indication. The stratification for calendar time also eliminates any seasonal variation that may be of concern.

9.2.7.2. Data Analysis for SCRI

9.2.7.2.1. Descriptive Analysis

In the SCRI study, descriptive analysis of characteristics of eligible ABRYSVO-exposed individuals will be performed.

9.2.7.2.2. Primary Data Analyses

A case-centered logistic regression approach will be used to analyze the data in this SCRI study.[53] Incidence rate ratios with 95% confidence intervals (to estimate relative risk) and attributable risk with 95% confidence intervals per 100,000 doses and 100,000 person-years (to estimate absolute risk) will be calculated.

If the SCRI study is conducted after 3 RCAs (4 seasons) in the absence of a statistically significant finding of higher risk of GBS associated with ABRYSVO vaccination from an RCA, the study will employ PPV-adjustment of the claims-identified GBS cases using the PPVs produced in Research Question 1.[51] If the SCRI study commences due to a statistically significant positive association between risk of GBS and ABRYSVO vaccination in an RCA, the GBS cases identified in claims will be confirmed via medical record review, where medical records could be retrieved. For GBS cases confirmed via medical record review, the date of GBS onset will be determined based on the clinician adjudicator, and the claims-based GBS date will not be used. GBS cases where medical records could not be retrieved will be adjusted based on the PPV of the GBS algorithm. For example, if medical records cannot be retrieved for 10 GBS cases and the PPV for the GBS algorithm is 80%, this will be readjusted to 8 GBS cases. A sensitivity analysis will restrict to chart-confirmed GBS cases.

9.2.7.2.3. Secondary Data Analyses

The following secondary analyses will be conducted for the SCRI:

1. A secondary risk window of 1-21 days and secondary control window of 43-84 days will be utilized in a secondary analysis.

2. Although the primary study population will not be required to meet the algorithm definition for increased risk of RSV-LRTD, a secondary analysis will restrict to the population who meet the algorithm definition (Table 3).

3. A secondary analysis will restrict to chart-confirmed GBS cases.

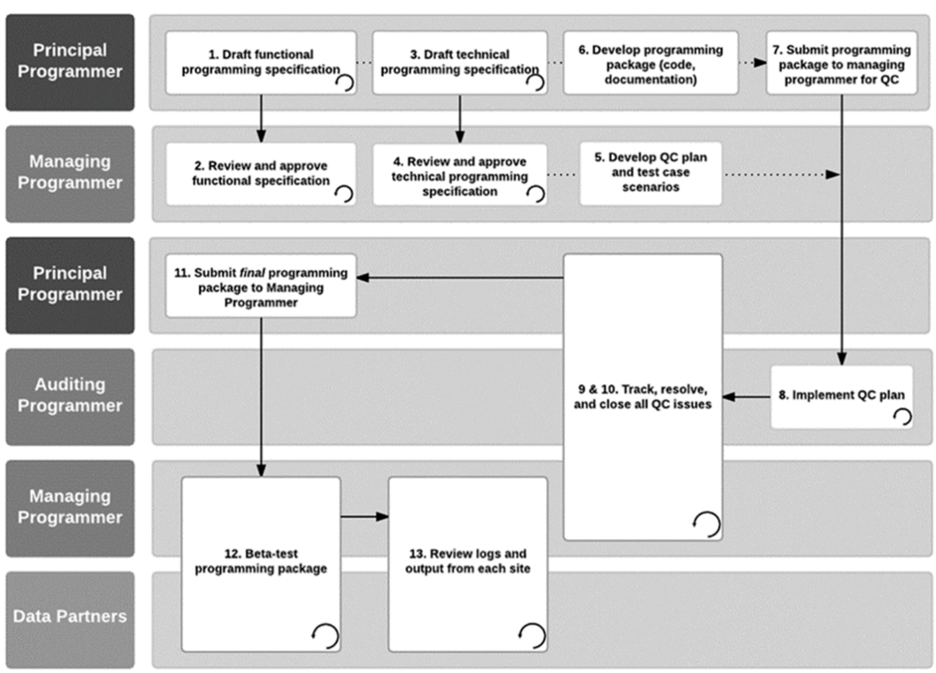
4. A secondary analysis that assumes different PPVs in the control and risk windows will be conducted, to be detailed in the SAP.

9.2.8. Quality Control

For all of analyses except perhaps the medical record review objective in Research Question 1, the RPs that will participate in the study are also participants in the US FDA's Sentinel System and curated, quality checked datasets, in the SCDM will be used. These datasets will follow the same data QA procedures as the Sentinel System. The Sentinel QA 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 data RPs. Full QA processes and details on the Sentinel database curation approach are documented on the Sentinel website.[54,55] The data curation approach is consistent with guidance set forth by the US FDA in its current recommendations for data QA, Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data, Section IV.E Best Practices – Data Sources: Quality Assurance (QA) and Quality Control (QC), published in May 2013.[55,56] This Guidance describes best practices that particularly apply to observational studies designed to assess the risk associated with a drug exposure using electronic healthcare data.

HPHCI adopts standard SAS programming QA and QC processes used by the Sentinel System to check SAS programs and deliverables. Figure 4 illustrates the standard operating procedures for SAS programming QA and QC in the Sentinel System. This approach will be applied to all objectives except the medical record review.

Figure 4. Standard operating procedure for SAS programming quality assurance and quality control in the Sentinel System



To ensure high quality collection from the medical record review objective in Research Question 1, HPHCI will work closely with Pfizer and the RPs to develop data abstraction and adjudication forms, an appropriate database (e.g., REDCap) to capture the medical record review results, and a detailed medical record review plan. HPHCI will also develop standardized procedures for the medical record review that provide step-by-step guidance for the RPs, abstractors, and clinician adjudicators.

9.2.9. Limitations of the Research Methods for Research Question 2

An important limitation of these safety studies is that the rarity of GBS will make it challenging to quickly and robustly assess risk after ABRYSVO vaccination. Our ability to assess the risk of GBS after ABRYSVO vaccination will also depend on uptake of ABRYSVO. To mitigate these potential limitations, both the RCA and SCRI analyses will aggregate data from multiple large RPs.

Other limitations of these safety studies are related to the nature of administrative claims data and are not specific to the data sources included in this project. There is the potential for incomplete data for assessment, including misclassification of study variables due to billing and coding practices. Specifically, some elements that place an individual at increased risk of RSV-LRTD may not be medically attended and, thus, not in captured in claims data. To address this potential misclassification of the variable for increased risk of LRTD-RSV, which is an eligibility criterion for the historical comparator RCA, a concurrent comparator RCA will be conducted that does not require this restriction because it will be conducted among ABRYSVO vaccinees only. Further, there exists a potential for misclassification of GBS, even when utilizing validated algorithms. Hence, analyses will either adjust for this misclassification using the algorithm PPV or confirm GBS cases via medical record review. Vaccination status may be under-captured as participating national health plans do not have complete linkage with IIS sources and some IIS data may not be permissible to use for this project due to governance rules within the health plans. IIS vaccination data, which captures vaccinations in a given catchment area regardless of whether it generated a claim, will be leveraged when possible.

Limitations specific to the RCA include that a statistically significant signal does not necessarily imply a causal relationship between the exposure and the outcome. Also, historical comparators are vulnerable to secular trends in the outcome, which may result in uncertainty in the expected incidence proportions. To account for these limitations, an RCA with a concurrent comparator will also be conducted, and any statistically significant findings that arise in RCA will be followed up with a SCRI study to further refine and evaluate the potential signal.

Lastly, the study is restricted to commercially insured individuals, which may be different from the publicly insured and uninsured populations.

9.2.10. Other Aspects for Research Question 2

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

This study involves use of existing structured data and will include human review of unstructured data for the subset of patient charts that may be reviewed for validation purposes. Each data RP will obtain appropriate reviews and determinations from respective institutional review boards (IRBs) according to its site requirements or cede authority to HPHCI's IRB, if possible.

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

All data analyzed for this study, with the exception of review of medical records for chart validation, will exist as structured data.

10.1.1. Structured Data Analysis

The GBS epidemiology and incidence portion of Research Question 1 and safety analyses in Research Question 2 involve data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.1.2. Human Review of Unstructured Data: Chart Validation

During medical record review / chart validation in Research Question 1 and chart review activities in Research Question 2, RPs will remove and redact all direct patient identifiers as delineated in the Privacy Rule of HIPAA. A limited data set of PHI—including for example date of birth, date of vaccination, date of death, visit date, and diagnosis date—may be collected.

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

HPHCI will maintain a secure web-based portal to enable secure data transfer and document storage. An identification number will be used in place of direct patient identifiers to minimize risk. Patients' personal data will be stored at the individual data RP or at HPHCI in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. No individual patient data will be sent to Pfizer, unless related to AE reporting described in Section 12. Each data RP and HPHCI will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, each data RP and HPHCI shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural individuals with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, data RP results will be aggregated. For the RPs who have agreed to sharing their individual-level data with HPHCI and Pfizer, only individual patient data that is related to AE reporting described in Section 12 will be transferred to Pfizer. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the research agreement and applicable privacy laws.

For the RPs that will not share individual level data including any PHI data, the above agreement is not applicable and no data will be transferred to HPHCI, Pfizer, or other RPs.

10.2. Patient Consent

10.2.1. Structured Data Analysis

The GBS epidemiology and incidence portion of Research Question 1 and safety analyses in Research Question 2 involve deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.2.2. Human Review of Unstructured Data: Chart Validation

As the medical record review / chart validation component of this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

The Coordinating Center for the current study, HPHCI, has the responsibility to obtain approval of the study protocol, protocol amendments, and other relevant documents, if applicable, from an IRB/EC. Participating RPs can either cede IRB review to HPHCI or seek approval from their local IRB. All correspondence with the IRB/EC will be retained in the study files by HPHCI.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in:

- Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE)[57]
- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-ISPE Special Task Force on real-world evidence in health care decision making[58]
- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS)[59]
- EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology[60]
- FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment[56]
- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data[61]
- International Ethical Guidelines for Health-related Research Involving Humans issued by the CIOMS in collaboration with the World Health Organization (WHO)[62]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Structured Data Analysis

Research Questions 1 and 2 involve data that exist as structured data by the time of study start. In these data sources it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11.2. Human Review of Unstructured Data: Chart Validation

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the NIS AE monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the chart abstraction form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least 1 patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for “Illness,” “Study Drug,” and “DrugName” may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- "Your Reporting Responsibilities (YRR) with Supplemental Topics".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training statements must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current YRR with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within 60 calendar days of issuance by Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of analysis and interpretation will be delivered in the form of reports, as outlined in Section 6, Milestones. A manuscript reporting the results from the final safety analyses (RCA and SCRI, if applicable) may be submitted to a relevant peer-reviewed journal. Study results, including interim results, may be disseminated at scientific conferences and a manuscript(s) for the non-safety analyses may be submitted to a peer reviewed journal for publication. Additionally, the final report will be posted to the EU PAS Register.

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors.[63] When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed.[64]

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Epidemiology of Guillain-Barré Syndrome and Risk Associated with Exposure to ABRYSVO™ Among Vaccinees 18-59 Years of Age in the United States

EU PAS Register® number: N/A **Study reference number (if applicable):** C3671072

<u>Section 1: Milestones</u>	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for 1.1.1 Start of data collection[1]	☒	☐	☐	6

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

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8, 9.1.2, 9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1.1, 9.2.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1.2, 9.2.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1.1, 9.1.7, 9.2.1, 9.2.7
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))	☒	☐	☐	9.1.1, 9.1.7, 9.2.1, 9.2.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

[2] Date from which the analytical dataset is completely available.

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.1.2, 9.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1.1, 9.2.1
	4.2.2 Age and sex	☒	☐	☐	9.1.2, 9.2.2
	4.2.3 Country of origin	☒	☐	☐	9.1.2, 9.2.2
	4.2.4 Disease/indication	☐	☐	☒	
	4.2.5 Duration of follow-up	☒	☐	☐	9.1.2, 9.2.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1.2, 9.2.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.1.3, 9.2.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.1.1, 9.1.3, 9.1.7 9.2.1, 9.2.3, 9.2.7
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.1.2, 9.2.2
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.1, 9.2.2

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.3, 9.2.3
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1.3, 9.2.3
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.1.2, 9.2.3

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.1.3, 9.1.7, 9.2.3, 9.2.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.1.2, 9.2.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.1.1, 9.1.3, 9.1.7, 9.2.1, 9.2.3, 9.2.7

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)	☒	☐	☐	9.1.3, 9.1.7, 9.2.3, 9.2.7

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.1.3, 9.2.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.1.3, 9.2.3
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.1.3, 9.2.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.1.3, 9.2.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.1.3, 9.2.3

Section 9: Data sources		Yes	No	N/A	Section Number
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.1.3, 9.2.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.1.3, 9.2.3
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.1.3, 9.2.3
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.1.3, 9.2.3
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?	☒	☐	☐	9.1.7, 9.2.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.1.7, 9.2.7
10.3	Are descriptive analyses included?	☒	☐	☐	9.1.7, 9.2.7
10.4	Are stratified analyses included?	☒	☐	☐	9.1.7, 9.2.7
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.1.7, 9.2.7
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.1.7, 9.2.7
10.7	Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	9.1.7, 9.2.7

Comments:

Section 11: Data management and quality control		Yes	No	N/A	Section Number
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.1.6, 9.2.6
11.2	Are methods of quality assurance described?	☒	☐	☐	9.1.8, 9.2.8
11.3	Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations		Yes	No	N/A	Section Number
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☒	☐	☐	9.1.9, 9.2.9
	12.1.2 Information bias?	☒	☐	☐	9.1.7, 9.1.9, 9.2.7, 9.2.9
	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).	☒	☐	☐	9.1.1, 9.1.9, 9.2.1, 9.2.9
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)	☒	☐	☐	9.1.1, 9.2.1

Comments:

Section 13: Ethical/data protection issues		Yes	No	N/A	Section Number
13.1	Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4
13.2	Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3	Have data protection requirements been described?	☒	☐	☐	10

Comments:

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

Comments:

Section 15: Plans for communication of study results		Yes	No	N/A	Section Number
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Saranya Nair

Date: 24/April/2025

Signature:

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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