NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A post-authorisation safety study of ABRYSVO in immunocompromised, or renally or hepatically impaired adults aged 60 years and older in a real world setting in Europe and UK
Protocol number	C3671038
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EU Post Authorisation Study (PAS) register number	To be registered before the start of data collection
Active substance	Respiratory syncytial virus vaccine (bivalent, recombinant) J07BX05
Medicinal product	ABRYSVO
Product reference	EU/1/23/1752/001-007 PLGB 00057/1722
Procedure number	EMEA/H/C/006027
Marketing Authorisation Holder(s)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom

Joint PASS	No
Research question and objectives	The research question is: What is the incidence of safety events of interest among immunocompromised, or renally or hepatically impaired adults aged 60 years and older who receive ABRYSVO compared to a relevant comparator group who does not receive ABRYSVO? *Primary Study Objective* The primary study objective is to estimate the incidence rates and rate ratios of safety events of interest in immunocompromised or renally or hepatically impaired adults aged 60 years and older who receive ABRYSVO compared to a relevant comparator group who does not receive ABRYSVO (evaluated as separate populations and, if appropriate, as a combined population).
Country(ies) of study	United Kingdom, Spain, France
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABUCASIS	Ambulatory Medical Record
ACCESS	The vACCine covid-19 monitoring readinESS
AE	adverse event
AED	Accident and Emergency Department
AESI	adverse events of special interest
AIDS	Acquired Immunodeficiency Syndrome
ARI	acute respiratory infection
ATC	anatomical therapeutic chemical
ATT	average treatment effect in the treated
BIGAN	Big Data project of the Department of Health of the Government of Aragon
BLA	Biologics License Application
BMI	body mass index
BPE	The Bordeaux PharmacoEpi platform
CAR	chimeric antigen receptor
CCI	Charlson Comorbidity Index
CDM	common data model
CEICA	Clinical Research Ethics Committee of Aragon
CFR	case fatality rate
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CIP	code identifiant de présentation
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMU-C	Couverture Maladie Universelle Complémentaire
CNAM	The French National Health Insurance Fund (Caisse nationale de l'Assurance Maladie)
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
DAP	data access provider
DRE	Digital Research Environment
DSRU	Drug Safety Research Unit
DTP	Diphtheria, tetanus, and pertussis
DVT	deep vein thrombosis
EC	Ethics Committee
ECAP	Electronic health records in primary health care [PHC] of Catalan Health Institute
eFI	electronic frailty index
eGFR	Estimated glomerular filtration rate
EEA	The European Economic Area
EHR	electronic health record

Abbreviation	Definition
EMA	European Medicines Agency
EMIS	Egton Medical Information Systems
EPhMRA	European Pharmaceutical Market Research Association
EpiChron	The Epidemiology of Chronic Diseases and Multimorbidity
ES	Spain
ETL	extract, transform, load
EU	European Union
FAIR	Findable, accessible, interoperable, and re-usable
FDA	Food and Drug Administration
FISABIO	Foundation for the Promotion of Health and Biomedical Research in the Valencian Community
FR	France
GAIA	Gram-based Interaction Analysis
GBS	Guillain-Barré syndrome
GDPR	General Data Protection Regulation
GP	general practitioners
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good pharmacovigilance practices
HAV	hepatitis A virus
HBV	hepatitis B virus
HES	Hospital Episode Statistics
Hib	Haemophilus influenzae type b
HIV	human immunodeficiency virus
HMA	Heads of Medicines Agencies
HPV	human papillomavirus
HZ	herpes-zoster virus
IBD	irritable bowel disease
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10	International Classification of Diseases, Tenth Revision
ICD-10-ES	International Classification of Diseases, 10th Revision, Spanish Edition
ICMJE	International Committee of Medical Journal Editors
ICPC	International Classification of Primary Care
IDIAPJGol	Institut Universitari d'Investigació en Atenció Primària
IMI-ConcePTION	Innovative Medicines Initiative - Building an ecosystem for better monitoring and communicating safety of medicines use in pregnancy and breastfeeding
INR	International Normalized Ratio
IPCW	inverse probability of censoring weights
IRB	Institutional Review Board
ISO	International Organization for Standardization
IRR	incidence rate ratio

Abbreviation	Definition
ISPE	International Society for Pharmacoepidemiology
LRTD	lower respiratory tract disease
KDIGO	Kidney Disease: Improving Global Outcomes
MBDS	Minimum Basic Data Set at Hospital Discharge
MELD	model for end-stage liver disease
MenACWY	N meningitidis serogroups A, C, W, and Y
MMR	Measles, mumps and rubella
NHS	National Health Service
NI	non-interventional
OR	odds ratio
ORION	Hospital Medical Record
PASS	post-authorisation safety study
PHC	primary health care
PI	Principle Investigator
PMSI	Programme National de Médicalisation des Systèmes d'Information
PS	propensity score
QC	quality check
RENOIR	RSV vaccine Efficacy study iN Older adults Immunized against RSV disease
RMP	risk management plan
RSV	respiratory syncytial virus
RWD	real-world data
SAP	statistical analysis plan
SCR	serum creatinine concentration
SCRI	self-controlled risk interval
SD	standard deviation
SIA	Ambulatory Information System
SIDIAP	Information System for the Development of Research in Primary Care
SLE	systemic lupus erythematosus
SNDS	Système National des Données de Santé
SNIIRAM	Système National d'Informations Inter-Régimes de l'Assurance Maladie
SNOMED	Systematized Nomenclature of Medicine Clinical Terms
SOP	standard operating procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNF	tumor necrosis factor
TPV	Polio
UACR	urine albumin-to-creatinine ratio
UK	United Kingdom
UMCU	University Medical Center Utrecht
VAC4EU	Vaccine monitoring Collaboration for Europe

Abbreviation	Definition
VID	Valencia Health System Integrated Database
VZV	varicella zoster virus
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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Note: Country Coordinating Investigators have reviewed and contributed to this protocol.

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4. ABSTRACT

Title: A post-authorisation safety study of ABRYSVO in immunocompromised, or renally or hepatically impaired adults aged 60 years and older in a real world setting in Europe and UK

Version: 2.0

Date: 07 October 2024

Main authors: Cynthia de Luise; Fariba Ahmadizar; Laure Carcaillon-Bentata; Jérémy Jové; Mei Duh; Marianne Cunnington

Rationale and background

On 23 August 2023, PF-06928316 (hereafter ABRYSVO) was approved by the European Commission for active immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV), a major cause of respiratory illness in older adults. This marketing authorization is valid in all 27 European Union (EU) member states plus Iceland, Liechtenstein, and Norway. On 31 May 2023, the Food and Drug Administration (FDA) approved ABRYSVO for active immunization for the prevention of LRTD caused by RSV in individuals 60 years of age and older.

The EU marketing authorization for ABRYSVO in older adults is based on evidence from the pivotal Phase 3 clinical trial, RENOIR (C3671013, NCT05035212) which evaluated the efficacy, immunogenicity, and safety of a single 120 μg dose of PF-06928316 or prefusion F vaccine in adults 60 years or older.

As immunocompromised, renally and hepatically impaired older adults were not included in clinical trials that supported regulatory approvals, the safety profile of ABRYSVO in these populations is unknown.

This protocol describes a post-authorization safety study (PASS) to assess the safety of ABRYSVO in immunocompromised, or renally or hepatically impaired adults aged 60 and older in select European countries and in the UK, with data sources that can capture vaccine exposure in the target populations, and where outcomes and key covariates can be ascertained. This study is an additional pharmacovigilance activity (Category 3 study) in the approved EU risk management plan (RMP) for ABRYSVO.

Research question and objectives

The research question is: What is the incidence of safety events of interest among immunocompromised, or renally or hepatically impaired adults aged 60 years and older who receive ABRYSVO compared to a relevant comparator group who does not receive ABRYSVO?

The primary study objective is:

To estimate the incidence rates and rate ratios of safety events of interest in immunocompromised, or renally or hepatically impaired adults aged 60 years and older who

receive ABRYSVO compared to a relevant comparator group who does not receive ABRYSVO (evaluated as separate populations and if appropriate, as a combined population).

Study design

This is a retrospective, comparative cohort study using data access providers of the Vaccine Monitoring Collaboration for Europe (VAC4EU) that meet fit-for-purpose criteria. If appropriate, based on the outcome of interest, the study will also use a self-controlled risk interval (SCRI) design.

Population

The target population will consist of individuals who are immunocompromised, or renally or hepatically impaired (evaluated as separate populations and if appropriate, as a combined population) who are at least 60 years of age on the date of vaccination (i.e, index date for the vaccinated cohort) or on the matched index date (for the unvaccinated cohort), and who have at least 12 months of medical history in one of the data sources with no record of RSV vaccination in that 12 month period and who have at least one day of post-index follow up. Immunocompromised or renally impaired or hepatically impaired status will be ascertained via coded diagnoses, treatments, procedures, and/or laboratory values, as appropriate, at index date or in the 12-month baseline period prior to the index date.

Variables

The exposure of interest is ABRYSVO vaccination, which will be obtained from pharmacy dispensing records, general practice records, immunization registers, vaccination records, medical records, or other secondary data sources. Outcomes will be identified in participating databases with algorithms based on codes for diagnoses, procedures, and treatments. Standard algorithms for each outcome definition will be applied to participant data sources, based on the results of the ACCESS project, and will be tailored to the data source. Potential covariates may include the following information, as available in each data source: demographics; personal lifestyle characteristics; and clinical characteristics including comorbidities, comedication use, healthcare utilisation descriptors, other vaccinations, and surrogates of frailty. Covariates will be identified on the index date (or during the 12-month baseline period prior to the index date). These variables will be used to further characterize the patient populations of interest and/or to control for confounding.

Data sources

The study will utilise data from the following selected data sources: Clinical Practice Research Datalink (CPRD) Aurum (UK), Valencia Health System Integrated Database (VID) (ES), Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (SIDIAP) [Information System for the Improvement of Research in Primary Care] (ES), EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute (EpiChron) (ES), and Système National des Données de Santé (SNDS)[French nationwide healthcare database] (FR).

Study size

All individuals who meet the eligibility criteria during the study period in the select data sources will be included. The sample size will depend on the number of individuals administered ABRYSVO identified within the data sources during the study period, which will increase over time. The relative increases in rates to be detected will vary across outcomes of interest. For example, analyses using a comparative cohort design will have sufficient power (80%) to detect a 2-fold and 3-fold increased rate of arrhythmia associated with ABRYSVO, with a sample size of 1,178 and 393 individuals per cohort, respectively, assuming a baseline rate of 2,000 arrhythmia events per 100,000 person-years and equal numbers of individuals in the vaccinated and unvaccinated cohorts.

Data analysis

Baseline demographics and clinical characteristics for ABRYSVO vaccinated and unvaccinated individuals will be summarized using descriptive statistics. Descriptive statistics will also be used to summarize ABRYSVO uptake characteristics. Incidence rates per 1,000 patient years (and corresponding 95% CIs) will be calculated for all outcomes of interest in the ARBYSVO vaccinated and unvaccinated cohorts separately.

For the comparative cohort design, outcome specific incidence rates in the ABRYSVO vaccinated cohort will be compared to incidence rates in the unvaccinated cohort. Average treatment effect for the treated (ATT) weighting based on the propensity scores (PS) will be used to ensure baseline comparability between the vaccinated and unvaccinated cohorts. Stabilized inverse probability of censoring weighting (IPCW) will also be used if informative censoring between the cohorts is observed. After weighting, the distribution of baseline characteristics will be evaluated between the vaccinated cohort and the unvaccinated cohort, and variables that are inadequately balanced (standardized difference >10%) between the two cohorts will be included as regression model covariates in a doubly robust approach. Weighted Poisson regression models will be conducted, and incidence rate ratios and corresponding 95% confidence intervals (CIs) will be summarized.

For the SCRI design, the study population will include individuals who have received ABRYSVO, and experienced the specific outcomes of interest during the post-vaccination risk or control interval. Individuals who experienced a prespecified outcome following ABRYSVO vaccination serve as their own control by comparing the incidence of the outcome in the post-vaccination risk interval to the incidence of the outcome in a post-vaccination control interval using a conditional Poisson regression model. From this model, incidence rate ratios and 95% CIs will be reported.

Meta-analysis: Using the main estimates from each data source, appropriate random-effects meta-analytic methods may be used to obtain a combined effect estimate within each population of interest for both the comparative cohort and SCRI design analyses.

Milestones

- Protocol submission: on or before 31 March 2024

- Progress report: 30 September 2025 (or 12 months after protocol endorsement by EMA)
- Interim report 1: 30 September 2026 (or 24 months after protocol endorsement by EMA)
- Final study report: 28 September 2029

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	07 October 2024	Administrative	Section 4 Abstract	The study title in the abstract section has been updated to align with the wording on the study title page	Ensure consistent reference to the study title
2.0	07 October 2024	Substantial	Section 9.3.2 Outcome Definitions Section 9.7.4 Sensitivity Analyses	Section 9.3.2: Additional sensitivity analyses have been added for Guillain Barre syndrome, acute disseminated encephalomyelitis, and transverse myelitis to align with the risk intervals described within the ongoing study C3671031 Section 9.3.2: Atrial fibrillation and supraventricular arrhythmias have been added as a specific subgroup of interest within the overall arrhythmias group to allow consistency with the ongoing study C3671037. Additional sensitivity analyses for these outcomes have been added capturing risk intervals for those subgroups that align with study C3671037 Section 9.7.4 The details described above (for Section 9.3.2) have been added as sensitivity analyses Examples of negative control outcomes have been added to further emphasize this planned sensitivity analysis to assess residual confounding	To ensure consistency across ongoing ABRYSVO safety studies and to emphasize plans for the assessment of residual bias through robust sensitivity analyses

6. MILESTONES

Milestone	Planned Date[1]
Registration in the HMA-EMA Catalogue of RWD studies	Prior to start of data collection
Start of data collection[2, 3]	31 March 2025
Progress report[4]	30 September 2025
Interim report 1[5]	30 September 2026
End of data collection[6]	31 October 2028
Final study report	28 September 2029

1. Schedule is dependent on protocol endorsement date, uptake of ABRYSVO, approvals for data extraction and contracts with data access providers (DAPs). Some data extraction approvals may require a final or endorsed protocol.
2. Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts. Simple counts are not part of this definition.
3. Protocol endorsement is anticipated in Quarter 3, 2024. Start of data collection allows for 6 months after protocol endorsement to gain data access approvals. Deliverable dates will be updated once protocol endorsement date is known.
4. Progress report is anticipated 12 months after protocol endorsement.
5. Interim report is anticipated 24 months after protocol endorsement.
6. End of data collection is "the date from which the analytical data set is completely available".

7. RATIONALE AND BACKGROUND

RSV is a major cause of respiratory illness in both infants and older adults.[1] Older adults are at higher risk of RSV illness and have a greater risk of hospitalisation and mortality with RSV compared with younger adults.[2-10] Each year in Europe, it is estimated that RSV causes more than 270,000 hospitalisations and about 20,000 deaths in individuals 60 years and older.[11]

RSV illness commonly occurs in individuals with existing comorbidities, which are exacerbated due to RSV exposure.[10, 12-14] According to a study across 28 EU countries, RSV infection among older adults, especially those with underlying health conditions, is a significant contributor to acute respiratory infection (ARI) related hospitalisation.[15] Older adults with compromised immune systems, or pre-existing conditions such as kidney disorders, liver disorders, diabetes, heart disease, and lung disease, face the highest risk of contracting severe RSV infection, and therefore, are most likely to benefit from vaccination.[16, 17] RSV has been recognized as a significant cause of severe illness in immunocompromised populations, including hematopoietic stem cell transplantation recipients, patients undergoing intensive chemotherapy, and lung transplant patients.[1]

Immunocompromised individuals, who are susceptible to severe, persistent RSV infections, are known to have the highest morbidity and mortality from RSV.[12-14, 18] Other older adult patient populations at high risk of both infection and severe RSV illness include those who with renal or hepatic impairment.[19]

On 23 August 2023, PF-06928316 (ABRYSVO) was approved by the European Commission for active immunisation of adults 60 years of age and older for the prevention of LRTD

caused by RSV. On 31 May 2023, the FDA approved ABRYSVO for active immunization for the prevention of LRTD caused by RSV in adults 60 years of age and older.

The EU marketing authorization for ABRYSVO in older adults is based on evidence from the pivotal Phase 3 clinical trial, RENOIR (C3671013, NCT05035212) which evaluated the efficacy, immunogenicity, and safety of a single 120 µg dose of PF-06928316 in adults 60 years or older.[20, 21] As immunocompromised, renally and hepatically impaired older adults were not included in clinical trials that supported regulatory approvals, the safety profile of ABRYSVO in these populations is unknown.

This protocol describes a PASS to assess the safety of ABRYSVO in immunocompromised, or renally or hepatically impaired adults aged 60 and older in select European countries and in the UK, with data sources that can capture vaccine exposure in the target populations, and where outcomes and key covariates can be ascertained. This study is an additional pharmacovigilance activity (Category 3 study) in the approved EU RMP for ABRYSVO.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question

The research question is: What is the incidence of safety events of interest among immunocompromised or renally or hepatically impaired adults aged 60 years and older who receive ABRYSVO compared to a relevant comparator group who does not receive ABRYSVO?

8.2. Objectives

Primary Study Objective

To estimate the incidence rates and rate ratios of safety events of interest in immunocompromised or renally or hepatically impaired adults aged 60 years and older who receive ABRYSVO compared to a relevant comparator group who does not receive ABRYSVO (evaluated as separate populations and if appropriate, as a combined population).

9. RESEARCH METHODS

9.1. Study Design

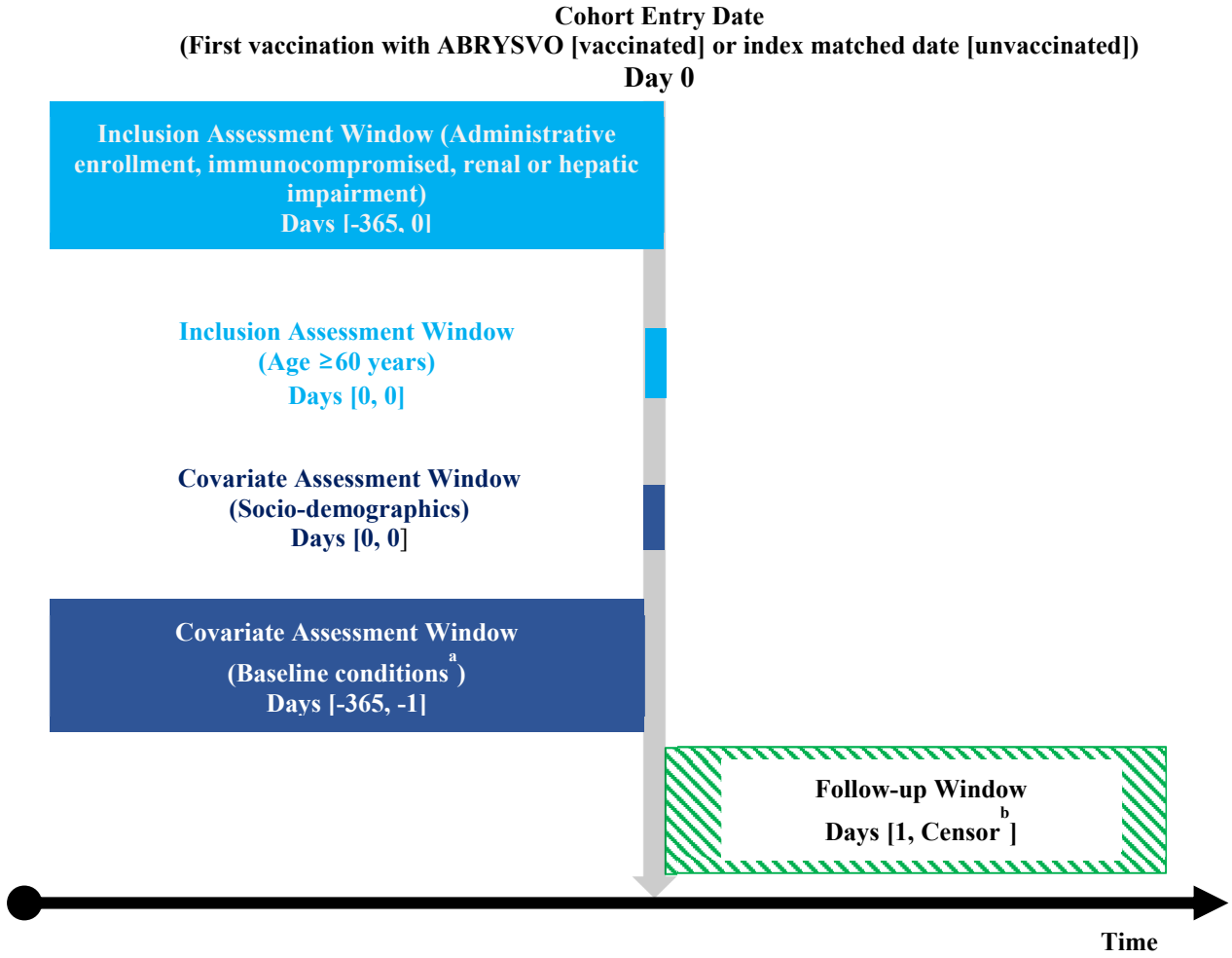
A retrospective comparative cohort design will serve as the primary study design. It will compare the incidence rate of outcomes of interest among those who received ABRYSVO to the incidence rate in a random sample of unvaccinated older adults from the same underlying population of interest (i.e, immunocompromised, renally impaired, or hepatically impaired, evaluated as separate populations and if appropriate, as a combined population). The index date for the vaccinated individuals will be defined as the date of administration of ABRYSVO. The unvaccinated cohort will be assigned an index date matched to a corresponding index date in the vaccinated cohort based on calendar time. Due to potential limitations in sample size, matching on additional variables will not be conducted. Instead, (PS) methods incorporating a greater number of covariates will be considered to create weight-adjusted vaccinated/unvaccinated cohorts.

In addition to the primary study design (i.e, comparative cohort design), for an appropriate subset of the study outcomes (see Table 1), the SCRI design will also be used. Among individuals vaccinated with ABRYSVO and experiencing a subset of outcomes, the incidence during a post-vaccination risk interval will be compared to the incidence in a post-vaccination control interval. The within-person SCRI design considers only vaccinated individuals with the specific outcome of interest and inherently controls for time-invariant confounders (such as sex, race, chronic illness, and health state). The risk and control intervals are based on a review of the published literature and precedence from previous studies of vaccine safety (see Table 1).

9.1.1. Primary Design - Comparative Cohort Design

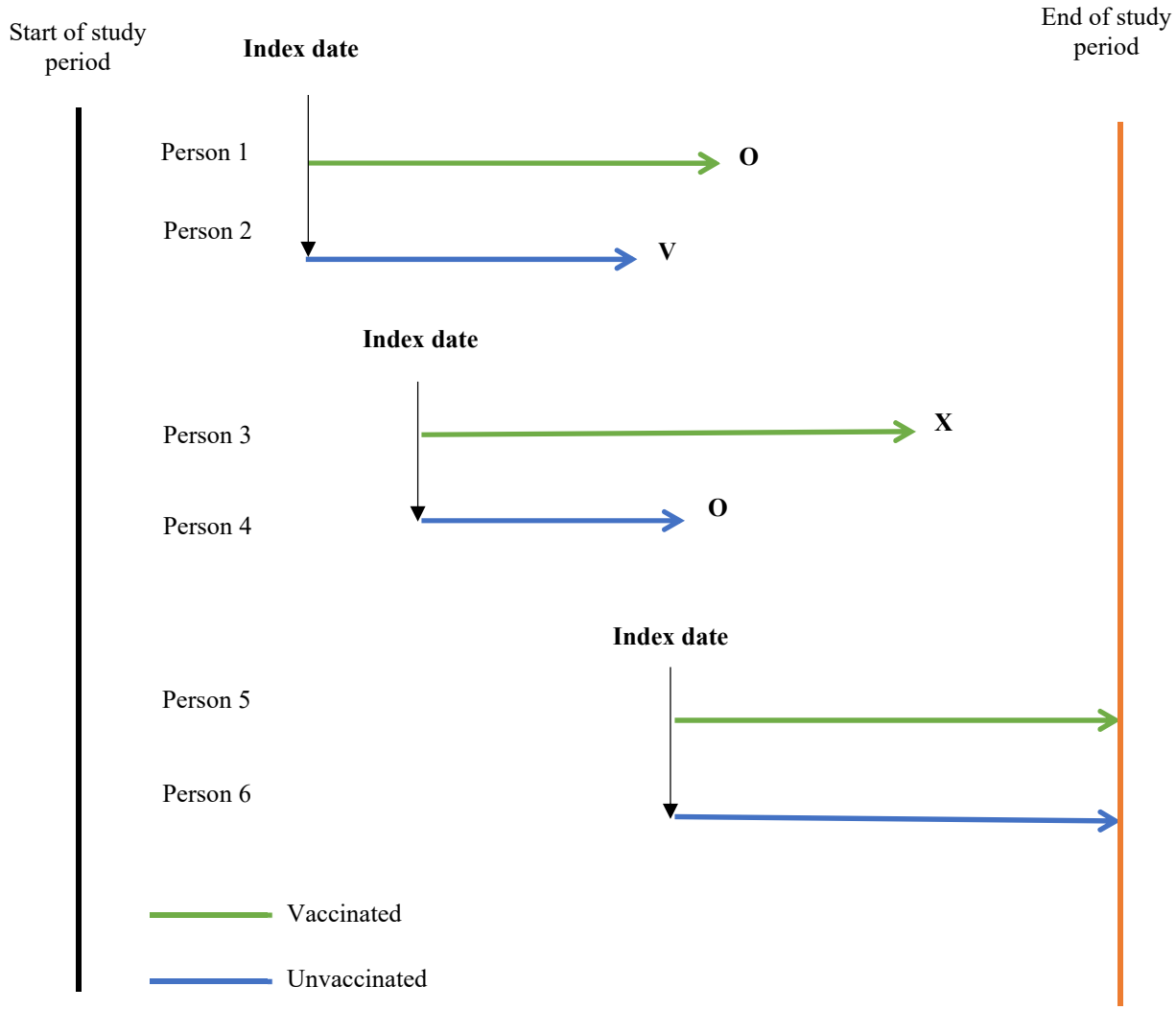
A comparative cohort design will be used to estimate incidence rates and incidence rate ratios of prespecified outcomes among immunocompromised, or renally impaired, or hepatically impaired older adults with and without receipt of the ABRYSVO vaccine.
Individuals in the unvaccinated cohort must have no record of an RSV vaccine on the index date or in the baseline period prior to index date or any other vaccine on the index date but can later receive ABRYSVO and enter the vaccinated cohort if all eligibility criteria are met. To address possible selection bias due to health seeking behaviours, unvaccinated individuals will be randomly selected from a population of patients who have regular use of preventive medical care, defined as at least one vaccination record in the year prior to the index date. The baseline period is defined as 12 months prior to the index date. The follow-up period will begin from day 1 (the day after ABRYSVO administration for vaccinated cohort, or the day after matched index date for the unvaccinated cohort) and continue to the earliest occurrence of an outcome, date of RSV vaccination (for unvaccinated individuals who later receive any RSV vaccine only), the end of administrative follow-up, end of the study period, or death. For those outcomes with a defined risk window, follow-up will also be truncated at the end of the risk window. To enhance comparability between the vaccinated and unvaccinated cohorts, ATT weights will be used. Weights, based on PS, will incorporate additional measures of healthcare utilization in the baseline period to further account for potential differences in healthcare seeking behaviour between the vaccinated and unvaccinated cohorts. However, as this study focuses on patients with chronically managed conditions, differences in healthcare seeking behaviour are not anticipated. IPCW will also be employed if informative censoring (i.e., differential rates of censoring during follow up) and high censoring rates are observed between the vaccinated and unvaccinated cohorts. Examples of patient follow-up scenarios are depicted in Figure 1 and Figure 2. Comparative analyses will also include variables that remain inadequately balanced between the two cohorts in a doubly robust approach. Further details are provided in Section 9.7.2 and Section 9.7.3.

Figure 1 Comparative Cohort Design



Notes:
a. Baseline conditions include comorbidities of interest, medications of interest, vaccination, healthcare utilisation, and/or surrogates of frailty.
b. Earliest of outcome of interest, receipt of RSV vaccine (for unvaccinated cohort), death, end of administrative enrollment, end of the study period (or risk window if applicable).

Figure 2 Index Matching and Follow-up Scenarios for Vaccinated and Unvaccinated in Comparative Cohort Design



O is occurrence of outcome of interest; V is vaccination with ABRYSVO, X is censoring event prior to end of study period

Notes:

Three scenarios: (a) Persons 1 and 2: during follow up the vaccinated individual has an outcome of interest; the unvaccinated control is censored at the date of vaccination of the control (b) Persons 3 and 4: follow up for the vaccinated person continues until follow up is censored at the end of the risk window while the control is followed until an outcome is observed, and; (c) Person 5 and 6: a control (Person 6) is index-matched for Person 5 at the time of vaccination and the pair are followed until the end of the study period. Neither experience an outcome of interest.

9.1.2. Self-controlled Risk Interval (SCRI) Design

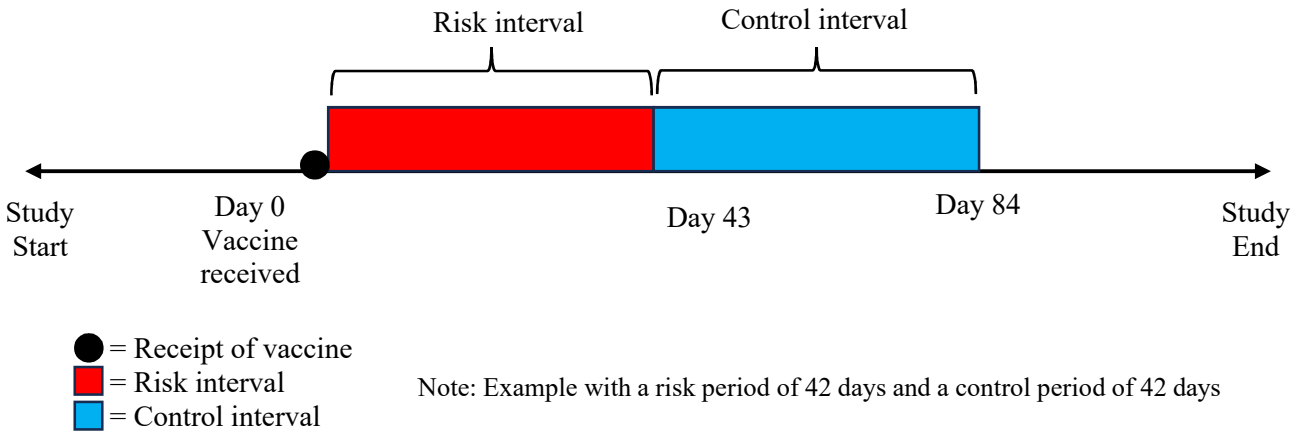
A SCRI design will be used for a subset of study outcomes that meet the necessary study design assumptions, as a complementary analytic approach. The assumptions for a SCRI design include that the outcome must have acute onset and short latency, as well as a relatively well-defined risk interval. The assumptions underpinning the SCRI also require that occurrence of the outcome does not affect the probability of exposure. Table 1 in Section 9.3 indicates outcomes for which a SCRI analysis is deemed a valid approach.

The SCRI design uses information from cases (i.e, vaccinated individuals who experience an outcome) to compare the incidence of an outcome in the risk interval following vaccination to the incidence in a post-vaccination control interval within the same individual.[22, 23]

Unlike the comparative cohort design, which may suffer from potential vaccine exposure under-ascertainment and misclassification as well as potential residual confounding, the SCRI design is a within person analysis that implicitly controls for time invariant confounders. Time varying confounders still need to be controlled for but with short, defined risk windows, the risk of time varying confounding is limited.

Risk intervals will be applied starting on the day after vaccination (Day 1), for a duration of time specific to each outcome; Table 1 in Section 9.3 defines the risk interval proposed for each outcome. A prespecified post-vaccination control interval will be used for each outcome of interest. The post-vaccination control interval will occur after the risk interval associated with ABRYSVO administration to avoid potential differential reporting of outcome in the pre- and post-vaccination periods. The risk and control intervals are based on a review of the published literature and precedence from previous studies of vaccine safety (see Table 1). As an example, the SCRI design with 42-day risk interval and 42-day post-vaccination control interval for Guillain-Barré syndrome (GBS) is presented in Figure 3 below.

Figure 3 Self-controlled Risk Interval Design



9.2. Setting

For the implementation of this study, we will use electronic healthcare databases in Europe. The selected data sources and two-letter country codes are as follows:

- Clinical Practice Research Datalink (CPRD) Aurum (UK)
- Valencia Health System Integrated Database (VID) (ES)
- Information System for the Improvement of Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP]) (ES)
- EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute (EpiChron) (ES)
- Système National des Données de Santé (SNDS) (FR)

9.2.1. Inclusion Criteria

Patients meeting the following criteria will be included in the study:

- *Vaccinated Cohort:* Vaccination with ABRYSVO
- *Unvaccinated Cohort:* No vaccination with ABRYSVO or other vaccines on the index date
- *Unvaccinated Cohort:* No vaccination with any RSV vaccine in the 12-months prior to index
- Each population of immunocompromised or renally impaired or hepatically impaired individuals must meet the population-specific inclusion criteria in **Section 9.2.1.1**, **Section 9.2.1.2**, and **Section 9.2.1.3**, respectively
- Age 60 years and older at index date
- A minimum of 12 months of administrative enrollment history prior to index in one of the selected data sources to ensure adequate characterisation of medical history
- A minimum of one day of follow up post-index
- For analyses of outcomes assessed with the SCRI design, the following additional criteria must be met. Note that the study population for each outcome-specific analysis will thus be different
    a. Have received ABRYSVO
    b. Have experienced an event of interest during the risk or control interval
    c. Have full accrual of data used to define the event in the risk and control intervals combined, after accounting for any data lag and timing of data extraction

9.2.1.1. Immunocompromised Population

Individuals must meet at least one of the following criteria at index date or in the 12-month baseline period prior to the index date (unless otherwise specified) to be eligible for inclusion in the immunocompromised population. Definitions will be aligned as closely as possible across participant data sources. Definitions may be modified if certain data elements are not available or are incompletely captured in some data sources.

- Diagnosed with a primary immunodeficiency/immune dysregulation disorder, also known as inborn errors of immunity, as defined by the European Society for Immunodeficiencies (ESID) Registry,[24] at any point in medical history
- Diagnosed with HIV/AIDS
- Diagnosed with hematologic malignancy (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia) with evidence of treatment at any point in medical history
- Diagnosed with solid malignancy with evidence of treatment within the last 5 years
- Diagnosed with rheumatologic/inflammatory conditions (e.g., Sjogren's syndrome, SLE, psoriatic arthritis, rheumatic arthritis, arthritis spondylarthritis, polymyalgia rheumatica, demyelination multiple sclerosis, polymyalgia rheumatica, IBD, autoimmune thyroiditis) and have evidence of treatment with chemotherapy, immune modulators, or high-dose or long-term systemic corticosteroids (>3 months) in the last 12 months
- Solid-organ transplant recipients or islet transplant recipients taking immunosuppressive therapy
- CAR-T-cell therapy or hematopoietic stem cell transplant recipients taking immunosuppressive therapy
- Active treatment with various immunosuppressive agents (e.g., high-dose systemic corticosteroids [20 or more mg of prednisone or equivalent per day when administered for 2 or more weeks] or long term systemic corticosteroid use (>3 months), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, TNF blockers, and other biologic agents that are immunosuppressive or immunomodulatory, active treatment with ATC code L04).

9.2.1.2. Renally Impaired Population

Individuals must have evidence of moderate or severe renal impairment, ascertained at index date or in the 12 months before index date using coded diagnoses and procedures or laboratory values as feasible.
In data sources where laboratory results are not available or where there are substantial levels of missingness, individuals with diagnosis codes that identify severe and moderate renal disease as part of the CCI by Ludvigsson et al[25] will be used. This includes but is not limited to:

- Hypertensive renal disease with renal failure
- Hypertensive heart and renal disease with renal failure
- Chronic nephritic syndrome
- Chronic tubulo-interstitial nephritis
- Chronic kidney disease (CKD)

Patients will be included in the renally impaired cohort if they have 2 different occurrences of those codes separated by at least 90 days in the baseline period. ICD-10 codes will be adapted to the specific disease coding system used in each data source.
In data sources where laboratory results are available (e.g., SIDIAP), individuals will also be included in the renally impaired cohort if:

- They have 2 eGFR test results < 60 mL/min/1.73 m^2—taken from Levey et al[26] separated by at least 90 days (with no normal values in between) but not more than 540 days OR
- They have 2 UACR results ≥ 30 mg/g separated by at least 90 days (with no normal values in between) and no more than 540 days (severe albuminuria)

Definitions for CKD stages are based on the KDIGO guidelines.[26, 27] Currently, albuminuria levels are also used to stratify levels of renal impairment.[27] The 3 microalbuminuria categories add prognostic information on renal and cardiovascular complications to the eGFR categories. However, patients in eGFR categories 1 and 2 (eGFR ≥ 60 mL/min/1.73 m2) and moderate albuminuria have a different clinical profile and normal to moderately increased risk of complications. Therefore, among patients with eGFR ≥ 60 mL/min/1.73m^2 only the patients with severe albuminuria will be considered. A potential limitation of using UACR test results is that clinicians use dipstick measurements as the main method of assessing UACR, and dipstick measurements are not captured in most data sources.
The eGFR will be defined using eGFR as recorded in the data source either by diagnosis codes or laboratory results as feasible. If eGFR is not recorded in the data source, it will be derived from creatinine levels using the 2021 CKD-EPI equation,[28] which removes the race-related coefficient, following recommendations from recent evidence and guideline statements.[29-32] The CKD-EPI equation is as follows:

$$eGFR = 142 \times \min\left(\frac{Scr}{\kappa}, 1\right)^{a1} \times \max\left(\frac{Scr}{\kappa}, 1\right)^{a2} \times c^{Age} \times \text{d (if female)}$$

Where:

Scr is serum creatinine concentration;

a1 = −0.241 for females and −0.302 for males;

a2 = −1.200 ; c = 0.9938; d = 1.012;

κ is 0.7 for female participants and 0.9 for male participants;

min indicates the minimum of Scr/κ and 1, and max indicates the maximum of Scr/κ and 1.

The exponent a1 is used for levels of creatinine ≤ 0.9 mg/dL for male participants and ≤ 0.7 mg/dL for female participants, and the exponent a2 is used for levels of creatinine > 0.9 mg/dL for male participants and > 0.7 mg/dL for female participants.

9.2.1.3. Hepatically Impaired Population

Individuals must have evidence of moderate or severe hepatic impairment, which will be ascertained at index date and in the 12 months before the index date using coded diagnoses and procedures or laboratory values as feasible.
In data sources where laboratory test results are not available, or where there are substantial levels of missingness, individuals will be considered in the target population if they have a diagnosis code that matches the category of moderate or severe hepatic disease according to the CCI revised by Glasheen et al[33] which has been shown to correlate with inpatient admissions and mortality rates. This definition includes but is not limited to:

- Oesophageal varices
- Gastric varices
- Alcoholic hepatic failure
- Toxic liver disease with hepatic necrosis
- Chronic hepatic failure
- Hepatic failure, unspecified
- Hepatic veno-occlusive disease
- Portal hypertension
- Hepatorenal syndrome

In addition, to maximize the inclusion of individuals with moderate or severe hepatic impairment, codes included in the adaptation of the CCI for mild liver disease by Ludvigsson et al[25] (e.g., viral hepatitis, autoimmune hepatitis) will be included if they coexist with an ascites code (R18).
In data sources where laboratory results are available (e.g., SIDIAP), severe chronic liver disease can be measured by a MELD score greater than 24.[34] The MELD score is calculated using serum bilirubin, serum creatinine, and International Normalized Ratio (INR) by the formula[35]:

$$MELD\ score = 9.57 \times log_e(\text{creatinine}) + 3.78 \times log_e(\text{total bilirubin}) + 11.2 \times log_e(\text{INR}) + 6.43$$

No exact correspondence exists between the Child-Pugh stages and the MELD scores. However, patients with MELD scores equal to or greater than 10 have similar mortality to patients with a Child-Pugh score of less than 10.[25] The same score threshold combined with elastography has clear prognosis implications for patients.[36] Thus, we propose to include in the study individuals with MELD scores equal to or greater than 10 to include additional individuals with moderate or severe hepatic impairment. Although there have been efforts to derive Child-Pugh scores from electronic healthcare data sources with identifiable rich clinical data,[37] those data may not be available in the data sources proposed for this study.

The Child-Pugh score requires data with enough granularity to differentiate clinical levels of severity for ascites and encephalopathy.[38] However, in each data source, the additional use of procedural codes or treatments for ascites and encephalopathy will be explored to improve the identification of the target population. Individuals with diagnosis or procedural codes indicating ascites or encephalopathy will be assigned 2 Child-Pugh score points for each clinical sign present (or 4 if they have both signs). The absence of each clinical sign will be assigned 1 point each (or 2 points if neither of the 2 signs are present). Thus, only the presence or absence of ascites and encephalopathy will be evaluated. It will not be possible to evaluate the severity of ascites and encephalopathy; thus, no individuals will be assigned 3 points. However, individuals with a Child-Pugh score of 7 or more will be included in a sensitivity analysis in those data sources with available laboratory results, thereby ensuring that individuals with at least Child-Pugh stage B are included.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Have a diagnosis for the specific outcome under study within the 12 months prior to the index date (to distinguish the recording of previous events from true new events) and at any time prior to the index date for diabetes type 1
2. Have received any RSV vaccinations during the 12-month baseline period

9.2.3. Source Population

The source population for the cohort design will be composed of all individuals registered in each of the participating healthcare data sources. The selected European populations are those underlying the data sources listed in Section 9.2.

9.2.4. Study Period

The study period will start from 23 August 2022 to allow at least 12 months of administrative enrolment before vaccination with vaccination possible from the date of approval in the EU. Data collection will extend through a minimum of three vaccination seasons (2023, 2024, and 2025). Patient follow-up will last for up to 12 months post-vaccination depending on the outcome; therefore, data collection will extend through the end of 2026, at a minimum. Vaccine uptake will be periodically monitored to inform the overall length of the study period, and additional vaccination seasons (with 12-month post-vaccination follow-up) may be added based on vaccine uptake and exposure accrual. Time lags for data availability will be taken into account for analysis and reporting purposes.

9.3. Variables

9.3.1. Exposure Definition

Exposure will be based on recorded prescription, dispensing, or administration of ABRYSVO. Vaccine receipt and date of vaccination will be obtained from all available sources that capture ABRYSVO vaccination, such as pharmacy dispensing records, general practice records, immunization registers, vaccination records, medical records, or other secondary data sources. Depending on the data source, vaccines will be identified via

nationally used product codes where possible. The main exposure of interest is in the receipt of ABRYSVO.

- **CPRD Aurum (UK):** Data on vaccine exposure will be identified using CPRD Product Codes (PRODCODE ID's) and/or Medical Codes (MEDCODE ID's) based on available codes in CPRD product and medical dictionaries. Vaccination data originate from the patient primary care electronic medical records held within CPRD. The information captured at the individual patient level includes the name of the vaccine; manufacturing company; dose; stage of the vaccine schedule (if applicable); administration route; administration location (e.g., general practice); date of administration; and medical observations, events, referrals, test results, and prescribed medications recorded by the GP prior to, on, or after the vaccination date.
- **VID (ES):** Data on vaccine exposure are obtained from patient level electronic records within the vaccine information system which captures information on vaccine type, manufacturer, number of doses, location and administration date, adverse reactions related to vaccines, and if applicable, risk groups. Vaccines information in the VID is updated daily.
- **SIDIAP (ES):** Data are available on all routine childhood and adult immunizations, including the antigen and the number of administered doses. Vaccination information originates from patient electronic medical records. For each patient, SIDIAP has the date and centre of administration, dose, brand, reasons for vaccination (e.g., risk of group), and other information related to vaccination.
- **EpiChron (ES):** The EpiChron cohort provides data of individuals' pharmacotherapeutic history, including vaccination, with prescriptions and dispensation of drugs in community pharmacies, coded according to the WHO ATC classification system.
- **SNDS (FR):** Exposure information is captured based on vaccines dispensed in community outpatient pharmacies. Exposure information will be coded using the ATC classification system as well as a specific French pharmacy codes (CIP) and European Pharmaceutical Market Research Association codes, with dates of prescription and dispensing.

9.3.1.1. Comparative Cohort Design

The exposure cohorts for the comparative cohort design will be defined as follows:

- The vaccinated cohort will be defined as individuals who were administered ABRYSVO.

To be included in the unvaccinated cohort, individuals must meet the following criteria:

- **No vaccine record on index date**: They must not have a record of receiving any vaccine, including the RSV vaccines, on the index date.

- **No RSV vaccination in baseline period**: They must not have a record of receiving any RSV vaccine during the 12-month baseline before the index date.

Note: If individuals in the unvaccinated cohort receive ABRYSVO during the follow-up period, they will be censored in the unvaccinated cohort and become eligible for inclusion in the vaccinated cohort if all other eligibility criteria are met.

9.3.1.2. SCRI Design

For the SCRI design, person-time in the risk interval will be considered "exposed," while person-time in the control interval will be considered "unexposed."
Risk intervals will be specific to the outcome of interest and are defined to reflect the duration of time post-vaccine exposure that an incident post-vaccine event is expected to occur based on biological plausibility. Events known to have a risk window limited to a defined period after vaccination are not well known for ABRYSVO and other RSV vaccines, therefore event-specific intervals will be defined based on prior post-marketing studies of other vaccines (where applicable), clinical trial data (where applicable), and passive post-marketing surveillance activities (as they become available).

9.3.2. Outcome Definitions

9.3.2.1. Safety Outcomes

Outcomes will be defined consistently across the data sources to the fullest extent possible.

Table 1 List of Select Adverse Events of Special Interest

Body system/ classification	Adverse event of special interest	Estimated risk window (days)[a].	Analytic Approach
Autoimmune diseases	Acute disseminated encephalomyelitis	1-42[39, b].	Cohort/SCRI
	Diabetes mellitus type I	1-365	Cohort
	Guillain-Barré syndrome	1-42[39, b].	Cohort/SCRI
	Narcolepsy	1-365[c.]	Cohort
	Thrombocytopenia (idiopathic)	1-42[40]	Cohort/SCRI
	Thrombosis thrombocytopenia syndrome	1-15[39]	Cohort/SCRI
Cardiovascular system [d.]	Acute cardiovascular injury	1–28[41]	Cohort
	Arrhythmia Specific subgroups of patients with atrial fibrillation and supraventricular arrhythmias will be identified for additional analyses	1–365[e. g.]	Cohort
	Coronary artery disease	1–365	Cohort

Table 1 List of Select Adverse Events of Special Interest

Body system/ classification	Adverse event of special interest	Estimated risk window (days)[a].	Analytic Approach
	Heart failure	1–365	Cohort
	Microangiopathy	1–365	Cohort
	Myocarditis	1–21	Cohort/SCRI
	Myocarditis and pericarditis	1–7	Cohort/SCRI
	Pericarditis	1–14	Cohort/SCRI
	Stress cardiomyopathy	1–365	Cohort
Circulatory system	Coagulation disorders: Disseminated intravascular coagulation, venous thromboembolism (pulmonary embolism, deep vein thrombosis), thrombotic microangiopathy, cerebral venous thrombosis, thrombotic thrombocytopenia syndrome, ischemic stroke, myocardial infarction, haemorrhage	1–28[39, f.]	Cohort/SCRI
	Single organ cutaneous vasculitis	1–28[f.]	Cohort/SCRI
	Thrombocytopenia with venous thromboembolism	1–15	Cohort/SCRI
Nerves and central nervous system	Bell's palsy	1–42[39]	Cohort/SCRI
	Generalised convulsion	0–42[39, , g.]	Cohort/SCRI
	Meningoencephalitis	1–42[39]	Cohort/SCRI
	Transverse myelitis	1–42[39, b. c.]	Cohort/SCRI
Respiratory system	Acute respiratory distress syndrome	1–365	Cohort
Skin and mucous membrane, bone and joints system	Erythema multiforme	1–42	Cohort
Other system	Anaphylaxis	0-1[39, , g.]	Cohort/SCRI
	Death (any causes)	0–365[, g.]	Cohort

Notes:
a. Day 0 is the date of vaccine administration (i.e, index date for the vaccinated cohort in the comparative cohort design and SCRI design) or matched index date (for the unvaccinated cohort in the comparative cohort design)
b. To align with ongoing postmarketing study C3671031, A Post-Authorization Safety Study of Guillain-Barré Syndrome (GBS) Following ABRYSVOTM Among Older Adults in the United States, sensitivity analyses will be performed for GBS, acute disseminated encephalomyelitis, and transverse myelitis using shorter risk intervals of 1-21 days, 5-28 days, and 1-21 days, respectively. Further details are outlined in Section 9.7.4.
c. Published risk and control intervals for demyelinating diseases and cranial disorders were applied to transverse myelitis and narcolepsy/cataplexy.
d. Please note that alternative risk windows were reported in other studies.
e. To align with ongoing postmarketing study C3671037, A Post-Authorization Safety Study of Atrial Fibrillation Following Respiratory Syncytial Virus Vaccine (ABRYSVOTM) Among Older Adults in the

Table 1 List of Select Adverse Events of Special Interest

Body system/ classification	Adverse event of special interest	Estimated risk window (days)[a].	Analytic Approach

Veterans Affairs Health System, sensitivity analysis will be performed for atrial fibrillation and supraventricular arrhythmias using a shorter risk interval of 0-3 days. Alternative risk intervals of 0-1 day or 0-30 days may also be considered. Details are provided in Section 9.7.4.
f. Similar risk and control intervals were applied to all cardiovascular and haematological disorders characterised by damage to the blood vessels and/or arteries and clotting (i.e, coagulation disorders and single organ cutaneous vasculitis).
g. Risk intervals for most outcomes start on Day 1 post-index, but for some outcomes, the risk interval starts on the day of vaccination due to biological plausibility of rapid onset following vaccination.

9.3.2.2. Outcome Identification

Outcomes will be identified in participant data sources with algorithms based on codes for diagnoses, procedures, and treatments. Proposed algorithms and diagnostic codes for all prespecified outcomes will incorporate definitions developed by the ACCESS project[42] and will be described in more detail in the statistical analysis plan (SAP). ACCESS developed harmonised definitions and code lists for the outcomes listed in **Table 1**. for application to routine healthcare data sources across Europe. These definitions were subsequently used for the calculation of background outcome rates to contextualize emerging COVID-19 vaccine safety data. Healthcare data covering approximately 130 million lives across 7 European countries and 22 data sources were used to generate background rates. Algorithms will be tailored to the data source and will consider the provenance of the medical records that have identified the outcome, e.g., primary care, access to hospital care, and access to emergency care.[43] Multiple algorithms for the same outcome may be included in the analysis, to assess the potential impact of differential misclassification. Several outcomes have been validated in previous VAC4EU studies.

Outcome onset will be primarily defined as the date of the healthcare encounter associated with the relevant diagnostic code. Most outcomes of interest are serious enough to warrant healthcare consultation close to the time of symptom onset. However, for those outcomes that might include a lag between the onset of symptoms and diagnosis in a healthcare setting (e.g., DVT or diabetes type 1), algorithms may incorporate additional considerations to capture onset dates closer to the time of symptom onset. These considerations will be detailed in the SAP. Sensitivity analyses may also be incorporated to assess assumptions around outcome onset for relevant outcomes.

9.3.3. Covariate Definitions

The following variables will be assessed at the date of vaccine administration (i.e, index date for the vaccinated cohort in the comparative cohort design and SCRI design) or matched index date (for the unvaccinated cohort in the comparative cohort design) or during the 12-month baseline period. These variables will be used to further characterise the patient populations of interest and/or to control for confounding. The prespecified outcomes may

have different sets of risk factors, and outcome-specific analyses may contain different covariate sets. Covariates with sufficient availability across data sources include:

- Demographics
    - Age which may be categorised as age categories in line with published background incidence rates from ACCESS (60-64, 65-69, 70-79, 80+ years) dependent on sample size.
    - Sex
    - Race and/or ethnicity, as appropriate in each country
    - Geographic region, as appropriate in each country
- Date of vaccination (categorised by month or year to assess trends in vaccine uptake)
- Comorbidities
    - History of anaphylaxis
    - History of allergies
    - Diabetes mellitus (types 1 and 2)
    - Hypertension
    - Cardiovascular disease
    - Cerebrovascular disease
    - Chronic respiratory disease (asthma, COPD, chronic bronchiectasis)
    - Haematological conditions
    - CKD
    - Dementia (i.e, Alzheimer's disease and related disorders, senile dementia)
    - Chronic liver disease
    - Cancer
    - Autoimmune disorders
    - Influenza infection or other respiratory infections
    - Charlson Comorbidity Index (may be included as the composite scale, or the scale components may be included as individual terms)
- Comedication use (prescriptions or dispensing, no over-the-counter medication use)
    - Analgesics
    - Antibiotics
    - Antiviral medications
    - Corticosteroids

  - Non-steroidal anti-inflammatory drugs
  - Psychotropics
  - Statins
  - Novel oral anticoagulants
  - Warfarin
  - Number of medications used
- Healthcare utilisation
  - Number of hospitalisations
  - Number of emergency department visits
  - Skilled nursing facility, nursing home, or extended care facility stay
  - Primary care utilisation
  - Cancer screening
  - Other preventive health services, as appropriate
- Other vaccinations
  - Seasonal influenza
  - COVID-19
  - Pneumococcal (conjugate or polysaccharide)
  - DTP
  - TPV
  - TV (MMR)
  - Haemophilus influenzae type b (Hib)
  - HAV
  - HBV
  - VZV
  - HZ
  - HPV
  - Meningococcal (MenACWY or Meningitis B)
  - Rotavirus

As feasible, the following covariates may also be considered pending confirmation of sufficient availability and completeness across participant data sources.

- Socioeconomic status (including social deprivation, housing, employment, and income, as feasible)

- Residency in a long-term care facility
- Care setting of vaccine administration
- Personal lifestyle characteristics
    - Smoking status
    - BMI
- Surrogates of frailty
    - Wheelchair use
    - Home hospital bed
    - Paralysis
    - Parkinson's disease
    - Skin ulcer
    - Weakness
    - Stroke/brain injury
    - Ambulance transport
    - Dementia
    - Difficulty walking
    - Home oxygen
    - Rehabilitation care
    - Psychiatric illness
    - Sepsis
    - Heart failure
    - Podiatric care
    - Bladder incontinence
    - Diabetes complications
    - Arthritis
    - Coagulation deficiencies
    - Vertigo
    - Lipid abnormalities
    - These may also be combined into a frailty index as an overall marker of ageing and vulnerability to poorer outcomes. For example, the eFI was developed using routine primary healthcare data to identify older people with mild,

moderate and severe frailty and has shown robust predictive validity for outcomes of mortality, hospitalisation and nursing home admission.[44]

9.4. Data Sources

This study will use data from secondary population-based healthcare databases reflecting electronic health records or insurance claims related to healthcare encounters. All data sources will have the ability to provide high-quality data on ABRYSVO vaccines (product types and dates), outcomes (diagnoses, procedures, and treatments), and important covariates. It is not currently known the extent to which the ABRYSVO vaccine and product types will be captured in data sources. At the proposal stage for this study, members of VAC4EU were offered the option to participate in the study based on study requirements (https://vac4eu.org/). Several data sources have indicated the ability to participate in the study and are described in the following subsections.

Data availability for each institution may be affected by third parties or external circumstances that are independent from the institution involved in the study as described below in Sections 9.4.1 to 9.4.5

9.4.1. CPRD Aurum (UK)

The CPRD collates the electronic medical records from a network of primary care general practitioners (GPs) in the UK who act as the gatekeepers of healthcare and maintain subjects' life-long medical history and records.[45-47] The Aurum dataset, based on practices employing the EMIS electronic medical record software, sources data from over 1,700 primary care practices and includes 47 million patients, of whom 16 million are currently registered and active.[48] GPs act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care, as necessary. Secondary care teams also provide feedback information to GPs about their patients, including key diagnoses. The data in the CPRD are updated approximately quarterly and include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death.[46] Electronic health data are coded by GPs using Read 2, SNOMED and local EMIS codes, and available in CPRD as MEDCODEIDs and PRODCODEIDs. Data include demographics, all GP/healthcare professional consultations, diagnoses and symptoms, results from laboratory tests, information about treatments (including prescriptions), data on referrals to other care providers, hospital discharge summaries (date and diagnostic Read/SNOMED/EMIS codes), hospital clinic summaries, preventive treatment and immunisations, and death (date and cause). Lag time for CPRD Aurum is usually approximately 1-3 months, although this may be extended due to CPRD database technical updates. Linkage of the CPRD primary care data with other subject-level datasets is available for English practices within CPRD Aurum that have consented to participate in the linkage scheme. These linkages include the Hospital Episode Statistics (HES) database, which contains details of all admissions to National Health System (NHS) hospitals in England (Admitted Patient Care,). The availability of

linkage to HES from CPRD Aurum is approximately 66% which equates to approximately 46.8 million individuals. Not all subjects in CPRD Aurum have linked data (e.g., if they live outside of England, if their GP has not agreed that their data may be used in this way). As with standard CPRD subjects, HES data are limited to subjects with research-standard data. The CPRD records are linked to the HES using a combination of the subject's NHS number, sex, and date of birth.[45] Additional CPRD-linked datasets include Death Registration data from the Office for National Statistics, which includes information on the official date and causes of death (using ICD codes), the CPRD Aurum Ethnicity Record and the Index of Multiple Deprivation (IMD) patient or practice level linked datasets

CPRD is listed under the ENCePP resources database, and access will be provided by the DSRU.

9.4.2. VID (ES)

The VID is a set of population-wide electronic databases covering residents of the Valencia region in Spain, representing approximately 5 million individuals[49]. All the information in the VID databases can be linked at the individual level through a unique personal identifier. The datasets in the VID are as follows:

- **The Population Information System (SIP)** provides basic information on health system coverage (e.g., dates and causes of Valencia health system entitlement or disentitlement, insurance modality, pharmaceutical copayment status, assigned healthcare department) as well as sociodemographic data (e.g., sex, date of birth, nationality, employment status, geographic location). SIP also includes the date of death captured from the Mortality Registry. The SIP database is the source of the unique patient identifier (the SIP number), which is then used to link health data across different healthcare data sources for Valencia.
- **The Ambulatory Medical Record (ABUCASIS)** is the electronic medical record for primary and specialist outpatient activity capturing 96% of the population since 2009. The two main database modules are: the Ambulatory Information System (SIA) and the Pharmaceutical Module (GAIA), including paediatric and adult primary care, mental healthcare, prenatal care, and specialist outpatient services, as well as the dates, visits, procedures, laboratory test results, diagnoses, and clinical and lifestyle information. It also includes information on several health programs (e.g., vaccination, healthy children, pregnancy, notifiable diseases), the primary care nurse clinical record, and the health-related social assistance record. The SIA module uses ICD-9-CM for coding diagnoses and, partially ICD-10-ES for data from 2019 onwards.
    - The SIA module also uses the Clinical Risk Groups system to stratify the morbidity of the entire population.
    - The GAIA Pharmaceutical module stores data on all outpatient pharmaceutical prescriptions and dispensings, including both primary care and outpatient hospital departments, using the ATC classification system and the

National Pharmaceutical Catalogue, which allow the identification of the exact content of each dispensing. GAIA does not include in-hospital medication or medication administered in the Accident and Emergency Department (AED). GAIA provides detailed information on prescriptions issued by physicians, such as the duration of treatment and dosage.

- **The Hospital Medical Record (ORION)** provides comprehensive information covering all areas of hospital-based specialist care, from admission, outpatient consultations, inpatient, emergencies, diagnostic services (e.g., laboratory tests, imaging, microbiology, pathology), pharmacy, surgery, critical care, prevention and safety, social work, at-home hospitalisation, and day-hospitalisation. ORION is currently in the process of being integrated for the whole region, with several databases already fully integrated and available for all hospitals, including the Minimum Basic Data Set at Hospital Discharge (MBDS) and the AED clinical record.
    - **The MBDS** is a synopsis of clinical and administrative information on all hospital admissions and major ambulatory surgery in the Valencia health system hospitals, including public-private partnership hospitals (approximately 450,000 admissions per year in the region). The MBDS includes admission and discharge dates, age, sex, geographic area and zone of residence, main diagnosis at discharge, up to 30 secondary diagnoses (comorbidities or complications), clinical procedures performed during the hospital episode, and the diagnosis-related group(s) assigned at discharge. The MBDS currently uses ICD-10-ES coding system. Since 2015, MBDS has also included a “present on admission” diagnosis marker and information on tumour morphology.
    - **The AED clinical record** was launched in 2008 and collects triage data, diagnoses, tests, and procedures performed in public emergency departments. As with the MBDS, the current coding system is ICD-10-ES. Diagnosis codification was approximately of all emergency visits 75% in 2017.

Data on vaccine exposure may be obtained from the VID, which includes information on vaccine type, manufacturer, number of doses, location and administration date, adverse reactions related to vaccines, and if applicable, risk groups. Information in the VID is updated daily. All databases included in the VID are updated frequently (every 1 to 3 months), except the MBDS database, which is updated every 6 months.

9.4.3. SIDIAP (ES)

SIDIAP was created in 2010 by the Catalan Health Institute and the IDIAPJGol Institute.[50] The database captures healthcare data collected since January 2006 during routine visits from 278 primary care centres linked to the Catalan Health Institute in Catalonia (northeastern Spain). Overall, SIDIAP covers 5.8 million people and is highly representative of the Catalan population (80%). The pseudo-anonymized health data held within SIDIAP originate from, or are linked to, various sources:

- ECAP (electronic health records in PHC of Catalan Health Institute) including comprehensive demographic information, clinical and referral events (with diagnoses captured as ICD-10 codes) registered by primary care health professionals (e.g., GPs, paediatricians, and nurses) and administrative staff in the primary care EHRs, vital signs (height, weight, body mass index, blood pressure), primary care laboratory test results, drug prescriptions issued in the PHC (captured as ATC codes), sickness leave and date of death.
- Pharmacy invoice data corresponding to the PHC drug prescriptions
- Database of diagnoses at hospital discharge

Linkages to the hospital discharge database occur on a project-by-project basis.
SIDIAP includes all routine childhood and adult immunizations, including the antigen and the number of administered doses.
The SIDIAP database is updated twice per year, in January and July. The SIDIAP data have been shown to fit-for-use for epidemiological research, specifically within VAC4EU projects with respect to the characterization of use for vaccine coverage, benefits, and risk assessments.[50]

9.4.4. EpiChron (ES)

In 2005 the EpiChron Research Group on Chronic Diseases established the EpiChron Cohort Study which used the computerized medical records of patients living in Aragon, a region of north-eastern Spain, to study chronic diseases and multi-morbidities.[51] The cohort was originally approved by the Clinical Research Ethics Committee of Aragon (CEICA). Both cross-sectional and longitudinal studies on multi-morbidity and comorbidity of major index chronic diseases, as well as pharmaco-epidemiological studies, were completed to identify causal relationships among risk factors, diseases and drugs, development of chronic diseases and multimorbidity, and the incidence of adverse health outcomes.[51] The EpiChron cohort was subsequently extended to enable additional research including the safety of COVID-19 vaccines.

The EpiChron Cohort Study now links socio-demographic and clinical anonymized information for the inhabitants of Aragon region, and it is built from the platform of healthcare big data of Aragon (BIGAN). The BIGAN platform integrates a technical infrastructure and a data lake gathering individual data from the regional health service information systems, including primary care, specialized care, hospitalisations, emergency room episodes, drug prescriptions, image diagnosis, laboratory tests, diagnostics, vaccination, medical history and demographics from the users of the public health system of Aragon. This includes about 2 million individuals with historic data, and an active population of 1.3 million individuals.

Within the data lake individual data streams are linked at the individual patient level based on a unique patient health identifier. Diagnoses are coded initially according to the ICPC or ICD coding systems and are subsequently grouped into diagnostic clusters, if needed, using open software (i.e, Clinical Classifications Software). Drug prescriptions and dispensations, including for vaccines, are coded according to the WHO ATC classification system.

9.4.5. SNDS (FR)

The SNDS is the French nationwide healthcare database. It currently covers the overall French population (about 67 million persons) from birth (or immigration) to death (or emigration), irrespective of changes to a person's occupation or retirement status.[52] Using a unique pseudonymized identifier, the SNDS merges all reimbursed outpatient claims from all French health care insurance schemes (SNIIRAM database), hospital-discharge summaries from French public and private hospitals (PMSI database), and the national death register.[52] SNDS captures healthcare data from 2006 onwards and captures information on:

- **Socio-demographic characteristics** including gender, year of birth, and area of residence. Socioeconomic status can be derived from the presence of CMU-C (which describes full insurance coverage due to low-income status, deprivation index, and a composite indicator that gives information on patient socioeconomic status based on its geographic residence.
- **Death data** including month, year, and cause. However, there may be lags in death dates (e.g., as of January 2024, cause of death data were available to the end of 2020).
- **Long-Term Disease registration** with diagnoses captured with ICD-10 codes.
- **Occupational accidents and diseases.**
- **Outpatient reimbursed healthcare expenditures** for visits, medical procedures, nursing acts, physiotherapy, lab tests, dispensed drugs, medical devices, and transports, etc. For each expenditure, associated costs, prescriber, caregiver information (specialty, private/public practice) and the corresponding dates are provided. Indication and results are not available.
- **Inpatients encounters** capturing the primary and associated ICD-10 diagnostic codes from hospital discharge summaries with the date and duration of the hospital stay, the performed medical procedures, and the related costs. Drugs included in the DRG cost are not captured, though newer more expensive ones paid outside of DRG are available.
- **Medication dispensed in community outpatient pharmacies** recorded as dispensed preparation packs, with dates (prescription and dispensing): drug information includes ATC code, CIP code (French pharmacy coding system), and EPhMRA code; description of packs in number of tablets and strength; the number of packs dispensed; date of prescription and nature of prescriber, date of dispensing, and the dispensing pharmacy (anonymised). Information on underlying medical indication or date of drug injection are not available. Vaccinations are captured within this data file.

9.5. Study Size

The study will be conducted in a source population of the participating population-based electronic healthcare data sources from the VAC4EU network.

Table 2 shows the sample size calculations for select outcomes (i.e, anaphylaxis, GBS, and arrhythmia) using the comparative cohort design, assuming a two-sided alpha level of 0.05, an equal number of individuals for the vaccinated and unvaccinated cohorts, and a power of 80% across a range of IRRs. Given a lack of published background incidence rates for outcomes among the specific populations of interest (i.e, adults aged 60 and older who are immunocompromised or renally impaired or hepatically impaired), published incidence rates from general populations aged 60 years and older in VAC4EU databases[42] were used to estimate rates in the unvaccinated cohort. As an example, to detect an IRR of 2 for arrhythmia with a power of 80% and two-sided alpha level of 0.05, a sample size of 1,178 vaccinated individuals and 1,178 unvaccinated individuals is needed. This assumes a background rate of 2,000 arrythmia events per 100,000 person-years among the unvaccinated cohort. To detect an IRR of 3, this would decrease to 393 vaccinated and 393 unvaccinated individuals.

Table 2 Number of Individuals Needed to Detect Different Rate Ratios for Selected Outcomes with a Range of Background Rates

Outcome	Background rate per 100,000 person-years[a]	Background rate per person during risk interval[b]	Incidence rate ratio	Sample size	
				Vaccinated cohort	Unvaccinated cohort
Anaphylaxis	10	0.0000005	2	47,093,279	47,093,279
			3	15,697,760	15,697,760
			5	5,886,660	5,886,660
			10	2,131,795	2,131,795
	15	0.0000008	2	29,433,300	29,433,300
			3	9,811,100	9,811,100
			5	3,679,163	3,679,163
			10	1,332,372	1,332,372
Guillain-Barré syndrome	6	0.0000069	2	3,412,557	3,412,557
			3	1,137,519	1,137,519
			5	426,570	426,570
			10	154,478	154,478
	10	0.0000115	2	2,047,534	2,047,534
			3	682,512	682,512
			5	255,942	255,942
			10	92,687	92,687
Arrhythmia	2,000	0.0200000	2	1,178	1,178
			3	393	393

Table 2 Number of Individuals Needed to Detect Different Rate Ratios for Selected Outcomes with a Range of Background Rates

Outcome	Background rate per 100,000 person-years[a]	Background rate per person during risk interval[b]	Incidence rate ratio	Sample size	
				Vaccinated cohort	Unvaccinated cohort
			5	148	148
			10	54	54
	5,000	0.0500000	2	471	471
			3	157	157
			5	59	59
			10	22	22

Notes:
a. Due to a lack of published background incidence rates of outcomes of interest among the study-specific population (i.e., adults aged 60 and older who are immunocompromised or renally impaired or hepatically impaired), background rates of outcomes among adults aged 60 and older from general European populations ,published in Supplement 1, Table 1 of Willame et al (2023)[53] using VAC4EU databases were used as the basis of sample size and power calculations. A range of background rates were used to address potential differences in underlying rates between the general and study-specific populations (i.e., higher and lower background incidence rates of outcomes than were published in Willame et al.). Sample size and power calculations may be updated during the study as new and relevant background rate data emerges. Key study design features will be reviewed in the light of any updated sample size and power calculations.
b. Assuming a two-sided alpha = 0.05, power of 80%, and a ratio of 1:1 of vaccinated to unvaccinated.
Examples of background IR accounting for the risk window:
Anaphylaxis (10/100,000 person-years)/365 * risk window (risk window 2 days) = 0.0000005
GBS (6/100,000 person-years)/365 * risk window (risk window 42 days) = 0.0000069
Arrhythmia (2,000/100,000 person-years)/365 * risk window (risk window 365 days) = 0.02

9.6. Data Management

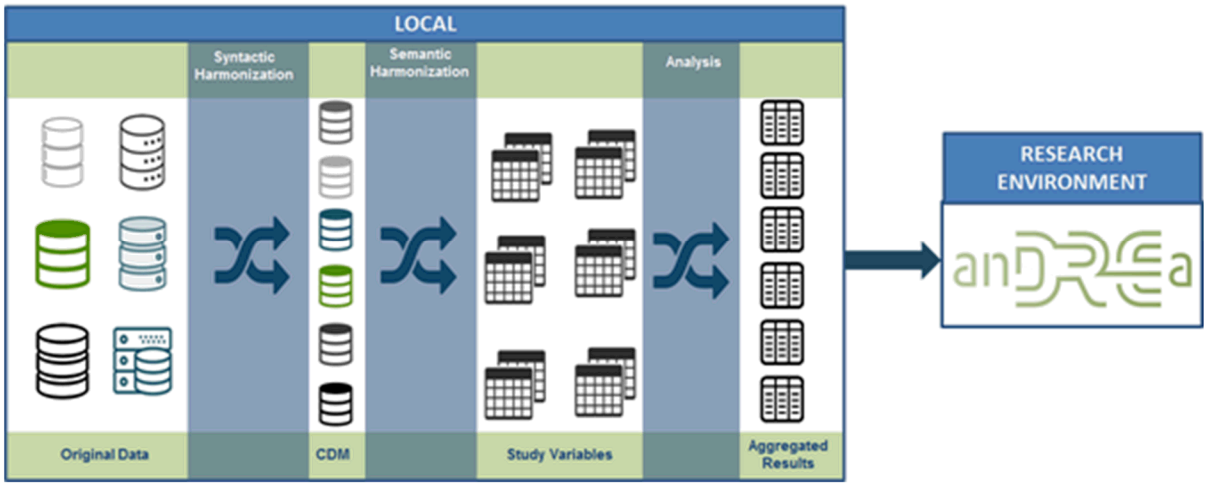
This study will be conducted in a distributed manner using a common protocol, common data model (CDM), and common analytics programs based on existing health data. The following steps will be implemented:

1. Extract Transform Load (ETL) of data to a CDM: To harmonise the structure of the datasets stored and maintained by each data partner, a shared syntactic foundation is used. The CDM that will be used has been developed within the IMI-ConcePTION project.[54] In this CDM, data are represented in a common structure, but the content of the data remain in their original format. The ETL design for each study is shared in a searchable FAIR catalogue. The VAC4EU FAIR data catalogue is a meta-data management tool designed to contain searchable meta-data describing organisations that can provide access to specific data sources. FAIR is defined as findable, accessible, interoperable, and re-usable. Data quality checks will be conducted to

measure the integrity of the ETL as well as internal consistency within the context of the CDM.

2. Second, to reconcile differences across terminologies, a shared semantic foundation is built for the definition of events of interest within a study by collecting relevant concepts in a structured fashion using a standardised event definition template. The Codemapper tool is used to create diagnosis code lists based on completed event definition templates for each outcome and comorbid risk condition based on the approach taken in the ACCESS project. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), one or more algorithms are constructed (typically one sensitive, or broad, algorithm and one specific, or narrow, algorithm) to operationalise the identification and measurement of each event. These algorithms may differ by database, as the components involved in the study variables may differ. Specifications for both ETL and semantic harmonisation will be shared in the catalogue.
3. Third, following conversion to harmonised study variable sets, R programs for the calculation of incidence will be distributed to data access providers for local deployment. The aggregated results produced by these scripts will then be uploaded to the DRE for pooled analysis and visualisation (see Figure 4). The DRE is made available through UMCU/VAC4EU (https://www.andrea-consortium.org/). The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate (https://www.andrea-consortium.org/azure-dre/).

Figure 4 Data Management Plan



9.6.1. Data Extraction

Each DAP will create ETL specifications using the standard ConcePTION ETL design template (accessible via this link: https://docs.google.com/document/d/1SWi31tnNJL7u5jJLbBHmoZa7AvfcVaqX7jiXgL9uAWg/edit). Following completion of this template and review by study statisticians, each DAP will

extract the relevant study data locally using their preferred software (e.g., Stata, SAS, R, Oracle). These data will be loaded into the CDM structure in csv format. These data remain local (see Figure 4).

9.6.2. Data Processing and Transformation

Data processing and transformation will be conducted using R code against the syntactically harmonized CDM. The R scripts will first transform the data in the syntactically harmonized CDM to semantically harmonized study variables (see Figure 4). Following creation of study variables, the data will be characterized. This characterisation will include calculation of code counts and incidence rates, as well as benchmarking within the data source (over time), between data sources and externally (against published estimates). Subsequently, R code to conduct study-specific statistical analysis against semantically harmonized study variables will be distributed and run locally to produce aggregated results. The R scripts for these processing and analysis steps will be developed and tested centrally and sent to the DAPs.

The R scripts are structured in modular form to ensure transparency. Functions to be used in the modules will be either standard R packages or packages specifically designed, developed, and tested for multi-database studies. Scripts will be double coded in R and quality checks will be thoroughly documented.

The DAPs will run the R code locally and send aggregated analysis results to the DRE using a secure file transfer protocol. In the DRE, results will be further plotted, inspected (for quality assessment), and pooled (if needed) for final reporting.

All final statistical computations will be performed on the DRE using R. Data access providers will have access to the workspace for script verification.

Aggregated results, ETL specifications, and a repository of study scripts will be stored in the DRE.

Within the DRE, each project-specific area consists of a separate secure folder called a ‘workspace’. Each workspace is completely secure, and researchers are in full control of their data. Each workspace has its own list of users, which can be managed by its administrators.

The DRE architecture allows researchers to use a solution within the boundaries of data management rules and regulations. Although the General Data Protection Regulation (GDPR) and Good (Clinical) Research Practice still apply to researchers, the DRE offers tools to control and monitor which activities take place within projects.

All researchers who need access to the DRE are granted access to study-specific secure workspaces. Access to this workspace is only possible with double authentication using an identification code and password together with the user’s mobile phone for authentication. Upload of files is possible for all researchers with access to the workspace within the DRE. Download of files is only possible after requesting and receiving permission from a workspace member with an ‘owner’ role.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed, and maintained by the sponsor and PI. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses will be reflected in a protocol amendment. The SAP will also provide additional detail regarding the evaluation of a threshold of excess risk for each of the outcomes of interest. This will be determined based on background incidences for each event, in addition to prespecified significance level (e.g., alpha = 0.01 or 0.05) and power. All analyses will be conducted using R version R-4.0.3 or higher.[55]

The SAP will contain additional detail of the data analysis and meta-analysis. One interim analysis and report may be conducted. The interim report will be limited to descriptive analyses. Comparative analyses will be included in the final report. Further details will be described in the SAP.

All analyses will be conducted separately for the 3 populations of interest: immunocompromised, renally impaired, or hepatically impaired; and if appropriate, in the combined population. Prior to any combined analysis, a Higgin's I2 statistic will be used to assess the heterogeneity in the primary outcomes across the 3 populations of interest. If the percentage of heterogeneity estimated by I2 is high (e.g., >50%; specific threshold to be specified in the SAP), a combined effect may be estimated using adapted methods such as a random-effects model.

9.7.1. Baseline Characteristics

Baseline demographics and clinical characteristics for individuals vaccinated with ABRYSVO and the unvaccinated cohort will be summarized using descriptive statistics, consisting of the mean, SD, median, inter-quartile range, minimum, and maximum values for continuous variables and frequency distributions for categorical variables. Descriptive statistics will also be used to summarize ABRYSVO uptake characteristics, including calendar year and month of vaccination and care setting of vaccination (e.g., outpatient clinic, pharmacy, inpatient ward if available).For the comparative cohort design analysis, crude standardized differences in the baseline characteristics will be calculated between vaccinated and unvaccinated cohorts before and after weighting. Standardized differences <10% will indicate that the baseline characteristics of ABRYSVO vaccinated and unvaccinated cohorts are balanced.

9.7.2. Incidence Rates of Outcomes

Incidence rates per 1,000 patient-years (and corresponding 95% CIs) will be calculated for prespecified outcomes (as described in Section 9.3.2) as the total number of incident events divided by the total observation time/person-time. The number of cases and incidence rates of each outcome will be reported for each of the populations of interest (i.e, immunocompromised, renally impaired, and hepatically impaired populations separately) in the vaccinated and unvaccinated cohorts.

For outcomes with unknown risk windows or those that require longer follow-up (e.g., death), the cumulative incidence will be computed, which will be estimated with a 1 − Kaplan-Meier survival curve, as well as with adjusted parametric incidence curves.[56] Time to outcome onset will be defined as the time from the index date until the occurrence of the prespecified outcome event or censoring. For most outcomes, the associated severity and rapidity of onset are likely to result in a healthcare encounter close to the time of outcome onset, so the date of onset will be assumed to be the date of the healthcare encounter. The SAP will elaborate on further analyses for outcomes that may have a time lag between symptom onset and a healthcare encounter (e.g., DVT, diabetes type 1).

For individuals without an outcome, the censoring date will be defined as the date of death, date of RSV vaccination (for unvaccinated individuals who later receive any RSV vaccine only), end of the administrative follow up, or the end of data availability, whichever occurs earliest. For outcomes with defined risk windows, censoring will also occur at the end of the risk window. For composite outcomes, follow-up will be censored at the date of the first occurrence of any of its components.

9.7.3. Safety Analyses

Several analyses corresponding to the comparative cohort and SCRI designs will be conducted to assess whether there is an increased risk of outcomes associated with ABRYSVO vaccination. Analyses will be conducted among all individuals meeting the study eligibility criteria.

- Incidence rates of prespecified outcomes among the vaccinated cohort will be compared to rates observed in the unvaccinated cohort.
- Self-controls: Among individuals who experienced prespecified outcomes following vaccination, the SCRI design will be used to compare the incidence of outcomes in the risk interval following vaccination to the incidence in the post-vaccination control interval in the same individual.

9.7.3.1. Comparison with Unvaccinated Cohort

For each of the immunocompromised, renally impaired or hepatically impaired populations respectively, the incidence rates of the prespecified outcomes following administration of ABRYSVO will be compared against the incidence rates of the prespecified outcomes among individuals who did not receive ABRYSVO or any other vaccine at index.

An ATT weighting will be used to ensure baseline comparability between the ABRYSVO vaccinated cohort and unvaccinated cohort. ATT weighting creates a “pseudo-population” in which the distribution of covariates is, on average, the same in each cohort.[57] Specifically, ATT weights will be calculated to allow for estimation of the average treatment effect among individuals receiving ABRYSVO.[57] This approach will be taken to ensure that inference from the analysis will be applicable to the vaccinated population. Individuals receiving ABRYSVO will receive an ATT weight of one. Individuals not receiving ABRYSVO will receive an ATT weight equal to the odds of receiving ABRYSVO conditional on their demographic and clinical characteristics as of the index date, which will be calculated based

on the PS. The PS is defined as an individual's probability of receiving ABRYSVO, conditional on observed baseline covariates, and will be calculated using a logistic regression model. To select the variables to be included in the PS logistic model, a systematic approach based on clinical relevance, prior research, and statistical criteria will be used. The PS logistic regression model may include the cohort variable (i.e, ABRYSVO versus unvaccinated control) as the dependent variable, the independent variables that are deemed clinically important and have shown good control of confounding for previous comparative vaccine studies (e.g., age, sex, place of residence, co-morbidity indices, socioeconomic status/education level),[58] and baseline covariates that have crude standardized differences ≥10% between the two cohorts. Specifically, ATT weights will be PS/(1-PS) for individuals with no record of ABRYSVO. The distribution of weights will be examined to assess extreme values, and truncation will be considered if necessary.

Individuals will be followed from the index date until death, end of administrative follow up (and/or risk interval), end of the study period, or the date of ABRYSVO/RSV vaccination (for unvaccinated individuals who later receive any RSV vaccine only), whichever occurs first. The degree of loss to follow-up will be examined. If the censoring rates differ by exposure group (i.e, indicating informative censoring) and high censoring rates (e.g., >20%) are observed, IPCW will be derived to account for informative censoring, where the weight will be calculated for each individual as the inverse of the probability of remaining uncensored during the risk interval. The stabilized IPCW will be calculated as follows, where A= vaccination, V = covariates to adjust, and C=0 represents that the patient has remained uncensored: (Pr[C=0 | A=1])/(Pr[C=0 | A=1,V=v]) for the vaccinated cohort; (Pr[C=0 | A=0])/(Pr[C=0 | A=0,V=v]) for the unvaccinated cohort.

The final weights will be calculated as the product of the ATT weight and IPCW (ATT x IPCW) if informative censoring is observed, and the ATT weight will be used as the final weight if informative censoring is not observed. The distribution of final weights (e.g., mean, SD, minimum, and maximum values) will be examined and extreme weights will be truncated or capped at the 1st and 99th percentile. After weighting, the distribution of baseline characteristics will be evaluated between the vaccinated cohort and the unvaccinated cohort, and variables that remain inadequately balanced (standardized difference >10%) between the two cohorts will be included as regression model covariates in a doubly robust approach.

Weighted Poisson regression models will be conducted to calculate IRRs of outcomes among vaccinated cohort vs. unvaccinated cohort. Incidence rate ratios will be summarized, and robust variance estimators will be used to calculate the corresponding 95% CIs.

9.7.3.2. SCRI Design

SCRI design with post-vaccination control interval will compare the incidence of prespecified outcomes occurring in the risk interval following ABRYSVO vaccination with the incidence of prespecified AESIs occurring during the post-vaccination control interval.

In order to account for the self-matched design, a conditional Poisson regression model will be used to estimate relative incidence and 95% CIs. The dependent variable will be the

number of events occurring during the risk or control window. The independent variables in all the models will be the type of window (risk or control), and the person-time in each considered window, which will be handled as an offset term. The SCRI inherently adjusts for both measured and unmeasured time constant factors such as sex and chronic health conditions with onset before the start of follow-up. Time-varying confounders may be included as covariates in regression models. Outcomes for which the SCRI design will be a complementary design, and corresponding risk windows for such outcomes are described in Table 1.

As noted in Section 9.2.1, individuals in the SCRI design will be required to have full accrual of data to define the outcome in the risk and control intervals combined. If an outcome of interest (e.g., cardiac outcome) substantially increases the mortality risk, death may prevent individuals from accruing the full follow-up period, leading to their exclusion from the SCRI study. To evaluate this possibility, the 30-day CFR will be calculated for each outcome. Outcomes with a high 30-day CFR (e.g., >20%) will be considered for further adjustment in the SCRI design. Approaches may include using the Farrington adjustment as the primary analysis or extending follow-up periods to include individuals who die following an outcome of interest in the SCRI analyses. The final 30-day CFR threshold, and details of the adjustment method, will be specified in the SAP.

9.7.3.3. Meta-analysis

For both the comparative cohort and SCRI designs, an appropriate random-effects meta-analytic method will be applied to the main estimates from each data source to obtain a combined effect estimate. The heterogeneity across data sources will be checked, and a forest plot will be produced with the data sources and the pooled estimate.

9.7.4. Sensitivity Analyses

As feasible, sensitivity analyses, as well as analyses to evaluate potential bias, may include, but are not necessarily limited to:

- Comparative cohort design with extended risk windows for the acute outcomes to assess potential outcome under-reporting and misclassification
    - The exception will be atrial fibrillation and supraventricular arrhythmias where shorter risk windows of 0-3 days (as well as 0-1 days and 0-30 days) will be considered to allow for greater consistency with the ongoing ABRYSVO safety study in the Veterans Affairs population (C3671037). Further details on alternative risk intervals will be provided in the SAP.
- SCRI with alternative risk and control intervals to assess potential exposure misclassification. In addition, to allow for greater consistency across ongoing ABRYSVO vaccine safety studies, specifically C3671031 and C3671037, the following risk intervals will be applied as sensitivity analyses for the following AESIs:
    - GBS: risk interval 1-21 days[59]
    - Acute disseminated encephalomyelitis: risk interval 5-28 days [60]
    - Transverse myelitis: risk interval 1-21 days [59, 61]

    - A SCRI analysis may also be considered for atrial fibrillation and supraventricular arrhythmias with risk intervals of 0-3 days, 0-1 days and 0-30 days to align with the planned SCRI analysis from study C3671037. Further details on alternative risk and control intervals will be provided in the SAP.
- SCRI with pre-vaccination control interval. If vaccination is deferred while unwell with symptoms related to outcomes, this may violate the assumption of the SCRI design that an outcome event should not alter the probability of subsequent exposure to vaccination. Defining a separate pre-vaccination window can assess these design assumptions and ensure that they are not violated.
- SCRI with a washout period between risk and control intervals, within the subset of outcomes for which an increased risk is detected
- For outcomes with CFR >20%, SCRI analysis incorporating Farrington adjustment or extending follow-up after death for full length of risk and control window
- Use of narrow and broader definition algorithms for outcomes to assess outcome misclassification (comparative cohort and SCRI)
- Descriptive analyses will be conducted to assess whether there is differential receipt of other vaccines in the follow up period between the vaccinated and unvaccinated cohort (comparative cohort design) and between the risk and control intervals (SCRI design). Differential receipt of vaccines during follow up may introduce potential time varying confounding. If differential patterns of vaccination during follow up are observed, the following approaches may be considered:
    - Comparative cohort analysis with censoring at receipt of another vaccine during follow-up
    - SCRI with analyses stratified by those who did and did not receive vaccinations during the risk or control interval
    - For individuals with receipt of other vaccines close to index (e.g.,30 or 45 days prior to index), comparative cohort and SCRI analyses will be repeated excluding those individuals
- Quantitative bias analysis to assess potential unmeasured confounding (comparative cohort)
- Negative control outcome analyses will be considered to assess potential unmeasured confounding, selection bias, and misclassification bias (for both comparative cohort and SCRI designs). As different AESIs may be associated with different care and medical encounter patterns reflecting different bias structures, careful consideration should be given to which negative controls are appropriate for which AESI analyses. As such, several negative controls may be considered for inclusion, including, but not limited to, accidental poisoning, appendicitis, cataracts, or non-vertebral fractures. Further details on the choice of negative control outcomes will be described in the SAP.

Further details and any additional sensitivity analyses that may be conducted will be described in the SAP.

9.7.5. Other Analysis

As feasible given sample sizes, the same analytical approaches will be applied to each study population (i.e, immunocompromised, renally impaired, or hepatically impaired population), stratified by subgroups of interest. The specific subgroups of interest will be detailed in the SAP.

9.7.6. Small Cell Count Rules

The small cell count rules specified in Table 3 will be taken into account when presenting results of the study. The cover page, statistical analysis, and results section of study reports will contain the following statement: *This report is for regulatory communications only. For any dissemination beyond regulatory authorities, please refer to the data protection rules, and apply the masking rules regarding small cell count restrictions in Section 9.7 and Table* 3.

Table 3 Small Cell Count Rules for Reporting Results

	CPRD	SIDIAP	SNDS	VID	EpiChron
Numbers to be masked	1-4	1-4	1-10	NA	1-4
Text to be redacted	1≤n≤4	1≤n<15	1≤n≤10	NA	1≤n≤4
Possible to share with PASS VAC4EU centres	No	Yes	No	Yes	No
Possible to share with regulatory authorities (report shared by MAH)	Yes	Yes	No	Yes	Yes
Comments	CPRD allows an exemption from the small cell suppression requirement for regulatory submissions to medicines regulatory agencies to inform policy decisions on the condition that the small	Not applicable	A clear statement about cell suppression is required		No comments

Table 3 Small Cell Count Rules for Reporting Results

	CPRD	SIDIAP	SNDS	VID	EpiChron
	cells will be suppressed if the regulators wish to publish the results in the interest of transparency.				

9.8. Quality Control

Rigorous quality control (QC) will be applied to all deliverables. Data transformation into the CDM will be conducted by each subcontracted research partner in its associated database, with processes as described in the following corresponding sections. Standard operating procedures (SOPs) or internal process guidance at each research centre will be used to guide the conduct of the study. These procedures include rules for secure and confidential data storage, backup, and recovery; methods to maintain and archive project documents; QC procedures for programming; standards for writing analysis plans; and requirements for scientific review by senior staff.

At UMCU, as the scientific coordinating centre responsible for central data management and analysis, all documents undergo QC review and senior scientific review. Data management and statistical analysis follow SOPs. All statistical analysis programmes will be double coded by an independent research partner who does not have access to the primary programmer's codebase. All discrepancies in outcome tables will be thoroughly documented, investigated and resolved. The same approach is applied for the University of Bordeaux as the scientific coleader centre.

At Julius Clinical, as the project coordinating centre, all key study documents will undergo QC review, senior scientific review, and editorial review. This will include the SAP and analytical programmes as Julius Clinical will also fulfil the QC programmer and QC statistician role. Senior reviewers with expertise in the appropriate subject matter area will provide advice on the design of research study approaches and the conduct of the study and will review results, reports, and other key study documents.

9.8.1. CPRD (UK)

The DSRU has information security policies in place to preserve the confidentiality, integrity and availability of the organization's systems and data. These include ensuring that the premises provide suitable physical and environmental security, all equipment is secure and protected against malicious software, the network can be accessed only by authorized staff, telecommunication lines to the premises are protected from interception by being routed overhead or underground, and personnel receive training regarding security awareness. The study will be conducted according to the International Society for Pharmacoepidemiology

Guidelines for *Good Pharmacoepidemiology Practices (GPP)*[62] and according to the *ENCePP Code of Conduct*.[63] Data quality is a high priority at the DSRU and is assured through a number of methods based on staff training, validated systems, error prevention, data monitoring, data cleaning, and documentation, including the following:

- Staff training on data processing standard operating procedures
- Data management plan for every research study outlining the legal basis for data collection, data flows, data access rights, data retention periods, etc.
- Routine data cleaning to screen for errors, missing values, and extreme values and diagnose their cause
- System process logs to document staff access, etc.

9.8.2. VID (ES)

After Ethical Review Board approval, raw data will be extracted in text file format and will undergo a data quality check. Data will be stored on secure servers at FISABIO in accordance with Spanish and data protection requirements and ensuring that no identifiable data will be stored longer than required. All the procedures that will be implemented for data collection, storage, protection, retention, and destruction will comply with national and EU legislation. The research team will stay up to date with the detailed provisions of the EU GDPR, and which will supersede national legislation within the EU Member States.

9.8.3. SIDIAP (ES)

Data quality processes are implemented at each phase of the data flow cycle. QC checks are performed at the extraction and uploading steps. To assess data completeness, the elements present are described by geographical areas, registering physician, time and the distribution function of values. Correctness is assessed by validity checks on outliers, out of range values, formatting errors and logical date incompatibilities. Completeness and correctness measures are used to inform decisions on the required transformations to improve data quality (e.g., harmonisation, normalisation, and clean-up) and the data fitness for the purpose of specific research projects.

9.8.4. EpiChron (ES)

The EpiChron cohort is built from the BIGAN platform which integrates a technical infrastructure and a data lake, collecting individual data from the regional health service information systems. The BIGAN platform includes several mechanisms to control and improve the quality of data, mainly in the ETL processes for capture and persistence in the data lake. These mechanisms include validation rules (for example, for dates and time intervals) and cross-checks with master tables, requiring that certain coded data exist in a standardised dictionary. Analyses of the distribution of variables are also carried out periodically, to detect ‘outliers' that identify errors in the data capture or transformation processes. Generally, records that do not pass the quality assurance procedures are kept in a ‘holding' area for review and decision to discard or reprocess. The resulting databases are pseudonymised to encrypt individual-level identification codes, protecting individuals’

privacy and complying with data protection laws. They are stored on a central computer server, with access restricted to the members of the research group, via a two-step authentication process. The research group comprises a multidisciplinary qualified team including public health specialists, epidemiologists, clinicians, pharmacists, statisticians, and data managers, who are all trained in data management and data protection.

9.8.5. SNDS (FR)

All key study documents will undergo a quality control review, senior scientific review, and editorial review. Senior reviewers with expertise in the appropriate subject matter area will provide advice on the design of research study approaches, the conduct and management of the study, and will review results, reports, and other key study documents.

BPE has implemented a quality management system for all its activities and is ISO 9001:v2015 certified for its activities in pharmaco-epidemiology research. CNAM data extraction will be validated using the expected population size estimated using the SNDS. All statistical logs are kept and can be provided. In the case of interim analyses, the database for the interim analysis is locked and kept for ulterior validation if needed.

9.9. Limitations of the Research Methods

This study is subject to limitations related to both the study design and use of secondary healthcare data.

Use of a distributed data network with data contributed from different data sources means there may be differences in healthcare practice, data provenance, data availability and completeness that may introduce differential bias. For example, some data sources may capture laboratory data to enable the application of more specific definitions of the study population. However, the application of a common protocol and common semantically harmonised study definitions aims to limit these differences. In addition, the increase in sample size and generalisability from working across multiple data sources and countries outweighs this potential limitation given the populations of interest are relatively rare.

This study relies on the accuracy of codes and algorithms recorded in the participating healthcare databases to identify the study populations of interest, as well as vaccination exposure and outcomes of interest. In terms of the capture of the immunocompromised, renally and hepatically impaired populations of interest, it is possible that patients with more severe disease may be more likely to have their diagnoses captured via documented codes and thereby be included in the study population. If the absolute risk of an outcome following vaccination differs by severity of underlying disease, there may be some over-estimation of outcome incidence in the target population. However, for comparative analyses, this limitation should not apply. Exposure identification will be based on pharmacy dispensing records, general practice records, immunization registers, medical records, or other secondary data sources. The ability to identify specific ABRYSVO vaccine products and dates of vaccination in these data sources is reflected in Section 9.3.1. However, it is possible that individuals vaccinated outside the healthcare system will not be recorded in healthcare databases, thereby leading to potential bias because of exposure misclassification within the

comparative cohort design. Use of the complementary SCRI design, where appropriate, is therefore a strength as this relies upon individuals for which there is a record of vaccination and is not subject to potential misclassification of vaccination status. It is also possible that some outcomes are the result of immunization errors occurring during the administration of ABRYSVO. This information is not collected regularly and will not be accounted for with the current protocol.

Similarly, outcomes are based on coded events captured in the databases and misclassification due to coding errors, or use of sub-optimal algorithms, may lead to misclassification bias. The databases proposed for this study all have access to linked primary and secondary care data to maximize capture of outcomes of interest. In addition, this study proposes to use outcome algorithms from the ACCESS project which have now been widely applied in vaccine safety studies, with additional validation completed in previous studies. To further assess the potential for misclassification, more sensitive and specific algorithm versions can be applied in sensitivity analyses. Differential ascertainment of outcomes is a potential limitation within the comparative cohort design if the vaccinated and unvaccinated populations have different healthcare seeking behaviour which not only influences their probability of vaccination, but also access to care for outcomes. Given this study focuses on populations with chronically managed conditions, differential outcome reporting is not anticipated due to the frequent nature of healthcare encounters in the populations of interest; but differential healthcare seeking behaviour will still be adjusted for (as feasible) through PS-based ATT weighting.

Further, outcome onset is defined by the timing of the healthcare encounter at which the diagnosis is recorded. For outcomes with rapid onset that are serious enough to warrant an interaction with the healthcare system, the date of onset will closely reflect the date of the diagnosis associated healthcare encounter. Some outcomes may have a longer lag period between symptom onset and diagnosis. For these outcomes, sensitivity analyses can be used to explore potential impact of mis-specification of outcome onset.

A limitation common to both the comparative cohort and SCRI designs is that any uncertainty regarding risk periods may lead to misclassification and attenuation of risk estimates. However, this will be minimized by using risk intervals based on prior evidence of biological plausibility. The potential for misclassification of the risk period will also be investigated by varying risk intervals within sensitivity analyses.

Administration of other vaccines during follow-up is a potential time varying confounder. Similarly, receipt of other vaccine shortly before the index date may confound the observed outcome risks. The potential for time varying confounding will be assessed by descriptively evaluating whether there is differential receipt of other vaccines during follow-up between the vaccinated and unvaccinated cohorts within the comparative cohort design, as well as between the risk and post-vaccination control intervals for the SCRI design. If the distribution of non-ABRYSVO vaccine administration is imbalanced, additional analyses will be conducted to account for this imbalance. These may include censoring follow-up at receipt of additional vaccines in the comparative cohort design and stratifying analyses by receipt of additional vaccines for the SCRI design. To explore the residual effects of

vaccination receipt prior to index, sensitivity analyses can be considered excluding individuals with prior receipt of vaccines within a pre-specified time window (e.g., 30 or 45 days prior to index).

Finally, a limitation of the cohort design is the potential for residual confounding from unmeasured confounders. Potential confounders will be accounted for in the statistical analysis using ATT weighting to achieve balance and adjustment for known confounders between cohorts. However, unmeasured confounding may remain due to variables not being captured within the routine healthcare datasets or being subject to missingness. As feasible, the potential for residual confounding will be explored in several ways: The within-person SCRI design will also be applied where appropriate which accounts for time invariant confounding, and additional sensitivity analyses including negative controls will be considered to further quantify the potential for residual confounding.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/pseudonymized structured format and contains no patient personal information.

10.2. Patient Consent

As this study involves deidentified/pseudonymized structured data, which are subject to the General Data Protection Regulation; 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 (e.g., informed consent forms if applicable) from the relevant IRBs/ECs or data source governance committees. All correspondence must be retained. Copies of IRB/EC approvals or waivers must be forwarded to Pfizer.

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 the following paragraphs:
This study will adhere to the *GPP*[60] and has been designed in line with the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology*.[62, 63] The *ENCePP Checklist for Study Protocols* will be completed (see ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS).[64]

The study is a post-authorisation study of vaccine safety and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation tripartite guideline *Pharmacovigilance Planning E2E*[65] and provided in the

EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety* Studies,[66] and with the 2012 EU pharmacovigilance legislation, adopted 19 June 2012 and updated as of 13 October 2017.[67]

The study will be registered in the HMA-EMA Catalogue of RWD studies[68] before the start of data collection. Regular updates will be provided to regulatory agencies regarding data collection through planned study progress and interim reports, as well as additional routine regulatory communication (e.g. via periodic safety update reports).

The research team and study sponsor should adhere to the general principles of transparency and independence in the *ENCePP Code of Conduct*[63] and the ADVANCE Code of Conduct.[69] The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigour, and will follow generally accepted research practices described in the ISPE GPP,[70] CIOMS International Ethical Guidelines for Epidemiological Studies,[71] ENCePP Guide on Methodological Standards in Pharmacoepidemiology,[72] FDA Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment,[73] and FDA Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.[74] An independent scientific advisory committee will be set-up, comprising experts in vaccine safety studies.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Structured Data Analysis

This study involves 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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As per EMA GVP Module VIII, the study and its protocol will be registered in the HMA-EMA Catalogue of RWD studies prior to the start of data collection. Progress and final study reports will be posted as well. The study protocol and reports will be submitted to the EMA as agreed in the risk management plan.

Results of analyses and interpretation will be delivered in report form.

Planned Reports:

Progress Report: 30 September 2025 (or 12 months after protocol endorsement)

Interim Report: 30 September 2026 (or 24 months after protocol endorsement)

Final Report: 28 September 2029

Study results will be published following guidelines, including those for authorship, established by the ICMJE. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed. Independent publication rights will be granted to the research team in line with Section VIII.B.5., Publication of study results, of the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies*.

Upon study completion and finalisation of the study report, the results of this PASS will be submitted for publication, preferably in a relevant peer-reviewed journal. Communication via other appropriate scientific venues will be considered.

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 that 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

16. ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: A post-authorisation safety study of ABRYSVO in immunocompromised, or renally or hepatically impaired adults aged 60 years and older in a real world setting in Europe and UK

EU PAS Register® number: To be registered before the start of data collection **Study reference number (if applicable):** Not applicable

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the HMA-EMA Catalogue of RWD studies	☒	☐	☐	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:	☒	☐	☐	8
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
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

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

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

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
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1, 9.7
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, 9.7
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:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.3
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.1, 9.2.4
	4.2.2 Age and sex	☒	☐	☐	9.2.1
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.2.1, 9.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1, 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)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.9
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
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?	☒	☐	☐	9.1, 9.3.1.1, 9.3.1.2

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?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2.2, 9.9
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)	☒	☐	☐	9.1.2, 9.7.3, 9.7.4, 9.9
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.1.1, 9.7.4

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.1.2, 9.7.4, 9.9

Comments:

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

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1, 9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
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)	☒	☐	☐	9.3.1, 9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1, 9.4
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2, 9.4
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7.5
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.4
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.4

Comments:

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

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
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).	☒	☐	☐	9.9
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)	☒	☐	☐	9.2, 9.5

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?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6.2, 9.7.6, 9.8,10.2

Comments:

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

Comments:

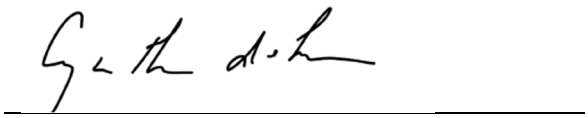
Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Cynthia de Luise

Date: dd/Month/year 14 March 2024

Signature:



18. ANNEX 3. ADDITIONAL INFORMATION

Not applicable

Document Approval Record

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De Bernardi, Barbara	07-Oct-2024 21:44:51	EUQPPV Approval
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