POST-AUTHORIZATION SAFETY STUDY (PASS) PROGRESS REPORT 1

Title	A Post-authorization 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 the UK
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Medicinal product	ABRYSVO
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ABBREVIATIONS AND ACRONYMS

Abbreviation	Meaning
AESI	Adverse event of special interest
BMT	Bone marrow transplant
BPE	Bordeaux PharmacoEpi
CCI	Charlson Comorbidity Index
CDM	Common Data Model
CEIm	Spanish Ethics Committees for Investigation with Medicinal Products
CEPS	Comité Économique des Produits de Santé (Economic Committee for Health Products)
CESREES	Comité d'Éthique pour les Recherches, les Études et les Évaluations dans le domaine de la Santé (Ethics Committee for Health Research and Evaluation)
CKD	Chronic kidney disease
CNAM	French National Health Insurance Fund
CNIL	Commission Nationale de l'Informatique et des Libertés, (French Data Protection Authority)
COSV	Conseil d'Orientation de la Stratégie Vaccinale (French Vaccine Strategy Steering Committee)
CPRD Aurum	Clinical Practice Research Datalink Aurum
DEAP	Data Expert and Access Partner
DSRU	Drug Safety Research Unit
eGFR	Estimated glomerular filtration rate
EpiChron	Epidemiology and Chronic Conditions Research Group in Aragon, Spain
ETL	Extract, Transform, Load (process)
EU	European Union
FISABIO	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (Health and Biomedical Research Foundation of the Valencia Region)
HAS	Haute Autorité de Santé (French Health Authority)
HIV	Human immunodeficiency virus
IACS	Instituto Aragonés de Ciencias de la Salud (Aragon Health Sciences Institute)
IBD	Inflammatory bowel disease
IDIAPJGol	Institut Universitari d'Investigació en Atenció Primària Jordi Gol, (Catalonia primary care research institute)
JCVI	Joint Committee on Vaccination and Immunisation
MELD	Model for End-Stage Liver Disease
MHRA	Medicines and Healthcare Products Regulatory Agency
NITAG	National Immunisation Technical Advisory Group
PASS	post-authorisation safety study
RDG	Research Data Governance
RSV	Respiratory syncytial virus
SAP	Statistical analysis plan
SCRI	self-controlled risk interval
SNDS	Système National des Données de Santé (French National Healthcare Database)
UACR	Urine albumin-to-creatinine ratio
UK	United Kingdom
US	United States
VAC4EU	Vaccine Monitoring Collaboration for Europe
VID	Valencia Integrated Database

1. MILESTONES

Milestone	Planned date	Actual date	Comments
Registration in the HMA-EMA Catalogues of RWD Studies	Prior to the start of data collection	25 February 2025	
Start of data collection[1]	01 October 2025		
End of data collection[2]	30 March 2029		
Study progress report[3]	30 September 2025		
Interim report[4]	30 September 2026		
Final study report	28 September 2029		

1. 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.
2. End of data collection is "the date from which the analytical data set is completely available."
3. The progress report is anticipated 12 months after protocol endorsement.
4. The interim report is anticipated 24 months after protocol endorsement.

2. EXECUTIVE SUMMARY TABLE

Section	Summary
Background	Respiratory syncytial virus (RSV) causes approximately 270,000 hospitalisations and 20,000 deaths annually in adults aged ≥60 years across Europe. Risk is highest in individuals with immunocompromising conditions, renal impairment, or hepatic impairment.
Vaccine	ABRYSVO (bivalent RSV prefusion F protein subunit vaccine) was approved for use in adults aged ≥60 years in the United States (US) in May 2023, in the European Union (EU) in August 2023 and in the United Kingdom (UK) in November 2023.
Study Rationale	Clinical trials excluded high-risk populations. This post-authorisation safety study (PASS) addresses this data gap by evaluating real-world vaccine safety in adults ≥60 years with relevant comorbidities.
Study Design	Multinational, observational study using two methods: (1) a matched cohort design comparing vaccinated and unvaccinated individuals assessing the risk of specified acute adverse events of special interest (AESIs); (2) a self-controlled risk interval (SCRI) design focused on acute AESIs.
Target Populations	Adults aged ≥60 years who are: (1) immunocompromised, (2) renally impaired, or (3) hepatically impaired.
Data Sources (DEAPs)	Data Expert and Access Providers (DEAPs) include France: Système National des Données de Santé (SNDS), via Bordeaux PharmacoEpi (BPE); Spain: EpiChron (Aragon), SIDIAP (Catalonia), Valencia Integrated Database (VID); England and Northern Ireland: Clinical Practice Research Datalink Aurum (CPRD Aurum), via Drug Safety Research Unit (DSRU)
National Vaccine Policy	France: ABRYSVO is authorised but not yet reimbursed for the target population. Spain: Not implemented for high-risk groups. UK: National programme for adults aged 75–79 years began February 2025.
Ethics and CDM Status	Most DEAPs have obtained ethics approval. However, SNDS is still waiting for authorisation from the French data protection authority (CNIL). The Common Data Model (CDM) transformation is not yet complete in most sources.
Early Vaccine Uptake	No uptake data available yet from France or Spain. In England and Northern Ireland (CPRD Aurum): approximately 340,000 immunocompromised individuals are eligible, with 2,800 vaccinated; 171,000 renally impaired eligible, with 1,616 vaccinated; 26,000 hepatically impaired eligible, with 135 vaccinated.
Challenges	Current absence of vaccine reimbursement in the target population in France; lack of vaccine access in Spanish study regions;
Next Steps	The next phase of the study will focus on finalising data access agreements and completing CDM transformation, with the goal of initiating formal analyses in all data sources with agreement for data access. Efforts will also prioritise the inclusion of additional DEAPs across Europe and beyond, such as Switzerland and Scotland, to enhance study coverage and extend generalisability. Work on the interim report will begin in October 2025; CDM transformation and onboarding activities have started.

3. RATIONALE AND BACKGROUND

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory tract infection in both infants and older adults.[1] Among adults aged 60 years and older, RSV is associated with significantly increased risks of hospitalisation and mortality compared with younger populations.[1-9] In Europe alone, RSV contributes to an estimated 270,000 hospitalisations and approximately 20,000 deaths annually in this older population.[10]

Older adults with underlying comorbidities, such as cardiovascular disease, chronic lung disease, diabetes, renal or hepatic impairment, and immunosuppressive conditions, are at particularly high risk of severe RSV outcomes.[10-18] A study from 28 European countries found that RSV infections in older adults, especially those with comorbid conditions, is a major contributor to acute respiratory infection (ARI)-related hospitalisations.[17]

Immunocompromised individuals, including recipients of haematopoietic stem cell transplants, individuals undergoing intensive chemotherapy, and lung transplant recipients, experience more severe, persistent RSV illness, and have the highest rates of RSV-associated morbidity and mortality.[12, 15, 18, 19] Similarly, older adults with renal or hepatic impairment are increasingly recognised as vulnerable to both infection and severe disease.[14]

ABRYSVO received regulatory approval from the United States (US) Food and Drug Administration (FDA) on 31 May 2023, and marketing authorisations from the European Commission on 23 August 2023 and the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) on 21 November 2023, for the prevention of lower respiratory tract disease (LRTD) caused by RSV in adults aged 60 years and older.

The approval was based on evidence from the pivotal Phase 3 RENOIR clinical trial (C3671013, NCT05035212), which demonstrated the efficacy, immunogenicity, and safety of a single 120 μg dose of ABRYSVO in healthy older adults.[11, 18] Early findings suggested that the minimum protective efficacy was two years, with the possibility of an extended duration of protection.[20] However, individuals with immunocompromising conditions or renal or hepatic impairment were excluded from these clinical trials, leaving a safety and effectiveness data gap for these high-risk populations.

To address this gap, this post-authorisation safety study (PASS) aims to evaluate the safety of ABRYSVO in adults aged 60 years and older with immunocompromising conditions or renal or hepatic impairment, using real-world data from selected EU countries and England and Northern Ireland. This PASS will focus exclusively on evaluating safety in high-risk populations and will not assess vaccine effectiveness.

This PASS is an additional pharmacovigilance activity (Category 3) in the EU/UK Risk Management Plan (RMP) and is also included in the US Pharmacovigilance Plan (PVP) for ABRYSVO. Given that the study population size depends on National Immunisation Technical Advisory Group (NITAG) recommendations and national implementation guidelines, this progress report documents vaccine uptake in the target populations and summarises study progress across participating countries based on available data and regulatory milestones.

4. RESEARCH OBJECTIVES

The primary research objective is to estimate the incidence rates (IRs) and incidence rate ratios (IRRs) of safety events of interest in immunocompromised, or renally or hepatically impaired adults aged 60 years and older who receive ABRYSVO compared with a relevant comparator group who does not receive ABRYSVO. The evaluation will be done in each population separately and, if appropriate, in the combined population.

4.1. KEY OBJECTIVES OF THE PROGRESS REPORT

This progress report addresses the following objectives aligned with the early phases of study implementation:

Objective 1: Review of National Guidelines and Recommendations
We reviewed national immunisation guidelines and recommendations available up to July 2025, including guidance from NITAGs, to assess the current or planned inclusion of ABRYSVO in vaccination programmes targeting high-risk adults aged ≥60 years. The findings are presented in Section 4.1 and summarised in Table 1.

Objective 2: Assessment of Ethical Approval Status
We documented the status of ethical and regulatory approvals based on information from data expert and access providers (DEAPs). These updates are presented in Section 6.4 and summarised in Table 2.

Objective 3: Evaluation of RSV Vaccine Uptake in High-Risk Populations
We evaluated the early implementation of RSV vaccination strategies in three high-risk adult populations aged ≥60 years: (a) immunocompromised individuals, (b) individuals with renal impairment, and (c) individuals with hepatic impairment. Data were obtained from participating databases or, if access was restricted due to contractual or ethical considerations, data were obtained from national reports. No data were available for France as RSV vaccination has not yet been introduced for these high-risk groups. Findings are discussed in Section 6.5 and summarised in Table 3.

Given that formal data collection is scheduled to begin in October 2025, this report focused on preparatory activities, feasibility assessments, and early implementation milestones.

Table 1. National RSV Vaccination Policy Status (ABRYSVO-specific)

Country	Data source / Region	ABRYSVO in Guidelines	Population(s) Prioritised	Reimbursement Status	Latest Update
France	SNDS	Yes	≥75 years, or ≥65 with heart/lung disease	Not yet reimbursed in older adults	Reimbursement under discussion with the French Economic Committee for Health Products
Spain	EpiChron (Aragon)	No	–	No	Not implemented in participating regions

Table 1. National RSV Vaccination Policy Status (ABRYSVO-specific)

Country	Data source / Region	ABRYSVO in Guidelines	Population(s) Prioritised	Reimbursement Status	Latest Update
	SIDIAP (Catalonia), VID (Valencia),				for the studied population
England and Northern Ireland	CPRD Aurum	Yes	Adults aged 75+ years[21]	Available via National Health System	February 2025: JCVI recommended routine and catch-up programme.[22]

4.2. REAL-WORLD DATA SOURCES AND ANTICIPATED SAMPLE SIZE

The study will use real-world data that are routinely collected in electronic health records and administrative claims databases in several European countries. The participating DEAPs will provide access to linked datasets that capture relevant information on RSV vaccine exposure, baseline comorbidities, and AESIs.

The data sources included are listed below.

4.2.1. France – SNDS via Bordeaux PharmacoEpi (BPE)

In France, estimates for risk groups were derived from national datasets and published algorithms, including estimation of immunocompromised people by the Conseil d'Orientation de la Stratégie Vaccinale (COSV) [23] an algorithm to identify chronic kidney disease in the SNDS and various estimations of liver diseases by aetiology using multiple data sources (Table 3). Although the estimates suggest that there are substantial numbers of eligible individuals in France, there is currently no vaccine uptake due to ongoing reimbursement negotiations and the absence of the vaccine from the national immunisation calendar.

4.2.2. Spain – Aragon (EpiChron)

Regional estimates for the eligible population sizes were drawn from local census data and the Aragon Morbidity Atlas. No data on vaccine uptake are currently available, as ABRYSVO has not yet been implemented in the Aragon region.

4.2.3. Spain – Catalonia (SIDIAP)

Estimates of the eligible population sizes for individuals with immunocompromising conditions, renal impairment, and hepatic impairment were based on local studies and the Catalan Transplant Organisation [Organització Catalana de Trasplantaments] (OCATT) registry. ABRYSVO has not yet been implemented in Catalonia for high-risk populations.

4.2.4. Spain – Valencia (VID)

Estimates of the eligible population sizes were derived from administrative health records and peer-reviewed literature. Vaccination has not yet been implemented in the Valencia region for the studied high-risk population groups.

4.2.5. England and Northern Ireland (CPRD Aurum)

CPRD Aurum (England and Northern Ireland) is the only data source participating in this study for which vaccine uptake data is available. Among older adults with risk conditions,[24] CPRD Aurum has recorded ABRYSVO vaccination for 2,800 immunocompromised individuals, 1,616 with renal impairment, and 135 with hepatic impairment. Estimates are based on diagnostic and medication codes recorded between 01 September 2024 and 03 July 2025.[25]

The anticipated study size will be determined by the number of eligible vaccinated individuals and the matched unvaccinated individuals available in each data source. Preliminary estimates will be refined following finalisation of ethical approvals and completion of data extraction into the CDM.

4.3. STUDY POPULATIONS

Each cohort will include individuals aged ≥60 years with at least one of the qualifying conditions, i.e., immunocompromised, renal impairment, or hepatic impairment.

4.3.1. Immunocompromised Population

To be eligible for inclusion in the immunocompromised population, individuals must meet at least one of the following criteria at the index date (time of vaccination) or in the 12-month baseline period before the index date, unless otherwise specified (see below). Definitions may be modified if certain data elements are unavailable or incompletely captured in some data sources.

- Diagnosed with a primary immunodeficiency or immune dysregulation disorder, also known as inborn errors of immunity, as defined by the European Society for Immunodeficiencies (ESID) Registry, at any point in their medical history;[26]
- Diagnosed with HIV/AIDS at any point in medical history;
- Diagnosed with haematologic malignancy, e.g., chronic lymphocytic leukaemia, non-Hodgkin lymphoma, multiple myeloma, acute leukaemia, with evidence of treatment at any point in medical history;
- Diagnosed with a solid malignancy with evidence of treatment in the last 5 years;
- Diagnosed with rheumatologic or inflammatory conditions, e.g., Sjogren's syndrome, systemic lupus erythematosus (SLE), psoriatic arthritis, rheumatic arthritis, arthritis spondylarthritis, polymyalgia rheumatica, demyelination multiple sclerosis, polymyalgia rheumatica, inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis, 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 haematopoietic stem cell transplant recipients taking immunosuppressive therapy;

- Active treatment with various immunosuppressive agents, e.g., high-dose systemic corticosteroids (≥20mg of prednisone or equivalent per day when administered for ≥2 weeks) or long-term systemic corticosteroid use (>3 months), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumour necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory, active treatment with Anatomical Therapeutic Chemical (ATC) code L04).

4.3.2. Renally Impaired Population

To be eligible for inclusion in the renal impaired population, individuals must have evidence of moderate or severe renal impairment, ascertained at the index date or within the 12 months preceding the index date, using coded diagnoses and procedures or laboratory values, as available.

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 Charlson Comorbidity Index (CCI) will be used.[27] 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).

Individuals will be included in the renal impaired cohort if they have two 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 renal impaired cohort if they have:

- two estimated glomerular filtration rate (eGFR) test results < 60 mL/min/1.73 m^2 separated by between 90 and 540 days, with no normal values in between;[28] OR

- two urine albumin-to-creatinine ratio (UACR) results ≥ 30 mg/g separated by between 90 and 540 days, with no normal values in between (severe albuminuria).

Definitions for CKD stages will be based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[28, 29] Currently, albuminuria levels will also be used to

stratify levels of renal impairment.[29] The three microalbuminuria categories will provide additional prognostic information to the eGFR categories about renal and cardiovascular complications. However, individuals in eGFR categories 1 and 2 (eGFR ≥ 60 mL/min/1.73 m^2) with moderate albuminuria have different clinical profiles and a normal to moderately increased risk of complications. Therefore, among individuals with eGFR ≥ 60 mL/min/1.73m^2, only those with severe albuminuria will be considered. A potential limitation of using the UACR test results is that clinicians often rely on dipstick measurements as the primary method of assessing UACR, and these measurements are not consistently 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 available. If eGFR is not recorded in the data source, it will be derived from creatinine levels using the 2021 CKD-EPI equation [30], which removes the race-related coefficient, following recommendations from recent evidence and guideline statements.[31-34]

4.3.3. Hepatically Impaired Population

To be eligible for inclusion in the hepatically impaired population, individuals must have evidence of moderate or severe hepatic impairment, which will be ascertained at the index date and in the 12 months before the index date using coded diagnoses and procedures or laboratory values, as available.

In data sources where laboratory test results are not available, or where there are substantial levels of missingness, individuals will be considered to be in the target population if they have a diagnosis code that matches the category of moderate or severe hepatic disease according to the revised CCI, which has been shown to correlate with inpatient admissions and mortality rates.[35] 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 maximise the inclusion of individuals with moderate or severe hepatic impairment, codes included in the adaptation of the CCI for mild liver disease,[27] 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 Model for End-Stage Liver Disease (MELD) score greater than 24.[36] The MELD score is calculated using serum bilirubin, serum creatinine, and International Normalised Ratio (INR) by the formula.[37]

No exact correspondence exists between the Child-Pugh stages and the MELD scores. However, individuals with MELD scores ≥10 have a similar mortality risk as individuals with a Child-Pugh score of less than 10.[27] The same score threshold combined with elastography has clear prognosis implications for patients.[38] Thus, we propose to include individuals with MELD scores equal to or greater than 10 in the study to include additional individuals with moderate or severe hepatic impairment. Although efforts have been made to derive Child-Pugh scores from electronic healthcare data sources with rich, identifiable clinical data,[39] those data may not be available in the proposed data sources for this study. The Child-Pugh score requires data with enough granularity to differentiate clinical levels of severity for ascites and encephalopathy.[40] 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 a 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 is present. Thus, only the presence or absence of ascites and encephalopathy will be evaluated. It will not be possible to assess 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 sensitivity analyses in data sources with available laboratory results, thereby ensuring that individuals with at least Child-Pugh stage B are included.

5. RESEARCH METHODS

This is a multinational, population-based observational study that will use two complementary designs to assess the safety of ABRYSVO among older adults (≥60 years) who are immunocompromised or have renal or hepatic impairment. The primary approach will be a comparative matched cohort analysis, in which vaccinated individuals will be matched with unvaccinated individuals who have similar clinical profiles, to evaluate the relative risk of AESIs. For acute AESIs, a self-controlled risk interval (SCRI) design will also be used. This case-only design will include vaccinated individuals who experience an acute AESI, and the incidence rates within predefined risk and control intervals post-vaccination will be compared.

AESIs will be identified using pre-specified diagnostic and procedural code lists. These include AESIs such as Guillain-Barré syndrome, anaphylaxis, myocarditis, and thromboembolic events. ICD-codes will be standardised across DEAPs and validated by clinical experts. The complete AESI coding list is presented in the statistical analysis plan (SAP).

The study will use data from healthcare and administrative databases accessed by DEAPs affiliated with the Vaccine Monitoring Collaboration for Europe (VAC4EU). These DEAPs will be responsible for extracting relevant data using codes for diagnosis, clinical procedures, and prescriptions. Participating data sources are from France, Spain, and the UK. Additional

details on the study design, including setting, inclusion and exclusion criteria, follow-up period, exposure and outcome definitions, and statistical analyses, are provided in the protocol (*Appendix 1*) and SAP (*Appendix 2*).

Contractual agreements have not yet been finalised for all DEAPs. All DEAPs have obtained ethical approvals except for SNDS in France, which is pending. Accordingly, data extraction and transformation into the Common Data Model (CDM) are still underway, and the statistical outputs and visualisations specified in the SAP cannot be included at this stage. In this report, we provide a narrative summary of the study implementation progress and preliminary insights into vaccine uptake, where data are available. Complete data extraction and formal analyses are expected to be available in time for inclusion in the interim report, which is due in September 2026 (Section 1).

6. STUDY PROGRESS

Implementation activities at the DEAPs are being tracked. Each DEAP is responsible for extracting data, transforming it into the CDM, and submitting aggregated results.

6.1. PROGRESS by DEAPs

Although three regional Spanish data sources (EpiChron, SIDIAP, and VID) are participating in this study, ABRYSVO has not yet been implemented in their respective regions for the high-risk populations under investigation. Consequently, no formal data extraction or transformation has begun in these data sources. This reflects the staggered nature of RSV vaccine introduction in Spain and highlights the need for future updates once the vaccine is implemented.

Implementation progress by data source is summarised below:

6.1.1. SNDS (BPE– France)

Ethical review by CESREES (Comité d'Éthique pour les Recherches, les Études et les Évaluations dans le domaine de la Santé [Ethics Committee for Health Research and Evaluation]) has been completed. Authorisation from the CNIL (Commission Nationale de l'Informatique et des Libertés, [French Data Protection Authority]) was obtained on July 10th. The last step entails the contract with the data holder CNAM (French National Health Insurance Fund), to be signed in order to be able to access the data. This step usually takes 8 to 12 months.

6.1.2. EpiChron (Aragon – Spain)

National-level approvals have been obtained. The vaccination programmes for the target populations are not yet in place in this region.

6.1.3. SIDIAP (Catalonia – Spain)

All required approvals have been obtained. Data extraction will begin when the regional vaccine rollout occurs.

6.1.4. VID (Valencia – Spain)

All local approvals have been obtained. ABRYSVO vaccination strategy for the upcoming season has just been publicly announced in Valencia, and this will be offered to immunocompromised individuals aged 18 and older.

6.1.5. CPRD Aurum (England and Northern Ireland)

Information on RSV vaccine use was obtained using the CPRD define tool. Inclusion and exclusion criteria were applied to identify usage within groups, such as those with hepatic impairment. Approval was obtained from the CPRD Research Data Governance (RDG) team, and feasibility studies in high-risk groups have been conducted, and preliminary data on vaccine uptake are available. The Extract, Transform, Load (ETL) process has been started.

6.2. PATIENT RECRUITMENT STATUS

As of the date of this report, patient-level recruitment and data extraction have not been fully initiated due to the following factors:

- **Recruitment status:** Preliminary feasibility counts are only available for CPRD Aurum (Section 6.5). However, no individuals have been enrolled in the study from any data source because data access and transformation are still pending, except in CPRD Aurum.
- **Challenges and mitigation:**
    - Lack of current reimbursement of RSV in the target population in France;
    - Limited vaccine availability in Spain's regional systems.

To mitigate these issues, DEAPs have prioritised onboarding, initiated partial data mapping, and received site-specific support. Additionally, VAC4EU is actively exploring the inclusion of new DEAPs and data sources from countries where ABRYSVO has already been rolled out, such as Switzerland and Scotland.

6.3. NATIONAL IMMUNISATION GUIDELINES AND RECOMMENDATIONS

ABRYSVO received centralised marketing authorisation in August 2023, making it eligible for use across all EU Member States, Norway, Iceland and Liechtenstein. It has also been authorised by the UK MHRA and is available in Switzerland. The vaccine is indicated for adults aged ≥60 years as well as pregnant individuals to protect their infants.

Despite regulatory authorisations, integration into national immunisation programmes remains limited. Current policies are evolving and primarily focus on high-risk populations. However, formal reimbursement or implementation is often contingent on additional evidence regarding safety, effectiveness, and cost-effectiveness. This study aims to address these gaps by generating real-world safety data to support decision-making by NITAGs and payers.

A summary of national vaccination policies for ABRYSVO in the countries participating in the study is provided in Table 1.

6.3.1. France

In France, ABRYSVO is authorised for adults aged ≥60 years, and the *Haute Autorité de Santé* (HAS [French Health Authority]) issued a favourable opinion for reimbursement on 28 August 2024. HAS specifically recommends use in:

- Adults aged ≥75 years, and
- Adults aged ≥65 years with chronic respiratory conditions, e.g., COPD or cardiac conditions, e.g., heart failure.

The clinical benefit of ABRYSVO was assessed as moderate, based on data from the RENOIR trial showing efficacy against symptomatic RSV lower respiratory tract disease. However, HAS concluded that the added clinical benefit (ASMR) is V (no improvement) due to insufficient data on reductions in RSV-associated hospitalisations, ICU admissions, or mortality. The vaccine has not yet been included in the national vaccination calendar or made available through the public health programme. Reimbursement is currently under discussion with the *Comité Économique des Produits de Santé* (CEPS [Economic Committee for Health Products]), with additional steps pending, such as pricing negotiations and official publication.[40, 41]

6.3.2. Spain

Although the EMA has authorised ABRYSVO, it has not yet been included in Spain's national immunisation programme.[42] The national NITAG (Ponencia de Vacunas) is evaluating emerging data, with a focus on high-risk, older adults. Several autonomous communities have begun pilot implementations, but not in the regions covered by the study (Catalonia, Valencia, and Aragon). Broader adoption remains dependent on evaluations by the Ministry of Health and regional readiness.

6.3.3. United Kingdom

The UK MHRA has approved ABRYSVO for adults aged ≥60 years. The Joint Committee on Vaccination and Immunisation (JCVI) has reviewed RSV vaccination for this population, with discussions prioritising evaluation of safety, effectiveness, and cost-effectiveness in medically vulnerable groups.[22, 43] The JCVI has advised that a single dose of ABRYSVO should be offered to all adults turning 75 years old and, as a one-off catch-up programme, for all adults aged 75+ years old, noting that the timing of the vaccination will be essential to ensure protection ahead of and during any subsequent RSV season.

6.4. ETHICAL AND OTHER APPROVALS

As of June 2025, all participating DEAPs have obtained the necessary ethical and governance approvals. Table 2 provides a detailed summary of the approval status, data transformation progress, and analysis readiness for each DEAP.

In **France**, the Bordeaux PharmacoEpi platform (BPE) received CESREES approval in March 2025 and CNIL authorisation in July 2025 for the use of the SNDS database. A contract with Caisse Nationale de l'Assurance Maladie (CNAM [French National Health Insurance Fund], who own the data, for data access is being negotiated and access is expected in the first quarter 2026.

In **Spain**, IDIAPJGol (Institut Universitari d'Investigació en Atenció Primària Jordi Gol, [Catalonia primary care research institute]) has coordinated and obtained national approvals for all three data sources (EpiChron, SIDIAP, and VID). However, the Common Data Model (CDM) transformation has not yet started due to the lack of vaccine rollout in those regions.

In the **UK**, in March 2025, the RDG process granted access to CPRD Aurum. The ETL processes are underway to prepare for data transformation before analyses.

While approvals represent a significant milestone, none of the DEAPs are currently ready to initiate formal analyses due to pending technical onboarding and, in some cases, limited vaccine deployment.

Table 2. Overview of Ethics Approvals in Each Participating DEAP

DEAP Name	Data Source	Ethical Approval Status	CDM Transformation Status	Analysis Readiness*
BPE	SNDS	CESREES approved (13 March 2025); CNIL approved (10 July 2025); Contract with CNAM in progress (expected to be signed between March and May 2026)	Not started	Not yet feasible – pending vaccine reimbursement
IACS	EpiChron	CEIm IDIAPJGol Approved (26 February 2025)	Not started	Not started
IDIAPJGol	SIDIAP	CEIm IDIAPJGol Approved (26 February 2025)	Not started	Not started
FISABIO	VID	CEIm IDIAPJGol Approved (26 February 2025)	Not started	Not started
DSRU	CPRD Aurum	Approved (5 March 2025); RDG clearance obtained	ETL in progress	Awaiting finalisation of ETL

Abbreviations: CEIm: Spanish Ethics Committees for Investigation with Medicinal Products; **IDIAPJGol**, *Institut Universitari d'Investigació en Atenció Primària Jordi Gol*, a primary care research institute in Catalonia; **SIDIAP**, *Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària* (Information System for Research in Primary Care – Catalonia, Spain); **IACS**, *Instituto Aragonés de Ciencias de la Salud* (Aragon Health Sciences Institute); **EpiChron**, Epidemiology and Chronic Conditions Research Group in Aragon, Spain; **FISABIO**, *Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana* (Health and Biomedical Research Foundation of the Valencia Region); **VID**, Valencia Integrated Database; **BPE**, ***Bordeaux PharmacoEpi platform***, France; **SNDS**, *Système National des Données de Santé* (French National Health Data System); **CESREES**, *Comité d'Éthique pour les Recherches, les Études et les Évaluations dans le domaine de la Santé* (Ethics Committee for Health Research and Evaluation – France); **CNIL**, *Commission Nationale de l'Informatique et des Libertés*, the French Data Protection Authority; **CNAM** is the *Caisse Nationale de l'Assurance Maladie* (French National Health Insurance Fund); **DSRU** refers to the Drug Safety Research Unit, a UK-based research organization; **CPRD Aurum**, Clinical Practice Research Datalink Aurum, a UK primary care database; **RDG** Research Data Governance, CPRD's process for ethics and data access approvals; **ETL**, Extract, Transform, Load – a data processing pipeline to prepare datasets for analysis.
*"Analysis Readiness" refers to the ability to begin data analysis based on available data and completion of necessary approvals and transformations.

6.5. UPTAKE OF ABRYSVO IN ADULTS AGED ≥60 YEARS

This section provides a summary of the estimated number of eligible individuals in each of the three clinical risk groups: immunocompromised, renally impaired, and hepatically impaired, as well as preliminary data on vaccine uptake, for the five participating data sources in France, Spain, and the UK.

Table 3 provides a summary of eligible population estimates and observed vaccine uptake by data source and risk group.[23, 44-57]

Table 3. Estimations of Eligible Individuals and ABRYSVO Recipients by DEAP and Risk Group

Country / Data Source (Region)	Population Group	Eligible (≥60) (please confirm/update)	Rollout Status / Expectation (2025–2026)	Projected Uptake	Observed Number of Vaccinated Individuals (to date)
France – SNDS (National)	Immunocompromised	131,710[58], excluding HIV/PID/hematologic malignancies) including HIV[51] estimated total is ~170,000.[50] Including: SOT, BMT, dialysis, autoimmune disease on IS, lymphoma, CLL, HIV.	If agreement on price: National rollout live (≥75 age-based, routine + one-off catch-up; ≥65 with heart/lung disease (risk-based))	5% scenario: 8,500 (all ages) 20% scenario: 34,000 (all ages) 50% scenario: 85,000 (all ages)	Not available
	Renally impaired	Estimated ~3.9 million based on RENALGO-EXPERT algorithm applied to SNDS.[44]		5% scenario: 195,000 20% scenario:780,000 50% scenario: 2 million	Not available
	Hepatically impaired	~520,000 (all ages)[54] includes cirrhosis;[48] liver cancer;[45] NASH;[53] DILI;[55] HBV/HCV[46, 47]		5% scenario: 26,000 (all ages) 20% scenario: 104,000 (all ages) 50% scenario: 260,000 (all ages)	Not available
Spain – EpiChron (Aragon)	Immunocompromised	Not available	TBD	TBD	Not available
	Renally impaired	Estimated ~60,000 (2023) using census and Morbidity Atlas.	TBD	TBD	Not available

Table 3. Estimations of Eligible Individuals and ABRYSVO Recipients by DEAP and Risk Group

Country / Data Source (Region)	Population Group	Eligible (≥60) (please confirm/update)	Rollout Status / Expectation (2025–2026)	Projected Uptake	Observed Number of Vaccinated Individuals (to date)
	Hepatically impaired (severe)	~15,000 with severe liver disease (2023 est.).	TBD	TBD	Not available
Spain – SIDIAP (Catalonia)	Immunocompromised	Estimated 46,000–77,000 (regional autoimmune disease registry).	Adult RSV vaccination campaign expected in 2025–26	Likely 40–50% (based on influenza uptake)[59, 60]	Not available
	Renally impaired	231,000–400,400 with CKD. Source: OCATT 2022 report.			Not available
	Hepatically impaired	40,000–55,000 with NAFLD/NASH, viral hepatitis, cirrhosis.			Not available
Spain – VID (Valencia)	Immunocompromised	378,175 (2009–2014) with IC condition codes e.g., HSCT, SOT, RA, SLE, IBD, HIV.[52] Estímate ~179.919 IC >60 in Valencia.	ABRYSVO will be offered to immunocompromised individuals aged 18 and older starting October 2025.	50% scenario (similar to influenza vaccine uptake in the region): ~90.000	Not available
	Renally impaired (kidney failure)	Estimated ~6.747 in the region with kidney failure (all ages).[57] Estimated around 15% of the Spanish population has a renal condition (population in Valencia ~1.3 mill)[49]	TBD	TBD	Not available

Table 3. Estimations of Eligible Individuals and ABRYSVO Recipients by DEAP and Risk Group

Country / Data Source (Region)	Population Group	Eligible (≥60) (please confirm/update)	Rollout Status / Expectation (2025–2026)	Projected Uptake	Observed Number of Vaccinated Individuals (to date)
	Hepatically impaired (liver failure)	Estimated ~11.245 in the region years with liver failure (all ages).[57]	TBD	TBD	Not available
UK – CPRD Aurum (England and Northern Ireland)	Immunocompromised	340,295 identified using diagnostic and medicinal product codes (Sept 2024 – July 2025).	National rollout live (≥75 age-based, routine and one-off catch-up)	—	2,800
	Renally impaired	171,519 with recorded diagnostic codes (Sept 2024 – July 2025).		—	1,616
	Hepatically impaired	26,477 with diagnosis codes (Sept 2024 – July 2025).		—	135

Abbreviation: SNDS, *Système National des Données de Santé*; EpiChron, Aragon's health database (Instituto Aragonés de Ciencias de la Salud); SIDIAP, *Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària*; VID, Valencia Health System Integrated Databases; CPRD, Clinical Practice Research Datalink; COSV, *Conseil d'Orientation de la Stratégie Vaccinale*; HIV, human immunodeficiency virus; PID, Primary Immunodeficiency; SOT, solid organ transplant; BMT, bone marrow transplant; IS, immunosuppressants; CLL, chronic lymphocytic leukemia; IC, immunocompromised; HSCT, hematopoietic stem cell transplantation; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease; CKD, chronic kidney disease; OCATT, *Organització Catalana de Trasplantaments*; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; DILI, drug-induced liver injury; HBV, Hepatitis B virus; HCV, Hepatitis C virus, NA, not available.
Note: Uptake values in CPRD Aurum are based on diagnostic and medicinal codes recorded between Sept 2024 and July 2025. Denominator estimates represent all eligible individuals identified during that period

6.6. VACCINATION PATHWAYS

This section outlines the observed or expected delivery pathways for ABRYSVO administration in the areas covered by each participating DEAP. Information is based on local vaccination infrastructure, regulatory frameworks, and available rollout data as of July 2025. Delivery settings primarily include primary care, hospital-based services, and community pharmacies, where applicable. This section will be updated as rollout progresses across Spain and France, and as further evidence becomes available regarding access points and delivery effectiveness.

6.6.1. BPE (SNDS, France)

HAS recommends ABRYSVO for use in older adults. In line with recent policy updates. Community pharmacists in France are authorised to prescribe, deliver, and administer ABRYSVO under the same conditions of reimbursement as those for medical doctor prescriptions and administration. This will expand access beyond traditional healthcare settings. However, reimbursement has not yet been finalised for older adults, and rollout has not started.

6.6.2. Spain (EpiChron, Aragon; SIDIAP, Catalonia; VID, Valencia)

Across all three Spanish regions, RSV vaccination is expected to be delivered through primary care, the main channel for adult immunisation programmes. ABRYSVO has not yet been introduced, and delivery pathways remain theoretical or untested. In Valencia, published administrative data have provided population-level insights, though deployment logistics are not yet established.

6.6.3. DSRU (CPRD Aurum, England and Northern Ireland)

In the UK, ABRYSVO is primarily delivered through general practice (GP) surgeries. In England, select community pharmacies have also been commissioned to provide the vaccine as part of the NHS (National Health Service) services. This decentralised delivery model supports access for medically vulnerable individuals aged 75 years and older. CPRD Aurum has recorded vaccine uptake data based on routine healthcare coding.

6.7. ACTIONS TAKEN AND MITIGATION

Table 4 below summarises key delays and challenges encountered by each DEAP, along with mitigation actions or context. In response to delayed implementation in some regions, **additional DEAPs in other countries, such as Switzerland and Scotland, are being assessed** for inclusion in future phases of the study.

Table 4. Implementation Challenges and Mitigation Strategies by DEAP

DEAP	Challenges / Delays	Mitigation or Status Update
BPE (SNDS – France)	Although HAS has issued a favourable opinion on ABRYSVO for older adults (≥75 years or ≥65 with chronic respiratory/cardiac conditions), formal inclusion in the national vaccination calendar and reimbursement is pending. Pricing and regulatory steps remain incomplete.	In September 2025 reimbursement negotiations were ongoing with the Comité économique des produits de santé (CEPS). Inclusion in the vaccination calendar remains uncertain for the upcoming RSV season.
IACS (EpiChron – Aragon)	At the time of this report, there is no Spanish national-level recommendation or indication to vaccinate the high-risk population included in this study.	Vaccine implementation is not expected until national/regional guidance is issued. The DEAPs are ready for onboarding once policy changes occur.
IDIAPJGol (SIDIAP – Catalonia)	As of this report, there is no national-level recommendation or indication to vaccinate the high-risk population included in this study.	
FISABIO (VID – Valencia)	No official recommendation in place to vaccinate the study population at this time.	
DSRU (CPRD Aurum – England and Northern Ireland)	Not applicable.	ABRYSVO is already recommended and being rolled out in the UK; recruitment and data collection are underway.

Note: Exploration of additional DEAPs in other EU countries, e.g., Scotland, Switzerland, is underway.

6.8. CONCLUSIONS

Although ABRYSVO has been approved for use in older adults across the EU and UK, the status for national implementation and reimbursement is variable. In France, reimbursement negotiations are ongoing, and in Spain, the vaccine has not yet been introduced for high-risk populations in the participating regions. As of June 2025, all DEAPs have obtained ethics approval. However, delays in data access and incomplete data transformation in the CDM have prevented the initiation of formal analyses. Preliminary data from CPRD Aurum indicate some early uptake among immunocompromised, renally impaired, and hepatically impaired adults in England and Northern Ireland.

These early findings emphasise the importance of flexible study planning and adaptive timelines to allow for differential implementation. They also highlight the need to expand geographic coverage to generate robust, generalisable safety data. This study remains critical in addressing post-authorisation safety questions for at risk populations who were excluded from pre-licensure trials. The real-world evidence that will be gathered will support immunisation policies, inform NITAG recommendations, and contribute to equitable protection against RSV across Europe.

6.9. NEXT STEPS

6.9.1. Operational Implementation

- Finalise data use agreements: ensure data use agreements between the study sponsor (via Penta) and each DEAP (SNDS, EpiChron, SIDIAP, VID CPRD) are finalised

and active, in compliance with General Data Protection Regulation (GDPR) and local governance requirements.

- Complete CDM transformation and technical onboarding across all participating DEAPs.

- Initiate formal data extraction and analyses according to the study protocol and SAP.

6.9.2. Strategic Expansion

- Evaluate the potential inclusion of other DEAPs from regions with earlier ABRYSVO rollout, such as Scotland and Switzerland, to increase available data.

6.9.3. Stakeholder Coordination

- Submit the interim report, including statistical outputs and updated vaccine uptake data, in the next report.

- Continue engagement with NITAGs and national health authorities to align study deliverables with evolving vaccination policy needs.

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APPENDIX 1: STUDY PROTOCOL

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