

101191967 - GREG

Testing, improving, and co-creating Guidance and Tools for Real World Evidence Generation and Use for Decision-Making in Europe

WP5 – RWE for the Development and Evaluation of Medical Devices and Drug- Device Combinations

D5.1 Results of prevalence and characterisation

Lead contributor	Mike Du, Albert Prats-Urbe (2. UOXF)
Other contributors	Alexis Kim (2. UOXF) Aida Perramon-Malavez, Annette Rudolph (1. EMC) Jana Boleckova (19. EW) Mara Corbo (20. MDT) Santiago Royo Sierra, Francisco Estupiñan Romero, Jaime Meléndez-Cardiel, Enrique Bernal-Delgado (10. IACS)
Due date:	30 April 2026
Delivery date:	7 July 2026
Dissemination level	Public

This project is supported by the Innovative Health Initiative Joint Undertaking (IHI JU) under grant agreement No 101191967. The JU receives support from the European Union's Horizon Europe research and innovation programme and COCIR, EFPIA, Europa Bio, MedTech Europe, and Vaccines Europe.

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	2/111

Contents

Contents	2
Document History	4
Definitions	5
List of abbreviations	7
Executive Summary.....	8
1 Abstract	9
2 Introduction.....	11
3 Research Questions and Objectives.....	12
4 Methods	14
4.1 Study setting and data sources	14
4.2 Study period	15
4.3 Follow-up	15
4.4 Study population with inclusion and exclusion criteria	18
4.5 Variables	21
4.5.1 Events.....	21
4.5.2 Outcomes	29
4.5.3 Other Covariates, including confounders, effect modifiers and other variables	29
4.6 Study size.....	32
4.7 Statistical methods	32
4.7.1 Main statistical methods.....	33
4.7.2 Patient privacy protection.....	35
4.7.3 Methods to derive parameters of interest.....	35
4.7.4 Methods planned to obtain point estimates with confidence intervals of measures of occurrence.....	35
4.7.5 Methods to control for potential sources of bias	35
4.7.6 Methods to deal with missing data	36
5 Results	36

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	3/111

5.1 Participants	36
5.2 Main results	39
5.2.1 Baseline characteristics of underlying disease, disease progression, and device treatment cohorts	39
5.2.2 Annual Incidence rate and trends	41
5.2.3 Extrapolation of Incidence Estimates to European Population Levels	44
5.2.4 Comparison with the literature	46
5.2.5 Characterisation of the Underlying Disease, Disease Progression, and Device Received Cohorts	49
6 Discussion	84
6.1 Key results	84
6.2 Comparison with Previous Literature	84
6.3 Limitations of the research methods	85
6.4 Interpretation	86
6.5 Key methodology learning for future guidance	87
6.6 Generalisability	88
7 Conclusion	89
8 References	89
Annexes	91
Annex I: Results for Annual Period Prevalence	91
Annex II: Incidence Proportion	94
Annex III: Extrapolation results	97
Annex IV: Codelist for the underlying disease, initial surgery, disease progression and device received phenotype	99

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	4/111

Document History

Version	Date	Description
V1.0	18/06/2026	Version for formal review by Daniel Prieto-Alhambra (EMC) and Seamus Kent (EUR).
V2.0	25/06/2026	Revised version for formal review by GA.
V3.0	07/07/2026	Final version.

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	5/111

Definitions

Participants of the GREG Consortium are referred to herein according to the following codes:

1. Erasmus Universitair Medisch Centrum Rotterdam (EMC)
2. The Chancellor, Masters and Scholars of The University of Oxford (UOXF)
3. SYNAPSE Research Management Partners SL (SYNAPSE)
4. National Institute for Health and Care Excellence (NICE)
5. GETREAL Institute (GetReal)
6. Societe Europeenne De Cardiologie (ESC)
 - 6.1. Region Uppsala (REGION UPPSALA)
7. Erasmus Universiteit Rotterdam (EUR)
8. Stichting European Health Data and Evidence Network (EHDEN-F)
9. Stichting Eupati Foundation (EUPATI)
10. Instituto Aragones De Ciencias De La Salud (IACS)
11. University Of Galway (GALWAY)
12. The Hyve BV (THE HYVE)
13. University Of Dundee (UNIVDUN)
14. Universidade De Aveiro (UAVR)
15. Direktoratet for medisinske Produkter (NOMA)
16. Novo Nordisk A/S (NOVO)
17. Sanofi-Aventis Recherche & Developpement (SARD)
18. Bayer Aktiengesellschaft (BAYER)
19. Edwards Lifesciences Belgium BV (EW)
20. Medtronic Bakken Research Center B.V. (MDT)
21. Mölnlycke Health Care AB (MHC)
22. Institut De Recherches Internationales Servier (IRIS)
23. Pfizer Inc (PFIZER INC)
24. W. L. Gore & Associati S.R.L. (GORE S.R.L.)
 - 24.1. W. L. Gore et Associés S.A.R.L. (Gore S.A.R.L.)
 - 24.2. W. L. Gore & Associates BV (GORE BV)
25. Bristol-Myers Squibb Company Corp (BMS)
26. Boehringer Ingelheim International GmbH (BII GMBH)
27. Janssen Cilag SA (JCSPAIN)
28. GlaxoSmithKline Research & Development Limited (GSK)
29. AMGEN (AMGEN)
30. Sanofi US Services Inc. (Sanofi US Inc)
31. Sanofi-Aventis gulf F.Z.E. (SANOFI Gulf)
32. Sanofi Winthrop Industrie (SWI)
33. Sanofi Pasteur SA (Sanofi P SA)
34. Aventis Pharma Limited (Sanofi Pharma)
35. Sanofi Pasteur Limited Canada (Sanofi P L)
36. Edwards Lifesciences Sarl (EW SARL)
37. Edwards Lifesciences LLC (EW LLC)

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	6/111

38. Pfizer Hellas S.A. (Pfizer Hellas)
39. Pfizer AB (Pfizer AB)
40. Janssen Research & Development, LLC (JRDLLC)
41. Medical Device Business Services Inc (MDBSI)
42. Edwards Lifesciences SRL (EW SRL)
43. Edwards Lifesciences SL (EW SL)
44. Edwards Lifesciences SAS (EW SAS)
45. Edwards Lifesciences GmbH (EW GMBH)
46. Medtronic, Inc. (MDT Inc)
47. Medtronic France (MDT FR)
48. Medtronic Italia S.p.A. (MDT IT)
49. Medtronic Ltd (MDT LTD)
50. Pfizer R&D UK Limited (PFIZER R&D UK)
51. Pfizer Limited (PFIZER LTD)
52. Actelion Pharmaceuticals Ltd (ACTELION)
53. Medical Devices & Diagnostics Global Services, LLC (MDDGB)
54. The University of Edinburgh (UEDIN)

Grant Agreement (GA)	The agreement signed between the beneficiaries and the IHI for the undertaking of the GREG project (101191967)
Project	The sum of all activities carried out in the framework of the Grant Agreement.
Consortium	The GREG consortium, comprising the above-mentioned legal entities hereby referred as Participants of the GREG consortium.
Consortium Agreement (CA)	Agreement concluded amongst GREG beneficiaries for the implementation of the Grant Agreement (GA). Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the GA.

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	7/111

List of abbreviations

Abbreviation	Definition
CDM	Common Data Model
CHD	Congenital heart disease
DARWIN EU ®	Data Analysis and Real-World Interrogation Network
DUS	Drug utilization study
EU	European Union
OMOP	Observational Medical Outcomes Partnership
PPVI	Percutaneous pulmonary valve implantation
RVOT	Right ventricular outflow tract
RWD	Real-World Data
CDM	Common Data Model
CHD	Congenital heart disease
CPRD	Clinical Practice Research Datalink
BIGAN	Big Data project of the Department of Health of the Government of Aragon
Ev	Event
Pop	Population

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	8/111

Executive Summary

This deliverable generated methodological evidence on how routinely collected healthcare data can be used to estimate the number of patients with rare conditions relevant to orphan medical device designation in Europe. Orphan medical device designation requires evidence that a device is intended for a condition affecting no more than 12,000 people per year in the European Union. However, for many rare medical device indications, published literature and routine statistics provide limited evidence to assess this threshold. The relevant patient group may also be difficult to identify from a single diagnosis or procedure code.

Our work used transcatheter/percutaneous pulmonary valve implantation (TPVI/PPVI) as an applied example. TPVI/PPVI is used in selected people with congenital heart disease affecting the pulmonary valve or the right ventricular outflow tract. This report examined whether a rare device-relevant population could be estimated by defining three related groups: people with the underlying congenital heart disease, people with disease progression that could make them eligible for TPVI/PPVI, and people who received TPVI/PPVI or surgical pulmonary valve replacement.

We used real-world data mapped to the OMOP Common Data Model from two European data sources: CPRD GOLD in the United Kingdom and BIGAN in Aragon, Spain. We explored practical methodological choices, including how to define relevant patient groups, choose denominators, estimate incidence and prevalence, standardise estimates by age and sex and extrapolate results to the European population. Published and registry-based evidence was also reviewed to assess whether external sources could support estimation of the annual device-eligible population and comparison with real-world data estimates.

For the TPVI/PPVI use case, the disease progression cohort produced consistent estimates of the annual device-eligible population across both data sources. After age-sex standardisation and extrapolation to the European population, the estimated number of eligible individuals remained well below the European orphan medical device designation threshold of 12,000 people per year. Similar conclusions were obtained using alternative disease progression definitions, incidence proportions, and external registry benchmarking, demonstrating that the estimates were robust to different methodological assumptions.

Our findings demonstrate that standardised real-world data can produce transparent and reproducible estimates for device-relevant populations for rare conditions. A key methodological finding was that a disease-progression population can serve as a practical proxy for potential device eligibility, rather than relying solely on records of procedures already performed. This is useful when published evidence is limited or when direct treatment records are incomplete or unavailable. Unfortunately, this is a common limitation due to the scarcity of detail available on medical devices recorded in real world data.

Overall, this deliverable provides methodological learning to inform future guidance on orphan medical device designation. It highlights the need to define clinically meaningful populations, report available data history, test sensitivity to alternative definitions and incidence measures, compare with external evidence where available, and clearly document assumptions when extrapolating to the European population.

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	9/111

I Abstract

Background

Orphan medical device designation in the European Union requires evidence that a device is intended for a condition affecting no more than 12,000 individuals per year. For many rare medical device indications, published literature and routine statistics provide limited information for assessing this threshold. The relevant patient population may also be difficult to identify from a single diagnosis or procedure code. Routinely collected healthcare data mapped to the OMOP Common Data Model may help generate transparent and reproducible estimates for these rare populations.

Objective

This study aimed to generate methodological evidence on how OMOP-mapped real-world data can be used to estimate incidence and prevalence for orphan medical device designation, using transcatheter/percutaneous pulmonary valve implantation (TPVI/PPVI) as an applied example.

Methods

A population-level descriptive study was conducted using two European data sources: CPRD GOLD in the United Kingdom and BIGAN in Aragon, Spain. Four clinically relevant events were defined: Event (Ev)1, underlying congenital heart disease involving the right ventricular outflow tract or pulmonary valve pathway; Ev2, previous right ventricular outflow tract or pulmonary valve intervention; Ev3, residual or progressive right ventricular outflow tract or pulmonary valve dysfunction; and Ev4, receipt or history of TPVI/PPVI or surgical pulmonary valve replacement.

These events were used to define three study populations: Pop1, the underlying disease population, corresponding to Ev1; Pop2, the disease progression population, defined by Ev3 in combination with prior Ev1 and/or Ev2; and Pop3, the device received population, corresponding to Ev4. Pop2 was considered the main proxy for the potential device-eligible population.

All analyses were conducted independently within each data source using the same OMOP CDM phenotype definitions. Data source-specific incidence and prevalence estimates were age- and sex-standardised. Then, incidence estimates from the most recent three full years of available data were extrapolated to the European population. Sensitivity analyses explored alternative definitions of disease progression and incidence proportions. Published registry-based evidence was reviewed to assess whether existing external sources provided suitable estimates of the annual device-eligible population and to compare these estimates with those generated our data sources.

Results

In CPRD GOLD, disease progression incidence rate ranged from 0.12 to 0.32 per 100,000 person-years, while the incidence of device receipt ranged from 0.09 to 0.33 per 100,000 person-years. Similar estimates were observed in BIGAN, although small sample sizes prevented reporting of some results. For the disease progression cohort, the estimated annual number of affected individuals in the European population ranged from 185 to 1,424 using BIGAN and

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	10/111

from 688 to 1,691 using CPRD GOLD. Sensitivity analyses using alternative disease progression definitions and incidence proportions produced estimates that remained below the European orphan medical device designation threshold.

Discussion

This case study generated methodological learnings for future guidance on the use and best practices of RWE generation for orphan medical device designation. Published literature may be insufficient to estimate the annual device-eligible population, even for established devices, because it often reports broad disease burden, clinical cohorts, or procedure counts rather than population-based eligibility denominators. Defining a disease progression cohort provided a practical intermediate metric between the broad underlying disease population and the narrower treated population. The study also highlighted the importance of reporting the available calendar years of data, event counts, denominators, uncertainties, sensitivity analyses, and the assumptions used for European extrapolation.

Conclusion

This study supports the feasibility of using OMOP-mapped real-world data to generate evidence for orphan medical device population estimation. Using TPVI/PPVI as an applied example, the study showed how rare device-relevant populations can be defined, estimated, tested through sensitivity analyses, compared with published and registry-based estimates where available, and extrapolated to the European population. These findings will inform future guidance on using real-world data for orphan medical device designation.

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	11/111

2 Introduction

Orphan medical device designation in the European Union (EU) requires demonstrating that the device is specifically intended to benefit patients in the treatment, diagnosis, or prevention of a disease or condition that presents in not more than 12,000 individuals in the European Union per year; and at least one of the following criteria are met: there is insufficiency of available alternative options for the treatment, diagnosis, or prevention of this disease/condition, or the device will offer an option that will provide an expected clinical benefit compared to available alternatives or state of the art for the treatment, diagnosis, or prevention of this disease/condition, taking into account both device and patient population specific factors. For many rare medical device indications, published literature and routine statistics provide limited evidence for assessing whether this threshold is met. In addition, the relevant patient group is often difficult to identify from a single diagnosis or procedure code. Eligibility may depend on a combination of diagnosis, anatomy, previous treatment, disease progression, and potential need for a future procedure [19].

Routinely collected real-world data (RWD), including electronic health records, administrative claims, and clinical registries, may help address this evidence gap. With increasing international adoption of the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), diverse data sources can be used to support standardised case definitions, reproducible phenotyping, and comparable incidence and prevalence estimation across settings. However, methodological evidence is still needed on how RWD can be used to support robust population estimates for orphan medical device designation.

Key challenges include handling of small event counts, uncertainty around the most appropriate denominator population, and uncertainty when extrapolating data-source-level estimates to the EU population. Evidence is also needed on how to define clinically meaningful populations when the target population cannot be directly observed from a single code, particularly for new or pre-market devices where treatment records may be incomplete or unavailable.

This project aimed to generate methodological evidence to inform future guidance on estimating incidence and prevalence for orphan medical device designation using OMOP CDM-mapped real-world data. The work explored practical choices in case identification, denominator selection, temporal trend evaluation, heterogeneity assessment, uncertainty assessment, and extrapolation to the European population.

As an applied example, this project focused on rare cardiac conditions relevant to transcatheter or percutaneous pulmonary valve implantation (TPVI/PPVI). Conditions such as Tetralogy of Fallot, common arterial trunk, and other congenital heart diseases affecting the pulmonary valve or right ventricular outflow tract (RVOT) often require reconstruction of the RVOT. Initial management typically involves surgical correction in early life, which may include patch augmentation, implantation of a valved conduit, or pulmonary valve replacement [1].

Despite early intervention, many individuals require lifelong follow-up and may need further treatment because of residual lesions or progressive RVOT dysfunction, including pulmonary regurgitation, pulmonary stenosis, RVOT obstruction, or degeneration of implanted conduits or bioprosthetic pulmonary valves. For selected patients, TPVI/PPVI using bioprosthetic valves has become an important minimally invasive alternative to repeat surgery. Meta-analyses have shown that PPVI can reduce RVOT pressure gradients and the severity of pulmonary regurgitation, while maintaining a low complication rate [2]. Multiple valve systems are now available, including balloon-expandable and self-expanding designs, extending treatment to larger and more complex RVOT anatomies [3].

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	12/111

Using TPVI/PPVI as a case study, this deliverable examines how routinely collected healthcare data can be used to define relevant patient populations, estimate incidence and prevalence, assess uncertainty, compare results with external evidence, and extrapolate estimates to the European population. The findings are intended to support future methodological guidance for real-world evidence generation in orphan medical device designation.

3 Research Questions and Objectives

A. Primary research question and objective.

Table 1 Research questions and objectives

Objective:	Objective 1 to 3: To estimate the incidence and prevalence of three clinically relevant populations using OMOP-mapped real-world data: Population 1 , the underlying disease population; Population 2 , the disease progression or potential PPVI-eligible population; and Population 3 , the device-received population.
Hypothesis:	OMOP-mapped routinely collected healthcare data can be used to estimate the incidence and prevalence of rare device-relevant populations. Standardised DARWIN EU® tools can support consistent implementation and generate methodological insight into estimating rare device-relevant populations using real-world data.
Population (mention key inclusion-exclusion criteria):	All individuals registered in the participating databases from 1st January of each calendar year between 2006 and 2025, or the latest available date, whichever comes first. Three populations are defined as: Population 1, individuals with underlying congenital heart disease involving the right ventricular outflow tract or pulmonary valve pathway; Population 2, individuals with evidence of residual lesions or progressive RVOT/pulmonary valve dysfunction after prior underlying disease or intervention, representing the potential PPVI-eligible target population; and Population 3, individuals with recorded PPVI or surgical pulmonary valve replacement.
Event:	Event 1: underlying congenital heart disease involving the RVOT/pulmonary valve pathway. Event 2: prior RVOT/pulmonary valve intervention.

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	13/111

	Event 3: residual lesions or progressive RVOT dysfunction. Event 4: PPVI or surgical pulmonary valve replacement.
Comparator:	N/A
Outcome:	N/A
Time (when follow up begins and ends):	For annual incidence and prevalence estimation, follow-up will start on 1 January of each calendar year between 2006 and 2025 or start of data availability. Follow-up will end at the earliest of loss to follow-up, death, end of data availability, or end of the study period.
Setting:	Primary care / Hospital
Main measure of effect:	Annual Incidence rate, incidence proportion and prevalence of each defined population

B. Secondary research questions and objectives.

Table 2 Secondary research questions and objectives

Objective:	Objective 4: To compare estimations of incidence and prevalence from those obtained using RWD (e.g., EHR, claims databases) and from previous literature (e.g., national statistics or peer-reviewed journal articles). Objective 5: To characterise the patients in each population group. Objective 6: To characterise drug use and treatment patterns before and/or after RVOT reconstruction surgery. Objective 7: To assess consistency and variation in population estimates across the participating OMOP-mapped data sources. Objective 8: To compare methods for extrapolating incidence/prevalence results to the EU population level.
Hypothesis:	The OMOP common data model and the DARWIN EU (R) tools developed can be used to characterise patients and accurately define drug use before and after intervention. In addition to being obtained locally, the results can be extrapolated to the EU population level.
Population (mention key inclusion-exclusion criteria):	Three populations are considered: Population I , individuals with underlying congenital heart disease involving the RVOT/pulmonary valve

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	14/111

	pathway; Population 2 , individuals with evidence of residual lesions or progressive RVOT/pulmonary valve dysfunction after prior underlying disease or intervention, representing the potential PPVI-eligible target population; and Population 3 , individuals with recorded PPVI or surgical pulmonary valve replacement.
Event:	Event 1: underlying congenital heart disease involving the RVOT/pulmonary valve pathway. Event 2: prior RVOT/pulmonary valve intervention. Event 3: residual lesions or progressive RVOT dysfunction. Event 4: PPVI or surgical pulmonary valve replacement.
Comparator:	N/A
Outcome:	N/A
Time (when follow up begins and ends):	Follow-up for population characterisation are aligned with the population definitions used for the primary objective (2006 – 2025). For treatment-pattern analyses, relevant exposure windows will be defined before and/or after RVOT/pulmonary valve intervention. For comparison with external evidence sources and extrapolation, the time period will be aligned as closely as possible with the available real-world data and external evidence sources.
Setting:	Primary care / Hospital
Main measure of effect:	Counts (%), mean (SD), and median (IQR), as appropriate.

4 Methods

4.1 Study setting and data sources

A population-level descriptive analysis was conducted using real-world health databases mapped to the OMOP Common Data Model (OMOP-CDM). A description of data sources contributing to the analysis is provided in **Table 3**.

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	15/111

Table 3 Description of the selected data sources

Country	Name of Database	Healthcare Setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims data, registries)	Number of active subjects	Feasibility count of exposure	Data lock for the last update
United Kingdom of Great Britain and Northern Ireland	CPRD GOLD	Primary care	Electronic Health Records	17,649,004	NA	17/11/2025
Spain (Aragon)	BIGAN	Primary care, Outpatient Specialist visits, Hospital episodes, Outpatient Prescriptions, Lab determinations, Accidents and Emergency ward visits	EHR, ePrescriptions, Hospital claims, Public Health registries, Disease registries, Health care management and administration registries.	~1.3M	NA	17/02/2026

Clinical Practice Research Datalink GOLD, United Kingdom

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (<https://cprd.com>). CPRD GOLD comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices)).

BIGAN, Spain

The Big Data project of the Department of Health of the Government of Aragon (BIGAN) (<https://bigan.iacs.es/en/home>).

4.2 Study period

From 1st January 2006 (or start of data availability) until 1st January 2025 (or end of data availability).

4.3 Follow-up

For the incidence estimation (objectives 1 – 3), study participants were followed from the date of the first recorded event. Incident cases were defined as the first occurrence of the relevant event during the study period, with the required prior event history, where applicable: first recorded diagnosis within event group between 1st January 2006 and 31st December 2025 (or latest date available) after combined event of previous event groups' diagnoses. End of follow-up was defined as the earliest of the following: 1) loss to follow-up, 2) end of data availability, 3) date of death, 4) next event group diagnosis, or 5) end of study period (31st December 2025).

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	16/111

For the prevalence estimation (objectives 1 – 3), study participants were followed from the date of the first recorded diagnosis of the event group. End of follow-up was defined as the earliest of the following: 1) loss to follow-up, 2) end of data availability, 3) date of death, or 4) end of study period (1st January 2025).

The operational definition of the follow-up window is presented in **Table 4**.

	D5.1 Results of prevalence and characterisation			
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations		Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU	17/111

Table 4 Operational definition of time 0 (index date), other primary time anchors

Study population name(s)	Time anchor description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care setting	Code type	Diagnosis position	Incident with respect to...	Measurement characteristic/validation	Source of algorithm
All patients from the database eligible for the study – Analysis of Prevalent Use	Patient present in the database during the study period	1	Prevalent	n/a	IP/OP	n/a	n/a	Events as defined in table 7	n/a	n/a
All patients from the database eligible for the study – Analysis of incident use	Patient present in the database during the study period	1	Incident	inf	IP/OP	n/a	n/a	First diagnosis of each of the exposures defined in table 7	n/a	n/a

IP = inpatient; OP = outpatient

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	18/111

4.4 Study population with inclusion and exclusion criteria

The study population will include individuals within the event groups between the 1st of January 2006 and 31st of December 2025 (or latest date available). The populations of interest are, based on the defined events in section 3.5.1:

- **Pop 1: Patients with underlying CHD involving the RVOT/pulmonary valve pathway (Underlying disease population).** Pop 1 represents the population with underlying CHD involving the RVOT/pulmonary valve pathway, defined by the presence of Ev 1.
- **Pop 2: Patients who are eligible for PPVI (Target/ disease progression population).** Pop 2 represents the target population potentially eligible for PPVI. It is defined at a specified time point (e.g., the index date) as patients who meet the criteria for Ev 3 and have prior evidence of Ev 1 or Ev 2. To assess the robustness of the findings, three alternative disease progression definitions were evaluated. First, a 30-day lookback definition will require Ev 1 or Ev 2 to be recorded at least 30 days before the Ev 3 date. Second, a 365-day lookback definition will require Ev 1 or Ev 2 to be recorded at least 365 days before the Ev 3 date. Third, a stricter pathway definition will require evidence of both Ev 1 and Ev 2 at any time before the Ev 3 date. These alternative definitions were used to evaluate the sensitivity of the estimated device-eligible population to different assumptions regarding the disease progression pathway.
- This population may be operationally presented as a range, with the lower bound restricted to patients meeting Ev 3 plus both Ev 1 and Ev 2, and the upper bound including patients meeting Ev 3 plus either Ev 1 or Ev 2.
- **Pop 3: Patients who received PPVI or surgical PVR (Treated/device received population)** Pop 3 represents the treated population, defined at a specified time point by the presence of Ev 4.

To provide more general incidence estimates that are comparable to the current published literature, the entire population observed during the study period will be used as the denominator. The operational definitions of the inclusion and exclusion criteria are presented by means of **Table 5** and **Table 6**, respectively.

	D5.1 Results of prevalence and characterisation			
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations		Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU	19/111

Table 5 Operational definitions of inclusion criteria

Criterion	Details	Order of application	Assessment window	Care Settings ¹	Code Type	Diagnosis position ²	Applied to study populations:	Measurement characteristics/validation	Source for algorithm
Observation period in the database during the period 2006-2025 (or the latest available)	Individuals were considered under observation if the index date occurred within a valid record in the OBSERVATION_PERIOD table. Follow-up started at the observation period start date and ended at the observation period end date. Individuals contributed person-time only while under observation.	N/A	N/A	primary care, secondary care (i.e in- and outpatient specialist care)	N/A	N/A	All individuals within the selected databases	N/A	N/A
Washout period (only for incidence analysis)	Individuals were considered at risk of an incident event if they had no prior record of the outcome during the available observation period before the index event. Incident events were defined as the first occurrence after cohort entry and within a valid observation period.	After	inf days	primary care, secondary care (i.e in- and outpatient specialist care)	N/A	N/A	All individuals within the selected databases	N/A	N/A

¹ IP = inpatient, OP = outpatient, ED = emergency department, PC = primary care, OT = other, n/a = not applicable

² Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	20/111

Table 6 Operational definitions of exclusion criteria

Criterion	Details
Record not in observation	Exclude patients with an observation period in the observational period table.
Missing the record date	Exclude patients without a record date from the clinical tables.

¹ IP = inpatient, OP = outpatient, ED = emergency department, PC = primary care, OT = other, n/a = not applicable

² Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	21/111

4.5 Variables

4.5.1 Events

The patient populations of interest in this project are defined based on the event groups. They can be broadly divided into two groups: the Eligible for PPVI population and the underlying disease population. The Eligible for PPVI population represents the target population, that is, the group to be assessed for whether it meets the criteria for an orphan subpopulation.

The target population is characterised by the following clinical pathway. First, patients have congenital heart disease associated with abnormalities of the right ventricular outflow tract (RVOT) and/or pulmonary valve (PV). Second, as part of prior treatment for the underlying congenital condition, they undergo RVOT- or PV-related interventions. The anatomical substrate created by these prior interventions may subsequently serve as a prerequisite structural condition that allows PPVI to be technically feasible in the future. Third, over time, these patients may develop residual lesions or progressive deterioration of RVOT/PV function, resulting in a clinical state in which reintervention becomes necessary and the applicability of PPVI is evaluated.

Accordingly, in order to generate epidemiologic estimates for the patient population of interest within the available analytic environment, each of these clinical conditions and treatment states has been operationalized as a separate Event, and the target population will be identified and analysed through combinations of these Events.

In defining the Events, a range of information types has been incorporated, including conditions, procedures, and situations/history/status concepts. Given the mapping constraints of the database environment, it was considered more appropriate to use broad or umbrella terms, rather than overly narrow or highly specific codes, to reduce the risk of underestimation. Given that this project is being conducted in the context of orphan designation, adopting a more permissive approach that may allow for overestimation rather than underestimation was considered the more conservative strategy and was deemed more appropriate from a regulatory perspective. The full list of concepts included to define these events are included in **Annex IV**.

<Events>

- Ev 1: Underlying CHD involving the RVOT/pulmonary valve pathway (Baseline disease)
- Ev 2: History of RVOT/PV intervention (RVOT/PV intervention history)
- Ev 3: Residual lesions or progressive RVOT dysfunction (Recurrent/residual RVOT dysfunction)
- Ev 4: History of PPVI or Surgical PVR (PPVI/Surgical PVR history)

	D5.1 Results of prevalence and characterisation			
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations		Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU	22/111

Table 7 Operational definitions of outcome/events

Event group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position ²	Applied to study populations	Incident with respect to...	Measurement characteristic s/ validation	Source of algorithm
Underlying CHD involving the RVOT/pulmonary valve pathway (Baseline disease)	Definition: Congenital heart disease (CHD) involving, affecting, or structurally associated with the right ventricular outflow tract (RVOT), pulmonary valve (PV), or right ventricle-to-pulmonary artery (RV-PA) continuity, including conditions that directly cause RVOT/pulmonary valve abnormalities or commonly require RVOT reconstruction, RV-PA conduit placement, or subsequent pulmonary valve/RVOT reintervention. • Includes conditions such as: <Tier 1: Direct RVOT/PV> • Q21.3 — Tetralogy of Fallot Q22.0 — Pulmonary valve atresia Q22.1 — Congenital pulmonary valve stenosis Q22.2 — Congenital pulmonary valve insufficiency Q24.3 — Pulmonary infundibular stenosis Q22.3 — Other congenital malformations of pulmonary valve <Tier 2: Conotruncal CHD> Q20.0 Common arterial trunk Q20.1 Double outlet right ventricle Q20.3 Discordant ventriculoarterial connection <Tier 3: PA/Outflow Anomalies> Q25.5 Atresia of pulmonary artery Q25.6 Stenosis of pulmonary artery Q21.4 Aortopulmonary septal defect Q25.79 Other congenital malformations of pulmonary artery Q25.71 Coarctation of pulmonary artery <Tier 4: Extended Right-sided CHD> Q22.5 Ebstein's anomaly Q22.6 Hypoplastic right heart syndrome	NA	Calendar year	Primary and secondary care	SNOMED	NA	All individuals present in the database during the study period	NA	NA	NA

	D5.1 Results of prevalence and characterisation			
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations		Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU	23/111

Event group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position ²	Applied to study populations	Incident with respect to...	Measurement characteristic s/ validation	Source of algorithm
Q22.8 Other congenital malformations of tricuspid valve Q22.9 Congenital malformation of tricuspid valve, unspecified										
History of RVOT/PV intervention (RVOT/PV intervention history)	Definition: History of surgical intervention or procedures involving the right ventricular outflow tract (RVOT), pulmonary valve (PV), or right ventricle-to-pulmonary artery (RV-PA) continuity, indicating a post-surgical or post-procedural RVOT/pulmonary valve status relevant to subsequent RVOT dysfunction, reintervention, or consideration of PPVI. Includes procedures or situations such as: <RV-PA conduit procedures> Insertion of right ventricle to pulmonary artery conduit (procedure) Implantation of valved conduit from right ventricle to pulmonary artery (procedure) Revision of right ventricle to pulmonary artery conduit (procedure) Replacement of right ventricle to pulmonary artery conduit (procedure) Reconstruction of right ventricle to pulmonary artery continuity (procedure) History of right ventricle to pulmonary artery conduit placement (situation) Status post RV-PA conduit implantation (situation) Presence of right ventricle to pulmonary artery conduit (finding/situation) Status post RV-PA conduit replacement (situation) < Pulmonary valve replacement procedures>	NA	Calendar year	Primary and secondary care	SNOMED	NA	All individuals present in the database during the study period	NA	NA	NA

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	24/111

Event group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position ²	Applied to study populations	Incident with respect to...	Measurement characteristic s/ validation	Source of algorithm
	Pulmonary valve replacement (procedure) Surgical replacement of pulmonary valve (procedure) Implantation of prosthetic pulmonary valve (procedure) Replacement of pulmonary valve with valved conduit (procedure) History of pulmonary valve replacement (situation) Status post pulmonary valve replacement (situation) Presence of prosthetic pulmonary valve (finding) History of pulmonary valved conduit placement (situation)									
	<RVOT patch/reconstruction> Right ventricular outflow tract reconstruction (procedure) Repair of right ventricular outflow tract (procedure) Augmentation of outflow tract of pulmonary valve (procedure) Transannular patch repair of RVOT (procedure) Enlargement of right ventricular outflow tract (procedure) History of right ventricular outflow tract reconstruction (situation) Status post repair of right ventricular outflow tract (situation) Status post transannular patch repair (situation) Postprocedural RVOT state (situation)									
	< Named congenital procedures> Rastelli procedure (procedure) Ross procedure (procedure) Ross-Konno procedure (procedure) History of Rastelli procedure (situation) Status post Rastelli repair (situation) History of Ross procedure (situation) Status post Ross procedure (situation)									

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	25/111

Event group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position ²	Applied to study populations	Incident with respect to...	Measurement characteristic s/ validation	Source of algorithm
•										
Residual lesions or progressive RVOT dysfunction (Recurrent/residual RVOT dysfunction)	Definition: Residual lesions or progressive dysfunction involving the pulmonary valve (PV), right ventricular outflow tract (RVOT), or right ventricle-to-pulmonary artery (RV-PA) conduit, including regurgitant, stenotic, obstructive, or mixed lesion relevant to consideration of PPVI. Includes conditions such as: <Pulmonary valve regurgitation> Pulmonic valve regurgitation (disorder) Pulmonary valve regurgitation Pulmonary valve insufficiency Pulmonic insufficiency <Pulmonary stenosis> Pulmonic valve stenosis (disorder) Pulmonary valve stenosis Pulmonary stenosis <RVOT obstruction> Right ventricular outflow tract obstruction (disorder) Postprocedural right ventricular outflow tract obstruction (disorder) <RV-PA conduit dysfunction> Right ventricle-to-pulmonary artery conduit obstruction RV-PA conduit stenosis RV-PA conduit dysfunction	NA	Calendar year	Primary and secondary care	SNOMED	NA	All individuals present in the database during the study period	NA	NA	NA

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	26/111

Event group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position ²	Applied to study populations	Incident with respect to...	Measurement characteristic s/ validation	Source of algorithm
	<Prosthetic pulmonary valve dysfunction> Prosthetic pulmonary valve obstruction Bioprosthetic pulmonary valve stenosis Prosthetic pulmonary valve dysfunction									
History of PPVI or Surgical PVR (PPVI/Surgical PVR history)	Definition: History of percutaneous pulmonary valve implantation (PPVI) or surgical pulmonary valve replacement (PVR), or documented post-procedural status following such treatment, involving the pulmonary valve, right ventricular outflow tract (RVOT), or right ventricle-to-pulmonary artery (RV-PA) continuity. Includes procedures or situations such as: <PPVI> Transcatheter pulmonary valve implantation (procedure) Transcatheter pulmonary valve replacement (procedure) Percutaneous pulmonary valve implantation (procedure) Percutaneous pulmonary valve replacement (procedure)	NA	Calendar year	Primary and secondary care	SNOMED	NA	All individuals present in the database during the study period	NA	NA	NA

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	27/111

Event group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position ²	Applied to study populations	Incident with respect to...	Measurement characteristic s/ validation	Source of algorithm
	Pulmonary valve implantation using transcatheter technique (procedure) Valve-in-conduit procedure at pulmonary position (procedure) Valve-in-valve procedure at pulmonary position (procedure) History of transcatheter pulmonary valve implantation (situation) Status post transcatheter pulmonary valve implantation (situation) History of percutaneous pulmonary valve implantation (situation) Status post percutaneous pulmonary valve implantation (situation) Presence of transcatheter pulmonary valve prosthesis (finding) Presence of prosthetic pulmonary valve (finding)									
	<Surgical PVR> Pulmonary valve replacement (procedure) Surgical pulmonary valve replacement (procedure) Replacement of pulmonary valve with prosthesis (procedure) Implantation of prosthetic pulmonary valve (procedure) Replacement of pulmonary valve with valved conduit (procedure)									

	D5.1 Results of prevalence and characterisation		
	WP5 – RWE for the Development and Evaluation of Medical Devices and Drug-Device Combinations		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	28/111

Event group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position ²	Applied to study populations	Incident with respect to...	Measurement characteristic s/ validation	Source of algorithm
	Pulmonary valved conduit replacement (procedure) History of pulmonary valve replacement (situation) Status post pulmonary valve replacement (situation) History of surgical pulmonary valve replacement (situation) Status post surgical pulmonary valve replacement (situation) Presence of prosthetic pulmonary valve (finding) History of pulmonary valved conduit placement (situation) •									

¹IP = inpatient; OP = outpatient; ED = emergency department; OT = other; n/a = not applicable

²Specify whether a diagnosis code is required to be in the primary position (i.e. main reason for encounter)

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	29/111

4.5.2 Outcomes

Not applicable.

4.5.3 Other Covariates, including confounders, effect modifiers and other variables

The study covariates are described conceptually, and the context or rationale for the choices are provided in this section. The operational definition of the covariates is described in **Table 8**.

Table 8 Operational definition of covariates (modified)

Characteristic	Details	Exp 1	Exp 2	Exp 3	Exp 4	Type of variable	Assessment window	Care Settings ¹	Code Type
Sex	Male, Female	○	○	○	○	binary	Index date	NA	NA
Age at index date	Age at index date in each event group	○	○	○	○	continuous	Index date	NA	NA
Age group	0, 1-4, 5 -9, 10-14,... and >80	○	○	○	○	categorical	Index date	NA	NA
Calendar Year at index date	Calendar year when index event occurs in each event group	○	○	○	○	continuous	Index date	NA	NA
Time since diagnosis of underlying condition	Interval between first observed diagnosis of underlying condition and the date of the subsequent event (e.g., RVOT reconstruction, PPVI eligibility, or PPVI procedure)	NA	○	○	○	continuous	Derived	NA	NA
Time from RVOT reconstruction to PPVI eligibility or procedure	Interval between RVOT reconstruction date and first eligibility-criteria date or first PPVI received date	NA	NA	○	○	continuous	Derived	NA	NA

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	30/111

Characteristic	Details	Exp 1	Exp 2	Exp 3	Exp 4	Type of variable	Assessment window	Care Settings ¹	Code Type
Underlying Conditions	<i>Tetralogy of Fallot (TOF), Common arterial trunk (truncus arteriosus),</i> <i>Pulmonary atresia with ventricular septal defect, Double outlet right ventricle with RVOT obstruction,</i> <i>Other congenital cardiac anomalies associated with RVOT dysfunction</i>	○	○	○	○	binary	-365 to 0, -Inf to 0	NA	SNOMED
RVOT reconstruction	<i>Patch augmentation of the RVOT (e.g., transannular patch),</i> <i>Implantation of a valved conduit between the right ventricle and pulmonary artery, Surgical pulmonary valve replacement</i>	NA	○	○	○	categorical	Index date	NA	NA
Treatment (medicines)	<i>β-blockers, anti-hypertensives (ACE inhibitors, ARBs, calcium channel blockers, diuretics, PDE-5 inhibitors), vasodilators, anti-arrhythmics, digitalis glycosides, anti-coagulants, antibiotics, steroids</i>	○	○	○	○	binary	-30 to 0, -365 to 0	NA	RxNorm
Developed condition requiring PPVI	<i>Primary criteria (Hemodynamic RVOT lesions)</i> <i>- Moderate-to-severe pulmonary regurgitation (PR)</i> <i>- Moderate-to-severe pulmonary stenosis (PS)</i> <i>- Other RVOT</i>	NA	NA	○	○	categorical	Index date	NA	NA

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	31/111

Characteristic	Details	Exp 1	Exp 2	Exp 3	Exp 4	Type of variable	Assessment window	Care Settings ¹	Code Type
	obstruction (e.g., conduit or prosthetic pulmonary valve stenosis) - PR or PS with right ventricular remodelling (dilation, hypertrophy, or dysfunction) Supporting criteria (Clinical or associated cardiac complications) -Heart failure requiring pharmacological therapy - Atrial or ventricular arrhythmia - Tricuspid regurgitation -Other associated cardiac abnormalities (e.g., aortic regurgitation, residual ventricular defect, or left ventricular dysfunction)								
PPVI type	Device and procedure	NA	NA	NA	O	categorical	Index date	NA	NA
Comorbidities	Diabetes mellitus, hypertension, chronic kidney disease, liver disease	O	O	O	O	categorical	Index date	NA	NA
Large scale characteristics	Patient-level characterisation with regard to baseline co-variables by pre-defined conditions/medications/procedure of interest.					binary	At index date and windows around index date (ID): [-7, ID] and [-30, ID]	NA	SNOMED, RxNorm

¹IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable, EXP = exposure.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	32/111

4.6 Study size

No formal sample size calculation was conducted because this was a descriptive study using available real-world data. However, precision was an important consideration because the device-eligible population was expected to be rare. It is expected to be of about 0.2 out of 1,000 live births if taking into account that the incidence of CHD varies between 5 and 9 per 1,000 living births, 20% of newborns have anomalies in the RVOT [3] and patients with RVOT obstructions requiring a PV device are about 25% . Hence, we would need around 2 million people in the database to observe 100 events. Therefore, the study prioritises large population databases.

4.7 Statistical methods

The type of analysis by study type is fixed as explained in Table 9.

It is a study in 4 steps:

1. Characterisation of both the underlying disease population and the device/procedure-eligible patients' subgroup will be undertaken, producing a standardised Table 1 summarising demographic and clinical characteristics (e.g., age, sex, comorbidities, prior procedures, socioeconomic status, healthcare utilisation). This will support comparisons of population profiles across databases and help explain differences in incidence and prevalence estimates relative to published literature or national statistics.
2. Characterisation of pharmacotherapy used pre and post intervention, in the form of a drug utilisation study.
3. Estimation of the incidence and prevalence of both the underlying disease and the device-eligible population, the latter being defined as the population eligible to undergo the procedure after considering comorbidities. For each use case, OMOP-based phenotypes will be developed to identify disease cases and device-eligible patients within each data source mapped to the OMOP CDM. Incidence and prevalence will be calculated using different prior observation history, and denominator definitions, and reported with 95% confidence intervals. More specifically, the analysis that will be performed are those represented in **Figure 1** and **Figure 2**. We will calculate the incidence proportion to compare our results with those reported in the literature. To address potential incomplete capture of events within the electronic health records data, estimates of incidence and prevalence will be contextualised using evidence from the published literature where available. Specifically, for intermediate populations along the clinical pathway, incidence proportions will be estimated directly from the study data and, where appropriate, compared with previously reported population-level estimates. These external data sources will not be used to replace primary estimates but to support interpretation and assess the plausibility of findings. All estimates will be stratified by age and sex to account for demographic differences in disease occurrence.
4. Methodological approaches for extrapolating incidence estimates to the EU-27 population will be assessed, including direct rate scaling and age-sex standardisation using EU-27 population statistics. These components will inform the development of methodological guidance for generating population estimates relevant to the $\leq 12,000$ -patients-per-year criterion for orphan medical device designation.

If fewer than three OMOP-mapped data sources are available, estimates from each data source will be age-sex standardised using EU-27 population statistics and extrapolated to the EU-27 population separately. Where at least two data sources are available, extrapolated estimates will be compared descriptively to assess consistency and variability across data sources.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	33/111

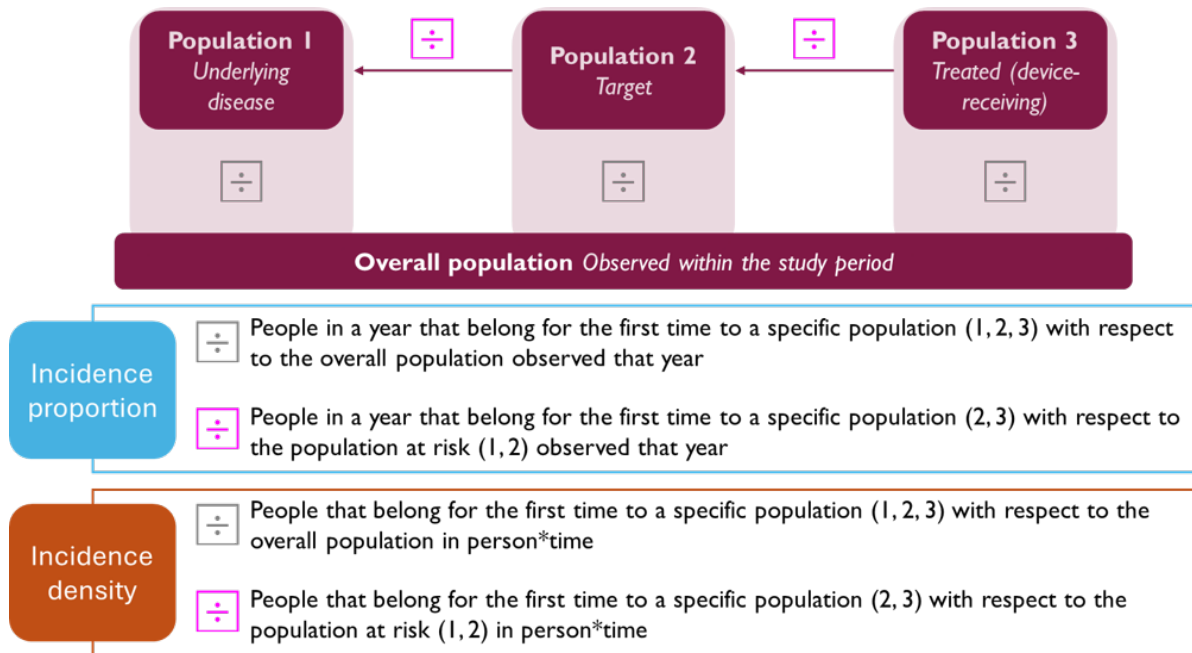


Figure 1 Scheme of the incidence calculations that will be performed in this study and the obtained outcomes

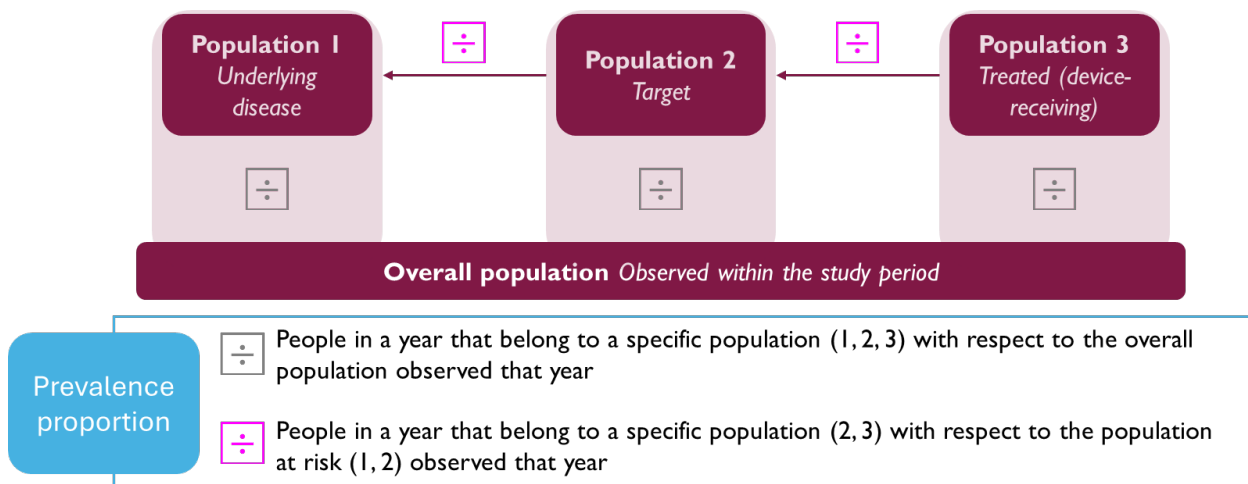


Figure 2 Scheme of the prevalence calculations that will be performed in this study and the obtained outcomes.

4.7.1 Main statistical methods

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	34/111

Table 9 Description of study types and types of analysis

Study type	Type of analysis
Population Level DUS	- Population-based incidence rates - Population-based prevalence of use of a drug/drug class
Patient Level DUS	- Characterisation of patient-level features - Frequency and % of indication/s - Estimation of minimum, p25, median, p75, and maximum initially prescribed or dispensed dose/strength - Estimation of minimum, p25, median, p75, and maximum treatment duration
Population-level descriptive epidemiology	- Incidence rates of the condition of interest - Prevalence rates of the condition of interest
Patient-level characterisation	- large-scale characterisation - Patient-level characteristics - Prognosis / progression to a pre-specified outcome - Standard care description

Population-level analyses estimate disease frequency and burden in the population; patient-level analyses evaluate characteristics or outcomes of individual patients.

The description of sensitivity analyses is presented by means of **Table 10**.

Table 10 Sensitivity analyses – rationale, strengths, and limitations.

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Sensitivity analysis I	Prior observation period 365 days	The effect of varying prior observation period on the result in the incidence-	We make sure that we analyse new diagnoses	Newborns will not be included

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	35/111

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
		prevalence calculation		
Sensitivity analysis 2	Prior observation period 30 days	The effect of varying prior observation period on the result in the incidence-prevalence calculation	We make sure that we analyse new diagnoses	Newborns will not be included

4.7.2 Patient privacy protection

No personal data will be processed by or shared by external partners from patients or healthcare professionals that are included in the data sources that participate in the GREG project for the conduct of non-interventional scientific studies. No personal data is shared by the data partners with the GREG use cases teams since data will only be provided in aggregated and therefore anonymised format.

4.7.3 Methods to derive parameters of interest

OMOP concept ID were used to define our parameters of interest, and we developed the phenotypes for this study following the DARWIN EU guideline on standardised and reproducible phenotypes [1].

4.7.4 Methods planned to obtain point estimates with confidence intervals of measures of occurrence

Open-source R packages published on CRAN were used for the analysis. The point estimates and confidence intervals method used in the study can be found from the documentation of the packages below.

- **Characterisation** using the *CohortCharacteristic* package (<https://darwin-eu.github.io/CohortCharacteristics/>)
- **Incidence and prevalence** calculation using the *IncidencePrevalence* package (<https://darwin-eu.github.io/IncidencePrevalence/>)
- **Drug utilisation** patterns using the *DrugUtilisation* package (<https://darwin-eu.github.io/DrugUtilisation/>) and/or the *TreatmentPatterns* package (<https://darwin-eu-dev.github.io/TreatmentPatterns/>)

4.7.5 Methods to control for potential sources of bias

Potential sources of bias include incomplete capture of diagnoses, procedures, or follow-up time, as well as misclassification of the event definitions used to identify the underlying disease, disease progression, and treated populations. These issues could lead to under- or over-estimation of incidence and prevalence; therefore, data-source-specific completeness, prior observation requirements, and 3 alternative population definitions will be assessed as sensitivity checks.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	36/111

4.7.6 Methods to deal with missing data

Missing data are a common challenge in routinely collected healthcare data. In this study, the analyses relied primarily on coded diagnoses and procedures, and missingness in underlying clinical information was assumed to be non-informative. Information on the completeness of coding and missing data mechanisms was not available and could not be formally assessed. Consequently, incomplete recording of diagnoses, procedures, or other relevant clinical information may have resulted in misclassification and represents a limitation of the study.

5 Results

5.1 Participants

Tables 11–14 summarise the sequential application of phenotype definitions and study restrictions used to derive the underlying disease, disease progression, strict disease progression, and device treatment cohorts.

For the underlying disease cohort, 5,246 qualifying records corresponding to 3,677 individuals were initially identified across BIGAN and CPRD GOLD. After removing overlapping records and restricting to the first qualifying event, 3,676 individuals remained. Restriction to the study period beginning in 2006 resulted in a final underlying disease cohort of 2,441 individuals, comprising 310 individuals from BIGAN and 2,131 individuals from CPRD GOLD.

For the disease progression cohort, 5,267 qualifying records corresponding to 4,326 individuals were initially identified. Application of the requirement for prior evidence of either the underlying disease or an initial intervention before the progression event reduced the cohort to 315 individuals. After restricting to the study period, the final disease progression cohort comprised 244 individuals, including 17 from BIGAN and 227 from CPRD GOLD.

Application of the pre-specified strict disease progression definition, which required evidence of both the underlying disease and a prior intervention, resulted in a substantially smaller cohort. Following all restrictions, 41 individuals remained, all from CPRD GOLD.

For the device treatment cohort, 270 qualifying records corresponding to 244 individuals were initially identified. After restricting to the first qualifying event and the study period, the final cohort comprised 213 individuals, including 24 from BIGAN and 189 from CPRD GOLD. The population included in the study for each data source, in regard to each event of interest, are represented in the attrition **Table 11**, **Table 12**, **Table 13** and **Table 14**

Table 11 Attrition of the underlying disease cohort. The table shows the sequential application of inclusion criteria and phenotype definitions used to identify patients with congenital or structural cardiac conditions associated with pulmonary valve disease, right ventricular outflow tract dysfunction, or related congenital heart disease pathways from the source population.

Exclusion	BIGAN		CPRD Gold (UK)		Total	
	Subjects	Records	Subjects	Records	Subjects	Records
Initial qualifying events	311	621	3,366	4,625	3,677	5,246
Record in observation	310	619	3,366	4,625	3,676	5,244
Not missing record date	310	619	3,366	4,625	3,676	5,244
Merge overlapping records	310	542	3,366	4,473	3,676	5,015

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 37/111

Exclusion	BIGAN		CPRD Gold (UK)		Total	
	Subjects	Records	Subjects	Records	Subjects	Records
Restricted to first entry	310	310	3,366	3,366	3,676	3,676
cohort_start_date after 2006-01-01	310	310	2,131	2,131	2,441	2,441
cohort_start_date before 2025-12-31	310	310	2,131	2,131	2,441	2,441
Exit at observation period end date, limited to current observation period	310	310	2,131	2,131	2,441	2,441

Population: Ev1 underlying disease cohort.

Table 12 Attrition of the disease progression cohort. The table shows the sequential application of inclusion criteria and phenotype definitions used to identify patients with evidence of residual or progressive pulmonary valve or right ventricular outflow tract dysfunction following prior disease history or intervention.

Exclusion	BIGAN		CPRD Gold (UK)		Total	
	Subjects	Records	Subjects	Records	Subjects	Records
Initial qualifying events	154	209	4,172	5,058	4,326	5,267
Record in observation	154	209	4,172	5,058	4,326	5,267
Not missing record date	154	209	4,172	5,058	4,326	5,267
Merge overlapping records	154	204	4,172	4,950	4,326	5,154
Restricted to first entry	154	154	4,172	4,172	4,326	4,326
Require 1 or more intersections for 1 or more of the cohorts: initial_surgery and underlying_disease. Intersection window: -Inf to -1 days relative to cohort_start_date	17	17	298	298	315	315
cohort_start_date after 2006-01-01	17	17	227	227	244	244
cohort_start_date before 2025-12-31	17	17	227	227	244	244
Exit at observation period end date, limited to current observation period	17	17	227	227	244	244

Population: Pop2 disease progression / eligible population, defined as Ev3 with prior Ev1 and/or Ev2 recorded on or before the Ev3 index date.

Table 13 Attrition of the strict disease progression cohort. The table shows the sequential application of inclusion criteria and phenotype definitions used to identify patients with evidence of residual or progressive pulmonary valve or right ventricular outflow tract dysfunction following prior disease history and intervention on RVOT.

Exclusion	BIGAN		CPRD Gold (UK)		Total	
	Subjects	Records	Subjects	Records	Subjects	Records
Initial qualifying events	154	209	4,172	5,058	4,326	5,267
Record in observation	154	209	4,172	5,058	4,326	5,267
Not missing record date	154	209	4,172	5,058	4,326	5,267

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 38/111

Exclusion	BIGAN		CPRD Gold (UK)		Total	
	Subjects	Records	Subjects	Records	Subjects	Records
Merge overlapping records	154	204	4,172	4,950	4,326	5,154
Restricted to first entry	154	154	4,172	4,172	4,326	4,326
Require 1 or more intersections for all 2 cohorts: initial_surgery and underlying_disease. Intersection window: -Inf to -1 days relative to cohort_start_date	0	0	44	44	44	44
cohort_start_date after 2006-01-01	0	0	41	41	41	41
cohort_start_date before 2025-12-31	0	0	41	41	41	41
Exit at observation period end date, limited to current observation period	0	0	41	41	41	41

Population: Strict disease progression cohort, using the pre-specified strict disease progression definition.

Table 14 Attrition of the device treatment cohort. The table shows the sequential application of inclusion criteria and phenotype definitions used to identify patients undergoing pulmonary valve replacement procedures, including percutaneous pulmonary valve implantation (PPVI), surgical pulmonary valve replacement (PVR), or related pulmonary valve device interventions

Exclusion	BIGAN		CPRD Gold (UK)		Total	
	Subjects	Records	Subjects	Records	Subjects	Records
Initial qualifying events	24	24	220	246	244	270
Record in observation	24	24	220	246	244	270
Not missing record date	24	24	220	246	244	270
Merge overlapping records	24	24	220	244	244	268
Restricted to first entry	24	24	220	220	244	244
cohort_start_date after 2006-01-01	24	24	189	189	213	213
cohort_start_date before 2025-12-31	24	24	189	189	213	213
Exit at observation period end date, limited to current observation period	24	24	189	189	213	213

Population: Ev4 PPVI/PVR treatment cohort.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	39/111

5.2 Main results

5.2.1 Baseline characteristics of underlying disease, disease progression, and device treatment cohorts

There are 2,131 patients in CPRD GOLD and 310 in BIGAN who were identified in the underlying disease cohort, compared with 227 and 17 in the disease progression cohort, and 189 and 24 in the device treatment cohort, respectively. Median cohort entry dates were earlier in CPRD GOLD than in BIGAN across all cohorts, reflecting differences in data availability: BIGAN data were available from 2017 onwards, whereas CPRD GOLD included observations from 2006 onwards.

Patients in the underlying disease cohorts were younger than those in the device treatment cohorts. In CPRD GOLD, the median age was 5 years (interquartile range [IQR] 0–29) in the underlying disease cohort, 9 years (IQR 3–19) in the disease progression cohort, and 29 years (IQR 19–44) in the device treatment cohort. Similar patterns were observed in BIGAN, where median age increased from 6 years (IQR 0–40) in the underlying disease cohort to 40 years (IQR 22–64) in the device treatment cohort. The largest age group in the underlying disease cohorts was 0–4 years in both databases.

Females represented 45.5% to 62.5% of patients in BIGAN and 42.7% to 52.2% in CPRD GOLD across cohorts. Median prior observation time increased across the progression and device treatment cohorts compared with the underlying disease cohorts in both databases.

Clinical characteristics recorded on or prior to the index date differed across cohorts. Pulmonary outflow tract disease, pulmonary stenosis, and direct RVOT pathway disease/intervention were among the most frequently observed characteristics in disease progression cohorts. Surgical pulmonary valve replacement procedures were more common in the device treatment cohorts, with all patients in BIGAN and 58.7% in CPRD GOLD having evidence of prior surgical pulmonary valve replacement recorded on or before the index date.

Table 15 Baseline characteristics of patients in the underlying disease, disease progression, and device treatment cohorts across BIGAN and CPRD GOLD.

Variable	BIGAN			CPRD Gold (UK)		
	Disease		Device received	Disease		Device received
	Underlying disease	progression n		Underlying disease	progression n	
Number subjects (N)	310	17	24	2,131	227	189
Age						
Median [Q25 - Q75]	6 [0 - 40]	11 [1 - 56]	40 [22 - 64]	5 [0 - 29]	9 [3 - 19]	29 [19 - 44]
Mean (SD)	21.42 (26.80)	26.29 (30.70)	41.96 (22.21)	17.66 (23.10)	14.95 (17.35)	32.96 (18.88)
Range	0 to 93	0 to 80	8 to 78	0 to 94	0 to 84	1 to 87
Age group (N%)						
0 to 4	146 (47.10%)	8 (47.06%)	0 (0.00%)	1,065 (49.98%)	76 (33.48%)	<5

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 40/111

Variable	BIGAN			CPRD Gold (UK)		
	Underlying disease	Disease progression	Device received	Underlying disease	Disease progression	Device received
5 to 17	43 (13.87%)	<5	<5	284 (13.33%)	89 (39.21%)	37 (19.58%)
18 to 39	42 (13.55%)	<5	8 (33.33%)	397 (18.63%)	37 (16.30%)	90 (47.62%)
40 to 64	45 (14.52%)	<5	7 (29.17%)	242 (11.36%)	19 (8.37%)	41 (21.69%)
65 to 150	34 (10.97%)	<5	5 (20.83%)	143 (6.71%)	6 (2.64%)	17 (8.99%)
Sex (N%)						
Female	141 (45.48%)	7 (41.18%)	15 (62.50%)	1,112 (52.18%)	97 (42.73%)	83 (43.92%)
Prior observation in days						
Median [Q25 - Q75]	300 [0 - 1,463]	1,268 [521 - 1,982]	1,468 [524 - 1,914]	338 [49 - 2,168]	2,173 [1,028 - 4,290]	3,212 [1,278 - 4,959]
Mean (SD)	801.01 (994.34)	1,333.53 (1,054.06)	1,340.04 (830.29)	1,476.10 (2,127.53)	2,742.08 (2,201.00)	3,265.20 (2,246.75)
Range	0 to 3,207	49 to 3,102	58 to 2,836	0 to 10,931	8 to 9,261	7 to 9,553
Any time on or prior index date - Condition (N%)						
Conotruncal congenital heart disease	28 (9.03%)	<5	0 (0.00%)	170 (7.98%)	11 (4.85%)	0 (0.00%)
Extended right-sided congenital heart disease	127 (40.97%)	9 (52.94%)	<5	594 (27.87%)	51 (22.47%)	7 (3.70%)
Prosthetic pulmonary valve dysfunction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary outflow tract disease	118 (38.06%)	13 (76.47%)	<5	1,110 (52.09%)	93 (40.97%)	10 (5.29%)
Pulmonary stenosis	72 (23.23%)	15 (88.24%)	<5	337 (15.81%)	122 (53.74%)	15 (7.94%)
RVOT obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	55 (2.58%)	9 (3.96%)	0 (0.00%)
Pulmonary valve regurgitation	<5	<5	11 (45.83%)	53 (2.49%)	110 (48.46%)	48 (25.40%)
Any time on or prior index date - Procedure (N%)						
Direct RVOT pathway disease/intervention	126 (40.65%)	13 (76.47%)	6 (25.00%)	1,097 (51.48%)	155 (68.28%)	40 (21.16%)
Named congenital cardiac repair procedure	0 (0.00%)	0 (0.00%)	0 (0.00%)	44 (2.06%)	65 (28.63%)	19 (10.05%)

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	41/111

Variable	BIGAN			CPRD Gold (UK)		
	Underlying disease	Disease progression	Device received	Underlying disease	Disease progression	Device received
Surgical Pulmonary valve replacement	6 (1.94%)	0 (0.00%)	24 (100.00%)	11 (0.52%)	18 (7.93%)	111 (58.73%)
RV-PA conduit procedure	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)	<5
RVOT patch reconstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5	<5	0 (0.00%)

<5 is suppressed less than 5 count. Characteristics were measured at cohort index date, defined as the first qualifying occurrence for each cohort definition. Demographic characteristics, follow-up history, and prior clinical history recorded any time on or before index date are summarised. The underlying disease cohort represents patients with congenital or structural cardiac conditions associated with pulmonary valve disease or right ventricular outflow tract (RVOT) dysfunction. The disease progression cohort represents patients with evidence of residual or progressive RVOT or pulmonary valve dysfunction following prior disease or intervention history. The device treatment cohort represents patients undergoing pulmonary valve replacement procedures, including transcatheter pulmonary valve implantation (PPVI) and surgical pulmonary valve replacement (PVR). Continuous variables are summarised using median [interquartile range], mean (standard deviation), and range. Categorical variables are presented as counts and percentages. Counts fewer than five are suppressed and displayed as <5.

5.2.2 Annual Incidence rate and trends

Annual incidence rates were estimated for new underlying disease cases, disease progression, and devices received in CPRD GOLD and BIGAN, where data were available. Incidence rates are reported per 100,000 person-years. Sensitivity analyses were conducted for disease progression using alternative definitions based on the minimum time between the underlying disease diagnosis (or initial intervention) and the progression event. Furthermore, a strict version of the disease progression was created in which both the underlying disease and the initial surgery must occur before disease progression event; the count was <5, so we cannot report the results. Annual incidence proportion and period prevalence estimates were also calculated; these results are presented in **Annex I** and **Annex II**.

In CPRD GOLD, the annual incidence of the new underlying disease cases ranged from 1.8 to 2.6 per 100,000 person-years between 2006 and 2024 (**Figure 3**). Annual estimates were 2.6 per 100,000 person-years in 2006, 2.2 per 100,000 person-years in 2017, and 2.1 per 100,000 person-years in 2024. In BIGAN, incidence estimates were available from 2017 onwards and ranged from 1.2 to 3.0 per 100,000 person-years. The incidence was 3.0 per 100,000 person-years in 2017 and 1.2 per 100,000 person-years in 2025.

In CPRD GOLD, annual incidence estimates for disease progression ranged from 0.12 to 0.32 per 100,000 person-years between 2006 and 2024 (**Figure 4**). The corresponding incidence of device receipt ranged from 0.09 to 0.33 per 100,000 person-years. In 2024, the incidence of disease progression was 0.28 per 100,000 person-years and the incidence of device receipt was 0.17 per 100,000 person-years. The incidence count for BIGAN were all less than 5 hence is suppressed and cannot be reported.

In the sensitivity analysis of disease progression definitions, three sensitivity analyses were conducted using different requirements for prior evidence of the underlying disease or initial intervention before the progression event (**Figure**

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	42/111

5). In the least restrictive definition, individuals were required to have prior records of the underlying disease or initial intervention before the progression event. In the second definition, this prior record was required to occur at least 30 days before the progression event. Under the most restrictive definition, the prior record was required to have occurred at least 365 days before the progression event. The incidence rates were similar across CPRD, all with overlapping 95% confidence intervals. Incidence estimates based on any prior record ranged from 0.09 to 0.33 per 100,000 person-years. Estimates requiring a record at least 30 days before the progression event ranged from 0.11 to 0.30 per 100,000 person-years. Estimates requiring a record at least 365 days before the progression event ranged from 0.09 to 0.22 per 100,000 person-years. In 2024, the incidence estimates were 0.28, 0.28, and 0.21 per 100,000 person-years for the any prior, ≥ 30 days prior, and ≥ 365 days prior definitions, respectively.

The incidence proportion was also estimated, and the trend was similar to the incidence rate; the results are included in the annex (17.1.2).

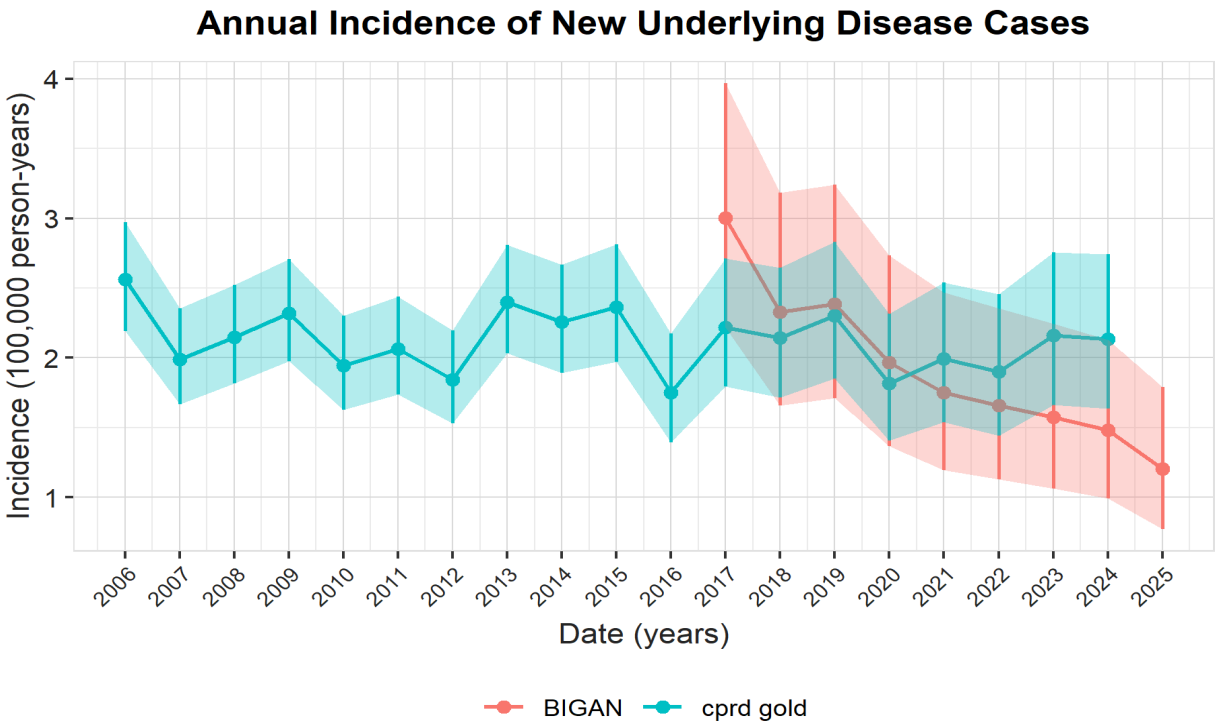


Figure 3 Annual incidence of new underlying disease cases in BIGAN and CPRD GOLD, 2006–2025. Incidence rates are presented per 100,000 person-years. Points represent annual incidence estimates and shaded areas indicate 95% confidence intervals. CPRD GOLD contributed data from 2006 onwards, while BIGAN contributed data from 2017 onwards.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	43/111

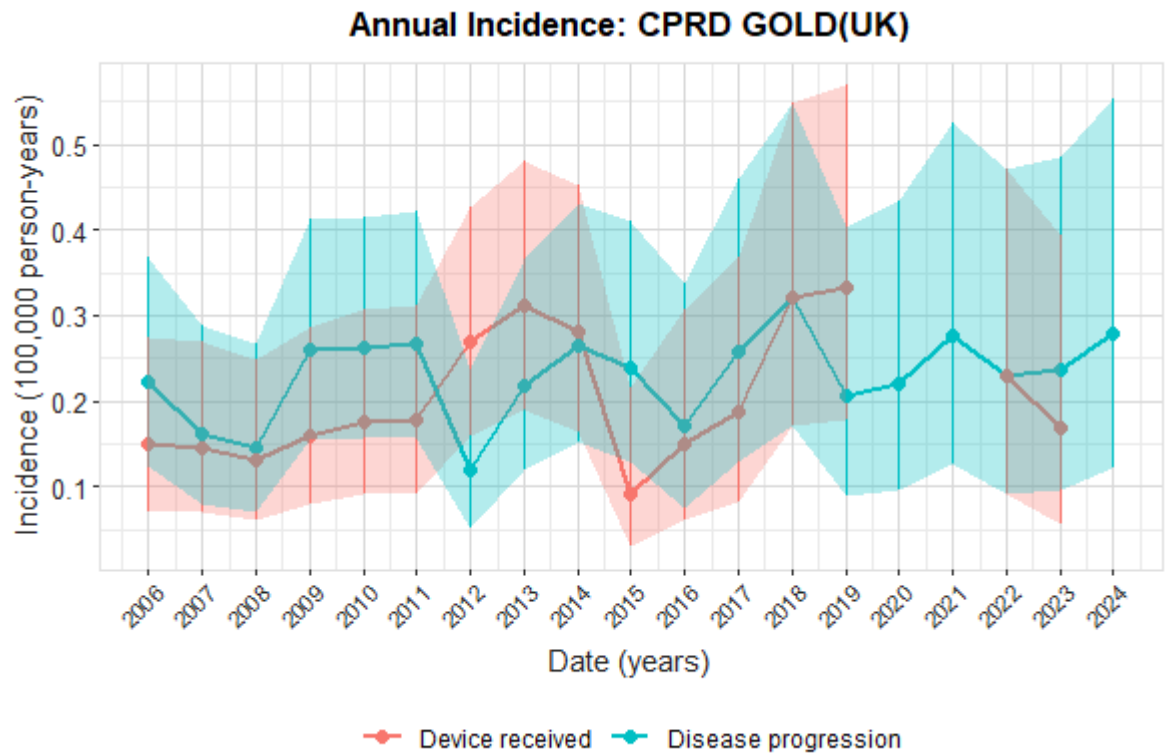


Figure 4 Annual incidence of disease progression and device receipt in CPRD GOLD (UK), 2006–2024. Annual incidence rates are presented per 100,000 person-years. Disease progression refers to patients with the underlying disease who progressed to require intervention, while device received refers to patients receiving the device of interest. Points represent annual incidence estimates and shaded areas indicate 95% confidence intervals.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	44/111

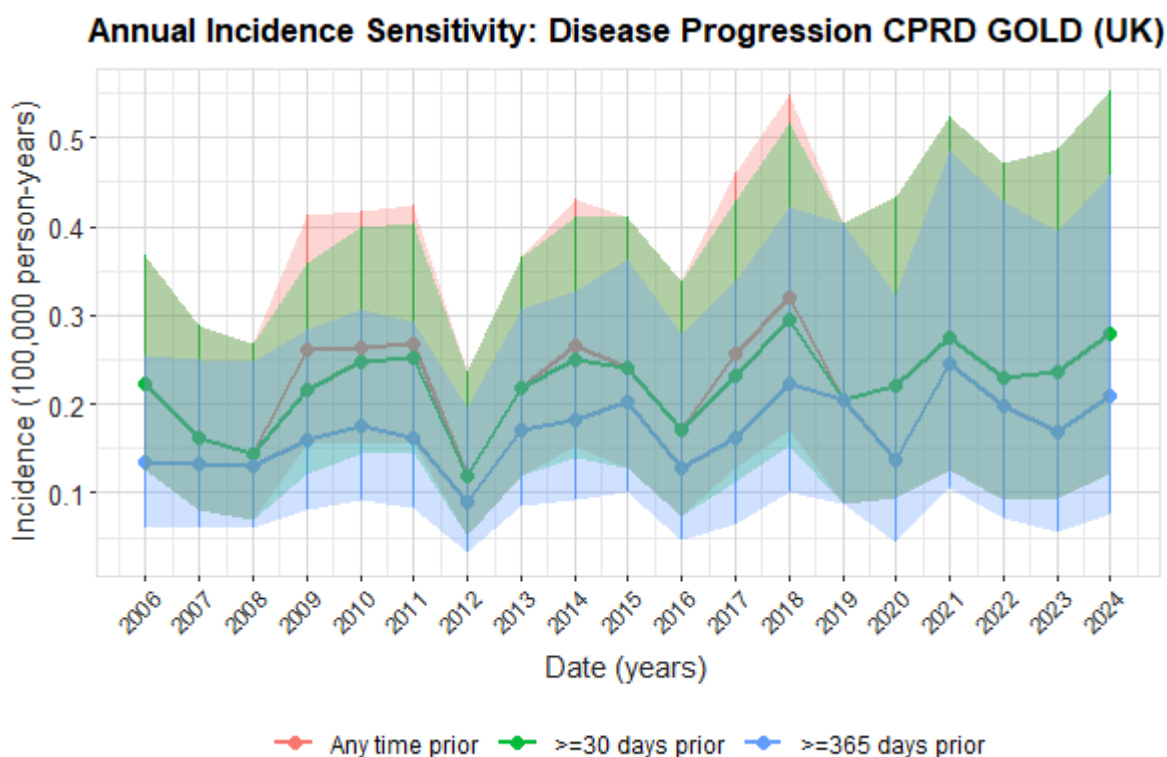


Figure 5 Annual incidence sensitivity analysis for disease progression definitions in CPRD GOLD (UK), 2006–2024. Annual incidence rates per 100,000 person-years are shown using three alternative disease progression definitions based on the minimum time between the underlying disease diagnosis (or initial intervention) and the disease progression event: any prior record, ≥ 30 days prior, and ≥ 365 days prior.

5.2.3 Extrapolation of Incidence Estimates to European Population Levels

Age-sex standardised incidence rates from the most recent three years of available data were extrapolated to the European population using the latest population and age strata data from the [official European website](#). The figures are also included in **Annex III** to estimate the annual numbers of individuals in the underlying disease, disease progression, and device-received cohorts (**Table 16**). The three-year estimates are presented in this section to avoid including the 2020 and 2021 COVID-19 pandemic years. Five-year pooled estimates are included in **Annex III** and show similar results. For estimating the orphan device population, the disease progression cohort was considered most relevant because it represents individuals who had progressed to the device-eligible population. We only have estimates from two data sources in this study, hence we cannot carry out the meta-analysis to estimate the pooled rate.

For the underlying disease cohort, the age-sex standardised incidence rate was 2.06 (95% CI: 1.59–2.54) per 100,000 person-years in BIGAN and 2.35 (95% CI: 2.00–2.69) per 100,000 person-years in CPRD GOLD. These corresponded to estimated numbers of 7,148–11,438 and 9,009–12,105 individuals in the European population, respectively.

For the disease progression cohort, the age-sex standardised incidence rate was 0.18 (95% CI: 0.04–0.32) per 100,000 person-years in BIGAN and 0.26 (95% CI: 0.15–0.38) per 100,000 person-years in CPRD GOLD. These corresponded to estimated numbers of 185–1,424 and 688–1,691 individuals in the European population, respectively.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	45/111

For the device received cohort, the age-sex standardised incidence rate was 0.10 (95% CI: 0.01–0.18) per 100,000 person-years in BIGAN and 0.17 (95% CI: 0.08–0.26) per 100,000 person-years in CPRD GOLD. These corresponded to an estimated 51–806 and 382–1,168 individuals in the European population per year, respectively.

Estimates using alternative disease progression cohort definitions, consistent with the incidence sensitivity analysis, showed similar results and are presented in the Annex (17.1.3).

Table 16 Incidence rates and estimated annual numbers of individuals in the European population for the underlying disease, disease progression, and device received cohorts.

Database name	Incidence Rate last 3 years pooled rate					
	BIGAN			CPRD Gold		
	Crude	Standardised	EU total, extrapolation	Crude	Standardised	EU total, extrapolation
Underlying Disease	1.42 (1.13-1.76)	2.06 (1.59-2.54)	7,148-11,438	2.06 (1.77-2.38)	2.35 (2.00-2.69)	9,009-12,105
Disease Progression	0.12 (0.05-0.25)	0.18 (0.04-0.32)	185-1,424	0.25 (0.16-0.38)	0.26 (0.15-0.38)	688-1,691
Device received	0.09 (0.03-0.20)	0.10 (0.01-0.18)	51-806	0.17 (0.09-0.28)	0.17 (0.08-0.26)	382-1,168

Results are based on the most recent three years of available data from BIGAN and CPRD GOLD. Crude and age-sex standardised incidence rates are presented per 100,000 person-years with 95% confidence intervals. Estimated annual numbers of individuals in the European population were obtained by applying age-sex standardised incidence rates to the European population. Ranges represent the corresponding 95% confidence intervals.

Table 17 Incidence proportion and estimated annual numbers of individuals in the European population for the underlying disease, disease progression, and device received cohorts.

Database name	Incidence proportion last 3 years pooled proportion					
	BIGAN			CPRD Gold		
	Crude	Standardised	EU total, extrapolation	Crude	Standardised	EU total, extrapolation
Underlying Disease	1.39 (1.11-1.73)	1.40 (1.09-1.71)	4,918-7,709	1.90 (1.63-2.19)	1.69 (1.44-1.94)	6,494-8,733
Disease Progression	0.12 (0.05-0.24)	0.13 (0.03-0.23)	145-1,047	0.23 (0.14-0.35)	0.21 (0.12-0.30)	551-1,352
Device received	0.08 (0.03-0.20)	0.08 (0.01-0.15)	42-662	0.16 (0.09-0.26)	0.16 (0.08-0.24)	346-1,059

Results are based on the most recent three years of available data from BIGAN and CPRD GOLD. Crude and age-sex standardised incidence rates are presented per 100,000 person-years with 95% confidence intervals. Estimated annual numbers

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	46/111

Incidence proportion last 3 years pooled proportion						
Database name	BIGAN			CPRD Gold		
Proportion	Crude	Standardised	EU total, extrapolatio n	Crude	Standardised	EU total, extrapolation
of individuals in the European population were obtained by applying age-sex standardised incidence rates to the European population. Ranges represent the corresponding 95% confidence intervals.						

5.2.4 Comparison with the literature

We identified several published registry studies, device-specific registries, and epidemiological studies relevant to congenital heart disease and pulmonary valve interventions and the papers found are presented in **Table 18**.

Zimmerman et al. reported population-level estimates for congenital heart disease, including incidence and prevalence at birth, across multiple countries and regions. These estimates were reported for congenital heart disease overall and were not restricted to pulmonary or RVOT-related conditions [5].

Two national registry studies reporting pulmonary valve intervention activity were identified. The German National Quality Assurance Registry reported 101 transcatheter pulmonary valve implantation procedures and 99 surgical pulmonary valve replacement procedures in 2021. The registry reported coverage of 73.0% for interventional procedures and 67.2% for surgical procedures. After accounting for the reported coverage, these figures corresponded to approximately 138 transcatheter pulmonary valve implantation procedures and 147 surgical pulmonary valve replacement procedures annually in Germany [6]. We used these results to extrapolate to the EU population and compared them to our estimates in Figure 10.4. The results overlapped with our estimates.

To extrapolate these estimates to the European population, the coverage-adjusted German counts were scaled by the ratio of the European population to the German population. This produced an estimated European annual procedure volume, which was used as an external benchmark and compared with the real-world data estimates in **Figure 6**. The benchmark estimates overlapped with the estimates derived from CPRD GOLD and BIGAN.

The Spanish congenital cardiac catheterisation registry reported 87 percutaneous valve implantation procedures in 2022 across participating centres. The registry was retrospective and voluntary, and no national coverage estimate was reported [7].

Additional device-specific registries were identified. The SAPIEN 3 transcatheter pulmonary valve replacement registry reported a mean patient age of 29.2 years among treated individuals [8]. The Melody and Edwards valve registries reported a mean patient age of 21.4 years among treated individuals [9,10]. However, it again provided only a count, without coverage information.

Studies describing the long-term management of repaired Tetralogy of Fallot and RVOT conduit populations were also identified. In repaired Tetralogy of Fallot populations, published studies reported that approximately 36–40% of patients required pulmonary valve replacement within 30 years after primary repair [11]. In a cohort of adults with Tetralogy of Fallot, 101 of 165 patients (61.2%) had undergone at least one pulmonary valve replacement. In RV-PA conduit

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	47/111

populations, one long-term follow-up study reported a 47.4% freedom from conduit replacement at a median follow-up of 8.7 years, corresponding to 52.6% requiring conduit replacement by follow-up. These estimates describe the frequency of later pulmonary valve intervention within repaired Tetralogy of Fallot and RVOT conduit cohorts and were not reported as annual population-based incidence rates.

Table 18 *Relevant literature on the incidence of underlying disease, disease progression and device-eligible cohorts for this study.*

Authors	Year	Country/ies	Reported
Oosterhof et al [12]	2006	The Netherlands	158 patients in the CONCOR registry between June 1986 and June 2005 received 175 surgical pulmonary valve replacements
Fraisse et al [9]	2014	France	Characterisation of 64 patients receiving PPVI (nos) between April 2008 and December 2010 in France
Zimmerman et al [5]	2020	Global	Globally 11,191,283 CHD patients
Dorobantu et al [13]	2020	United Kingdom of Great Britain and Northern Ireland	48 of 707 Tetralogy of Fallot patients (6.8%), aged 15 years or older from the UK National Congenital Heart Disease Audit Database (covering the period from 2000-2013) undergoing initial initial surgical pulmonary valve repair required a second pulmonary valve repair
Gröning et al [14]	2023	Denmark	384 patients included in the Danish National Patient registry and the EVITRA study (study period June 1986 to June 2005) received 546 pulmonary valve replacements (463 via surgical procedure and 83 via transcatheter placement)
Bokma et al [11]	2023	International	540 of 1,143 patients (47%) included in the international Tetralogy of Fallot INDICATOR registry (covering the period between January 2002 and September 2021) underwent pulmonary valve replacement (453 (84%) via surgical procedure and 87 (16%) via percutaneous placement)
Ballesteros Tejerizo et al [7]	2024	Spain	Description of interventions for adult CHD patients in 22 Spanish centres and in the Registry of Cardiac Catheterization and Interventional Cardiology of the ACI-SEC in the year 2022: in total 87 percutaneous pulmonary valve implantations; 51 of which (59%) in patients 18 years or older.
Hofbeck et al [6]	2024	Germany	200 percutaneous and surgical pulmonary valve replacements were performed in 2022 in around 70% of the German population.
Hascoët et al [8]	2024	International	Description of procedural and outcome data for percutaneous pulmonary valve implantation in a total of 840 CHD patients with RVOT dysfunction from 35 centres in 15 countries between 2014 and 2021
Pilati et al [15]	2025	Italy	396 patients receiving pulmonary valve replacement for a dysfunctional RVOT in seven Italian centres between July 2022 and April 2024. 230 (58%) underwent surgical intervention and 166 (42%) percutaneous pulmonary valve implantation (PPVI).

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	48/111

Authors	Year	Country/ies	Reported
Belahnech et al [10]	2025	Spain	Description of mid-term outcomes (procedural success, complications at index admission) for 76 patients undergoing percutaneous implantation of the Edwards Sapien valve in a single centre in Spain.
Protopapas et al [16]	2025	Europe	25-year summary of unadjusted aggregated heart surgery in CHD patients included in the European Congenital Heart Surgeons Association Congenital Cardiac Database (ECHSA-CCDB) covering 417 centres from 87 countries (72% from European countries) between 1999 and 2024. The summary includes 194,621 European CHD patients, and 257,798 procedures of which 11,813 (4.6%) concerned Tetralogy of Fallot repair (including percutaneous pulmonary valve implantation (PPVI)).
Huasheng et al [17]	2026	Global	Sex-stratified incidence, mortality and disability adjusted life years for CHD in children younger than 5 years between 1990 and 2021. In 2021 globally there were 1,191,984 incident CHDs of which 6,968 concerned patients in central Europe.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	49/111

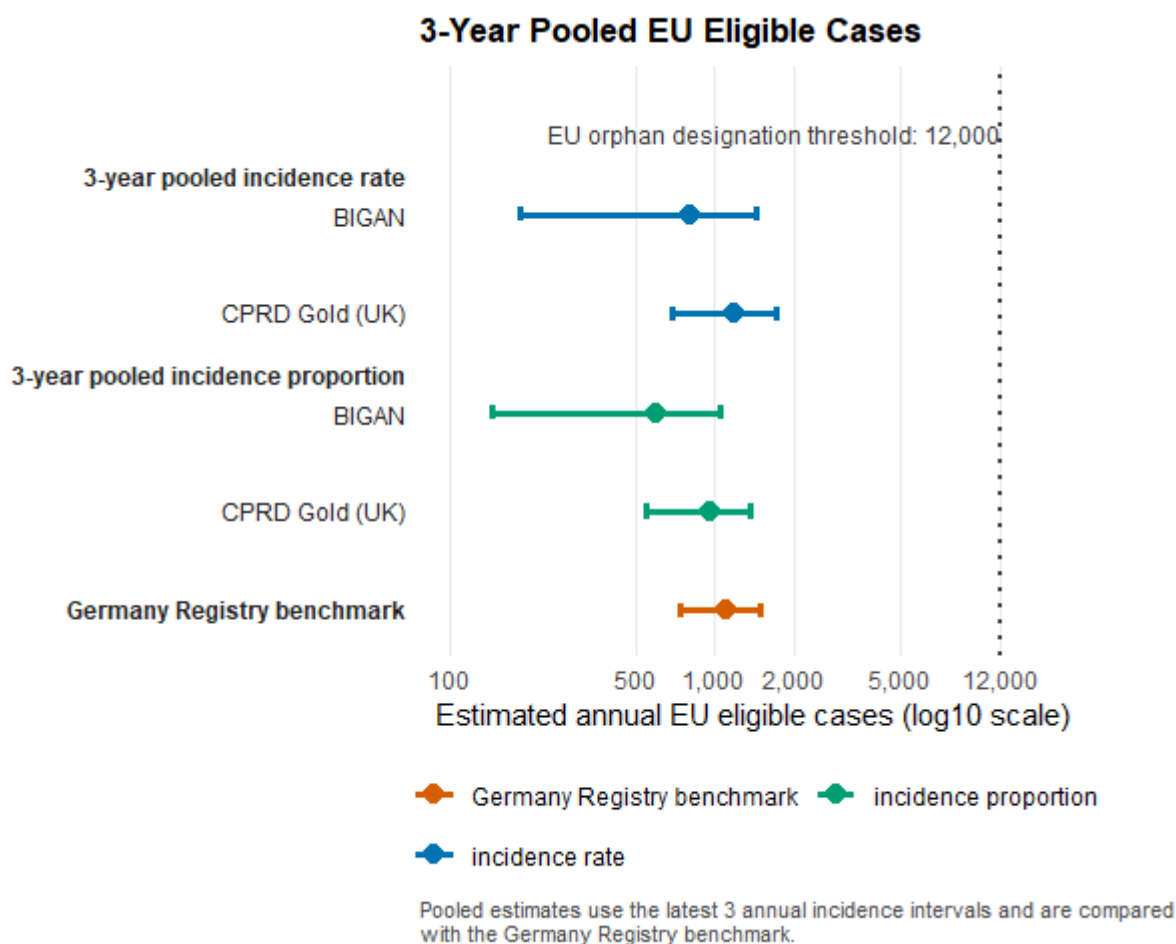


Figure 6 Estimated annual number of intervention-eligible individuals in the European population based on disease progression cohort definitions and external benchmark data. Estimated annual numbers of device-eligible individuals in the European population were derived from age-sex standardised disease progression incidence rates and incidence proportions using the most recent three full years of data from BIGAN and CPRD GOLD (UK). Points represent point estimates and horizontal lines represent 95% confidence intervals. Estimates are compared with an external benchmark derived from the German registry found from the literature.

5.2.5 Characterisation of the Underlying Disease, Disease Progression, and Device Received Cohorts

The section presents the results for large scale characterisation for conditions and medications for both databases.

Conditions

Table 19 and **Table 20** present the 25 most frequently recorded conditions concepts in the underlying disease, disease progression, and device received cohorts during the 365 to 31 days before index, 30 to 1 days before index, and on the index date.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	50/111

In the underlying disease cohort, congenital cardiac conditions were among the most frequently recorded concepts on the index date. In CPRD GOLD, the most common congenital cardiac concepts included Tetralogy of Fallot (19.0%), infundibular pulmonic stenosis (18.3%), pulmonary artery stenosis (12.7%), congenital anomaly of the pulmonary artery (10.0%), congenital stenosis of the pulmonary valve (8.9%), and Ebstein's anomaly (5.5%). Similar findings were observed in BIGAN, where Tetralogy of Fallot (23.6%), pulmonary artery stenosis (22.9%), atrial septal defect (15.2%), congenital stenosis of the pulmonary valve (13.6%), and ventricular septal defect (9.3%) were among the most frequently recorded concepts.

In the disease progression cohort, RVOT-related congenital and valvular conditions were observed across all time windows. In CPRD GOLD, the most frequently recorded concepts around the index date included pulmonic valve stenosis (33.9%), pulmonic valve regurgitation (26.0%), pulmonary incompetence, non-rheumatic (18.5%), pulmonary artery stenosis (10.6%), pulmonary stenosis, non-rheumatic (4.8%), and pulmonary valve stenosis with insufficiency (4.4%). In BIGAN, pulmonary artery stenosis accounted for 70.6% of records on the index date.

In the device received cohort, pulmonary valve and RVOT-related conditions were also recorded. In CPRD GOLD, the most frequently recorded concepts on the index date included pulmonic valve stenosis (33.9%), pulmonic valve regurgitation (26.0%), pulmonary incompetence, non-rheumatic (18.5%), pulmonary artery stenosis (10.6%), and pulmonary stenosis, non-rheumatic (4.8%). In BIGAN, pulmonary incompetence, non-rheumatic accounted for 37.5% of records on the index date, followed by essential hypertension (25.0%).

Counts in the disease progression and device-received cohorts were limited, particularly in BIGAN, resulting in the suppression of concepts with fewer than 5 records.

Medications

Table 21 and **Table 22** present the 25 most frequently recorded medications in the underlying disease, disease progression, and device received cohorts during the 365 to 31 days before index, 30 to 1 days before index, and on the index date.

In CPRD GOLD, the underlying disease cohort included records of cardiovascular medications during the year before index. The most frequently recorded cardiovascular medications included aspirin 75 mg dispersible tablets (6.6%), warfarin (4.3%), furosemide 40 mg (3.4%), bisoprolol 2.5 mg (1.2%), simvastatin 40 mg (1.3%), and ramipril 2.5 mg (1.1%). Vaccinations, including diphtheria, poliovirus, tetanus, pertussis, influenza, pneumococcal, meningococcal, measles, mumps, rubella, hepatitis B, and rotavirus vaccines, were also commonly recorded.

In the disease progression cohort, the most frequently recorded cardiovascular medications during the year before index included aspirin 75 mg dispersible tablets (5.3%), furosemide 40 mg (1.9%), warfarin 1 mg (1.5%), bisoprolol 2.5 mg (1.2%), warfarin 3 mg (1.2%), and ramipril 2.5 mg (1.1%). Additional medications recorded before index included omeprazole, lactulose, acetaminophen, and vitamin supplementation products.

In the device received cohort, cardiovascular medications recorded during the year before index included aspirin 75 mg dispersible tablets (9.1%), furosemide 40 mg (9.6%), bisoprolol 2.5 mg (7.5%), bisoprolol 5 mg (2.6%), ramipril 2.5 mg (2.6%), enoxaparin (5.3%), warfarin (4.3%), spironolactone 25 mg (4.3%), and amiodarone 200 mg (3.2%). Influenza vaccination (40.1%) was the most frequently recorded medication exposure during the year before index. On the index date, medication counts were fewer than five and were therefore suppressed.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	51/111

Table 19 Top 25 recorded clinical condition concepts by cohort and time window for BIGAN. The table shows the most frequently recorded clinical concepts for the underlying disease, disease progression, and device received cohorts across three time windows: 365 to 31 days before index, 30 to 1 days before index, and on the index date. Values are presented as count (%). Counts below 5 were suppressed and are shown

	BIGAN Conditions								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
1	Acute upper respiratory infection (257011) 47 (24.7%)	Acute upper respiratory infection (257011) 20 (8.7%)	Tetralogy of Fallot (320835) 73 (23.6%)	Acute upper respiratory infection (257011) 7 (41.2%)	Abnormal breathing (4305080) NA (NA%)	Pulmonary artery stenosis (4317288) 12 (70.6%)	Acute upper respiratory infection (257011) 7 (29.2%)	Abnormal breathing (4305080) NA (NA%)	Pulmonary incompetence, non-rheumatic (4111416) 9 (37.5%)
2	Congenital heart disease (312723) 19 (10.0%)	Congenital heart disease (312723) 16 (6.9%)	Pulmonary artery stenosis (4317288) 71 (22.9%)	Abdominal pain (200219) NA (NA%)	Acquired hypothyroidism (138384) NA (NA%)	Abnormal body temperature (4047791) NA (NA%)	Abdominal pain (200219) NA (NA%)	Aortic valve regurgitation (315564) NA (NA%)	Essential hypertension (320128) 6 (25.0%)
3	Cough (254761) 17 (8.9%)	Finding related to pregnancy (444094) 5 (2.2%)	Atrial septal defect (4289309) 47 (15.2%)	Abnormal body temperature (4047791) NA (NA%)	Acute respiratory failure (319049) NA (NA%)	Accelerated atrioventricular conduction (4057008) NA (NA%)	Abnormal breathing (4305080) NA (NA%)	Aortic valve stenosis (4189343) NA (NA%)	Acquired absence of organ (42537748) NA (NA%)
4	Fever (437663) 17 (8.9%)	Abdominal pain (200219) NA (NA%)	Congenital stenosis of pulmonary valve (313005)	Abnormal breathing (4305080) NA (NA%)	Acute upper respiratory infection (257011)	Acquired hypothyroidism (138384) NA (NA%)	Achalasia of esophagus (318186)	Chest pain (77670) NA (NA%)	Acute kidney injury (197320) NA (NA%)

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 52/111

	BIGAN Conditions								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
			42 (13.6%)		NA (NA%)		NA (NA%)		
5	Acute bronchitis (260139) 15 (7.9%)	Abnormal body temperature (4047791) NA (NA%)	Ventricular septal defect (434462) 29 (9.3%)	Acquired hypothyroidism (138384) NA (NA%)	Anxiety disorder (442077) NA (NA%)	Acute bronchiolitis (260125) NA (NA%)	Acne (141095) NA (NA%)	Clinical finding (441840) NA (NA%)	Anemia (439777) NA (NA%)
6	Colitis, enteritis and gastroenteritis presumed infectious (195453) 13 (6.8%)	Acquired hypothyroidism (138384) NA (NA%)	Congenital anomaly of pulmonary artery (435646) 27 (8.7%)	Acute bronchiolitis (260125) NA (NA%)	Cardiomegaly (314658) NA (NA%)	Acute bronchitis (260139) NA (NA%)	Acquired absence of organ (42537748) NA (NA%)	Cough (254761) NA (NA%)	Aortic valve regurgitation (315564) NA (NA%)
7	Disorder of teeth AND/OR supporting structures (201603) 13 (6.8%)	Acute bronchitis (260139) NA (NA%)	Congenital anomaly of tricuspid valve (4184499) 26 (8.4%)	Acute bronchitis (260139) NA (NA%)	Congenital stenosis of pulmonary valve (313005) NA (NA%)	Acute bronchospasm (46273539) NA (NA%)	Acquired diverticulum of esophagus (31884) NA (NA%)	Dysphagia (31317) NA (NA%)	Aortic valve stenosis (4189343) NA (NA%)
8	Viral disease (440029) 13 (6.8%)	Acute cerebrovascular insufficiency	Essential hypertension (320128) 24 (7.7%)	Acute bronchitis caused by rhinovirus (4112521)	Dementia (4182210) NA (NA%)	Acute respiratory syncytial virus	Acute kidney injury (197320)	Essential hypertension (320128)	Aortic valve stenosis with insufficiency

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 53/111

	BIGAN Conditions								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
		y (4164092) NA (NA%)		NA (NA%)		bronchitis (4110484) NA (NA%)	NA (NA%)	NA (NA%)	y (4111099) NA (NA%)
9	Chest pain (77670) 11 (5.8%)	Acute pharyngitis (25297) NA (NA%)	Congenital heart disease (312723) 22 (7.1%)	Acute laryngotracheitis (31597) NA (NA%)	Disorder of penis (196158) NA (NA%)	Acute tonsillitis (24660) NA (NA%)	Allergic rhinitis (257007) NA (NA%)	Heart failure (316139) NA (NA%)	Atherosclerosis of coronary artery without angina pectoris (764123) NA (NA%)
10	Vomiting (441408) 11 (5.8%)	Apnea (321689) NA (NA%)	Low birth weight infant (4171115) 18 (5.8%)	Acute respiratory syncytial virus bronchitis (4110484) NA (NA%)	Fever (437663) NA (NA%)	Acute upper respiratory infection (257011) NA (NA%)	Anxiety state (4113821) NA (NA%)	Type 2 diabetes mellitus (201826) NA (NA%)	Atrial fibrillation (313217) NA (NA%)
11	Conjunctival hyperemia (377283) 9 (4.7%)	Atopic dermatitis (133834) NA (NA%)	Ebstein's anomaly (4069182) 16 (5.2%)	Acute tracheitis (437903) NA (NA%)	Heart failure (316139) NA (NA%)	Alcoholic liver damage (201612) NA (NA%)	Aortic valve regurgitation (315564) NA (NA%)	–	Atrial flutter (314665) NA (NA%)
12	Diarrhea (196523) 9 (4.7%)	Atrial fibrillation (313217)	Disorder of fetus and/or newborn (441406)	Anorexia nervosa (436675)	Hyperlipidemia (432867)	Anemia (439777) NA (NA%)	Benign prostatic hyperplasia	–	Autoimmune thyroiditis (4281109)

	D5.I Results of prevalence and characterisation			
	WP5 – Medical Device		Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU	54/111

	BIGAN Conditions								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
		NA (NA%)	15 (4.8%)	NA (NA%)	NA (NA%)		^a (198803) NA (NA%)		NA (NA%)
13	Disorder of eye (375252) 9 (4.7%)	Backache (134736) NA (NA%)	Heart failure (316139) 15 (4.8%)	Anxiety state (4113821) NA (NA%)	Hypertensive heart disease without congestive heart failure (319034) NA (NA%)	Angina pectoris (321318) NA (NA%)	Bilateral stenosis of carotid arteries (37204002) NA (NA%)	–	Bacterial infection caused by Klebsiella pneumoniae (436339) NA (NA%)
14	Abdominal pain (200219) 8 (4.2%)	Blood in urine (437038) NA (NA%)	Discordant ventricular connection (432431) 13 (4.2%)	Apnea in newborn (318247) NA (NA%)	Respiratory failure (4256228) NA (NA%)	Anxiety disorder (442077) NA (NA%)	Bleeding from nose (4096682) NA (NA%)	–	Benign prostatic hyperplasia (198803) NA (NA%)
15	Constipation (75860) 8 (4.2%)	Chest pain (77670) NA (NA%)	Hyperlipidemia (432867) 13 (4.2%)	Atrial septal defect (4289309) NA (NA%)	Syncope and collapse (4206148) NA (NA%)	Aortocoronary bypass graft present (42537729) NA (NA%)	Bursitis (134453) NA (NA%)	–	Bleeding (437312) NA (NA%)
16	Pain of joint of	Colitis, enteritis and	Complete trisomy 21	Bacterial infectious	–	Atrial septal	Carcinoid syndrome (199771)	–	Carcinoid syndrome (199771)

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 55/111

	BIGAN Conditions								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
	knee (604800) 8 (4.2%)	gastroenteritis presumed infectious (195453) NA (NA%)	syndrome (439125) 12 (3.9%)	disease (432545) NA (NA%)		defect (4289309) NA (NA%)	NA (NA%)		NA (NA%)
17	Abnormal body temperature (4047791) 7 (3.7%)	Common cold (260427) NA (NA%)	Congenital atresia of pulmonary artery (4031766) 12 (3.9%)	Bacterial meningitis (436091) NA (NA%)	–	Bronchitis (256451) NA (NA%)	Cardiac arrhythmia (44784217) NA (NA%)	–	Cardiovascular system complication of procedure (43022062) NA (NA%)
18	Acute tracheitis (437903) 7 (3.7%)	Congenital disease (440508) NA (NA%)	Neonatal hypoglycemia (23034) 12 (3.9%)	Benign intracranial hypertension (312902) NA (NA%)	–	Cardiomegaly (314658) NA (NA%)	Cellulitis and abscess of finger (79898) NA (NA%)	–	Chronic atrial fibrillation (4141360) NA (NA%)
19	Dysphagia (31317) 7 (3.7%)	Contusion (441737) NA (NA%)	Patent ductus arteriosus (315922) 12 (3.9%)	Benign neoplasm of skin (138102) NA (NA%)	–	Chest pain (77670) NA (NA%)	Chronic kidney disease due to hypertension (44782429)	–	Chronic viral hepatitis B without delta-agent (439674) NA (NA%)

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 56/111

	BIGAN Conditions								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
							NA (NA%)		
20	Anxiety state (4113821) 6 (3.2%)	Cough (254761) NA (NA%)	Secondary pulmonary hypertension (4339214) 12 (3.9%)	Bronchitis (256451) NA (NA%)	–	Cholangitis (195856) NA (NA%)	Chronic kidney disease stage 3 (443597) NA (NA%)	–	Complete trisomy 21 syndrome (439125) NA (NA%)
21	Cystitis (195588) 6 (3.2%)	Cyanosis (438555) NA (NA%)	Congenital stenosis of tricuspid valve (4263510) 11 (3.5%)	COVID-19 (37311061) NA (NA%)	–	Chronic atrial fibrillation (4141360) NA (NA%)	Chronic passive congestion of liver (200451) NA (NA%)	–	Complication associated with device (43021974) NA (NA%)
22	Dizziness and giddiness (433316) 6 (3.2%)	Diarrhea (196523) NA (NA%)	Respiratory distress syndrome in the newborn (258866) 11 (3.5%)	Cataract (375545) NA (NA%)	–	Congenital anomaly of pulmonary artery (435646) NA (NA%)	Colitis, enteritis and gastroenteritis presumed infectious (195453) NA (NA%)	–	Complication of surgical procedure (434547) NA (NA%)
23	Low back pain (194133)	Disorder of fetus and/or	Urinary tract infectious	Chest pain (77670)	–	Congenital atresia of pulmonary	Combined disorders of mitral,	–	Congenital anomaly of pulmonary

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	57/111

	BIGAN Conditions								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
	6 (3.2%)	newborn (441406) NA (NA%)	disease (81902) 11 (3.5%)	NA (NA%)		artery (4031766) NA (NA%)	aortic and tricuspid valves (4108235) NA (NA%)		artery (435646) NA (NA%)
24	Nutritional deficiency disorder (435227) 6 (3.2%)	Disorder of integument (4028387) NA (NA%)	Neonatal jaundice (435656) 10 (3.2%)	Cholelithiasis AND cholecystitis without obstruction (201070) NA (NA%)	–	Congenital heart disease (312723) NA (NA%)	Complete trisomy 21 syndrome (439125) NA (NA%)	–	Congenital insufficiency of aortic valve (321107) NA (NA%)
25	Open wound (444187) 6 (3.2%)	Disorder of muscle (137275) NA (NA%)	Neonatal jaundice after preterm delivery (440847) 10 (3.2%)	Cholelithiasis without obstruction (444367) NA (NA%)	–	Congenital hypothyroidism without goiter (4130017) NA (NA%)	Concussion injury of brain (4001336) NA (NA%)	–	Congenital insufficiency of pulmonary valve (4035467) NA (NA%)
Top 25 concepts by cohort/window. Values are count (%); <5 is suppressed and is show as NA.									

as NA.

Table 20 Top 25 recorded clinical condition concepts by cohort and time window for CPRD GOLD. The table shows the most frequently recorded clinical concepts for the underlying disease, disease progression, and device received cohorts across three time windows: 365 to 31

	D5.I Results of prevalence and characterisation			
	WP5 – Medical Device		Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU	58/111

days before index, 30 to 1 days before index, and on the index date. Values are presented as count (%). Counts below 5 were suppressed and are shown as NA.

	CPRD GOLD (UK)								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
1	Acute upper respiratory infection (257011) 47 (24.7%)	Acute upper respiratory infection (257011) 20 (8.7%)	Tetralogy of Fallot (320835) 73 (23.6%)	Acute upper respiratory infection (257011) 7 (41.2%)	Abnormal breathing (4305080) NA (NA%)	Pulmonary artery stenosis (4317288) 12 (70.6%)	Acute upper respiratory infection (257011) 7 (29.2%)	Abnormal breathing (4305080) NA (NA%)	Pulmonary incompetence, non-rheumatic (4111416) 9 (37.5%)
2	Congenital heart disease (312723) 19 (10.0%)	Congenital heart disease (312723) 16 (6.9%)	Pulmonary artery stenosis (4317288) 71 (22.9%)	Abdominal pain (200219) NA (NA%)	Acquired hypothyroidism (138384) NA (NA%)	Abnormal body temperature (4047791) NA (NA%)	Abdominal pain (200219) NA (NA%)	Aortic valve regurgitation (315564) NA (NA%)	Essential hypertension (320128) 6 (25.0%)
3	Cough (254761) 17 (8.9%)	Finding related to pregnancy (444094) 5 (2.2%)	Atrial septal defect (4289309) 47 (15.2%)	Abnormal body temperature (4047791) NA (NA%)	Acute respiratory failure (319049) NA (NA%)	Accelerated atrioventricular conduction (4057008) NA (NA%)	Abnormal breathing (4305080) NA (NA%)	Aortic valve stenosis (4189343) NA (NA%)	Acquired absence of organ (42537748) NA (NA%)
4	Fever (437663) 17 (8.9%)	Abdominal pain (200219) NA (NA%)	Congenital stenosis of pulmonary valve (313005)	Abnormal breathing (4305080) NA (NA%)	Acute upper respiratory infection (257011)	Acquired hypothyroidism (138384) NA (NA%)	Achalasia of esophagus (318186)	Chest pain (77670) NA (NA%)	Acute kidney injury (197320) NA (NA%)

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 59/111

	CPRD GOLD (UK)								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
			42 (13.6%)		NA (NA%)		NA (NA%)		
5	Acute bronchitis (260139) 15 (7.9%)	Abnormal body temperature (4047791) NA (NA%)	Ventricular septal defect (434462) 29 (9.3%)	Acquired hypothyroidism (138384) NA (NA%)	Anxiety disorder (442077) NA (NA%)	Acute bronchiolitis (260125) NA (NA%)	Acne (141095) NA (NA%)	Clinical finding (441840) NA (NA%)	Anemia (439777) NA (NA%)
6	Colitis, enteritis and gastroenteritis presumed infectious (195453) 13 (6.8%)	Acquired hypothyroidism (138384) NA (NA%)	Congenital anomaly of pulmonary artery (435646) 27 (8.7%)	Acute bronchiolitis (260125) NA (NA%)	Cardiomegaly (314658) NA (NA%)	Acute bronchitis (260139) NA (NA%)	Acquired absence of organ (42537748) NA (NA%)	Cough (254761) NA (NA%)	Aortic valve regurgitation (315564) NA (NA%)
7	Disorder of teeth AND/OR supporting structures (201603) 13 (6.8%)	Acute bronchitis (260139) NA (NA%)	Congenital anomaly of tricuspid valve (4184499) 26 (8.4%)	Acute bronchitis (260139) NA (NA%)	Congenital stenosis of pulmonary valve (313005) NA (NA%)	Acute bronchospasm (46273539) NA (NA%)	Acquired diverticulum of esophagus (31884) NA (NA%)	Dysphagia (31317) NA (NA%)	Aortic valve stenosis (4189343) NA (NA%)
8	Viral disease (440029) 13 (6.8%)	Acute cerebrovascular insufficiency	Essential hypertension (320128) 24 (7.7%)	Acute bronchitis caused by rhinovirus (4112521)	Dementia (4182210) NA (NA%)	Acute respiratory syncytial virus	Acute kidney injury (197320)	Essential hypertension (320128)	Aortic valve stenosis with insufficiency

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 60/111

	CPRD GOLD (UK)								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
		y (4164092) NA (NA%)		NA (NA%)		bronchitis (4110484) NA (NA%)	NA (NA%)	NA (NA%)	y (4111099) NA (NA%)
9	Chest pain (77670) 11 (5.8%)	Acute pharyngitis (25297) NA (NA%)	Congenital heart disease (312723) 22 (7.1%)	Acute laryngotracheitis (31597) NA (NA%)	Disorder of penis (196158) NA (NA%)	Acute tonsillitis (24660) NA (NA%)	Allergic rhinitis (257007) NA (NA%)	Heart failure (316139) NA (NA%)	Atherosclerosis of coronary artery without angina pectoris (764123) NA (NA%)
10	Vomiting (441408) 11 (5.8%)	Apnea (321689) NA (NA%)	Low birth weight infant (4171115) 18 (5.8%)	Acute respiratory syncytial virus bronchitis (4110484) NA (NA%)	Fever (437663) NA (NA%)	Acute upper respiratory infection (257011) NA (NA%)	Anxiety state (4113821) NA (NA%)	Type 2 diabetes mellitus (201826) NA (NA%)	Atrial fibrillation (313217) NA (NA%)
11	Conjunctival hyperemia (377283) 9 (4.7%)	Atopic dermatitis (133834) NA (NA%)	Ebstein's anomaly (4069182) 16 (5.2%)	Acute tracheitis (437903) NA (NA%)	Heart failure (316139) NA (NA%)	Alcoholic liver damage (201612) NA (NA%)	Aortic valve regurgitation (315564) NA (NA%)	–	Atrial flutter (314665) NA (NA%)
12	Diarrhea (196523) 9 (4.7%)	Atrial fibrillation (313217)	Disorder of fetus and/or newborn (441406)	Anorexia nervosa (436675)	Hyperlipidemia (432867)	Anemia (439777) NA (NA%)	Benign prostatic hyperplasia	–	Autoimmune thyroiditis (4281109)

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 61/111

	CPRD GOLD (UK)								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
		NA (NA%)	15 (4.8%)	NA (NA%)	NA (NA%)		^a (198803) NA (NA%)		NA (NA%)
13	Disorder of eye (375252) 9 (4.7%)	Backache (134736) NA (NA%)	Heart failure (316139) 15 (4.8%)	Anxiety state (4113821) NA (NA%)	Hypertensive heart disease without congestive heart failure (319034) NA (NA%)	Angina pectoris (321318) NA (NA%)	Bilateral stenosis of carotid arteries (37204002) NA (NA%)	–	Bacterial infection caused by Klebsiella pneumoniae (436339) NA (NA%)
14	Abdominal pain (200219) 8 (4.2%)	Blood in urine (437038) NA (NA%)	Discordant ventricular connection (432431) 13 (4.2%)	Apnea in newborn (318247) NA (NA%)	Respiratory failure (4256228) NA (NA%)	Anxiety disorder (442077) NA (NA%)	Bleeding from nose (4096682) NA (NA%)	–	Benign prostatic hyperplasia (198803) NA (NA%)
15	Constipation (75860) 8 (4.2%)	Chest pain (77670) NA (NA%)	Hyperlipidemia (432867) 13 (4.2%)	Atrial septal defect (4289309) NA (NA%)	Syncope and collapse (4206148) NA (NA%)	Aortocoronary bypass graft present (42537729) NA (NA%)	Bursitis (134453) NA (NA%)	–	Bleeding (437312) NA (NA%)
16	Pain of joint of	Colitis, enteritis and	Complete trisomy 21	Bacterial infectious	–	Atrial septal	Carcinoid syndrome (199771)	–	Carcinoid syndrome (199771)

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 62/111

	CPRD GOLD (UK)								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
	knee (604800) 8 (4.2%)	gastroenteritis presumed infectious (195453) NA (NA%)	syndrome (439125) 12 (3.9%)	disease (432545) NA (NA%)		defect (4289309) NA (NA%)	NA (NA%)		NA (NA%)
17	Abnormal body temperature (4047791) 7 (3.7%)	Common cold (260427) NA (NA%)	Congenital atresia of pulmonary artery (4031766) 12 (3.9%)	Bacterial meningitis (436091) NA (NA%)	–	Bronchitis (256451) NA (NA%)	Cardiac arrhythmia (44784217) NA (NA%)	–	Cardiovascular system complication of procedure (43022062) NA (NA%)
18	Acute tracheitis (437903) 7 (3.7%)	Congenital disease (440508) NA (NA%)	Neonatal hypoglycemia (23034) 12 (3.9%)	Benign intracranial hypertension (312902) NA (NA%)	–	Cardiomegaly (314658) NA (NA%)	Cellulitis and abscess of finger (79898) NA (NA%)	–	Chronic atrial fibrillation (4141360) NA (NA%)
19	Dysphagia (31317) 7 (3.7%)	Contusion (441737) NA (NA%)	Patent ductus arteriosus (315922) 12 (3.9%)	Benign neoplasm of skin (138102) NA (NA%)	–	Chest pain (77670) NA (NA%)	Chronic kidney disease due to hypertension (44782429)	–	Chronic viral hepatitis B without delta-agent (439674) NA (NA%)

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 63/111

	CPRD GOLD (UK)								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
							NA (NA%)		
20	Anxiety state (4113821) 6 (3.2%)	Cough (254761) NA (NA%)	Secondary pulmonary hypertension (4339214) 12 (3.9%)	Bronchitis (256451) NA (NA%)	–	Cholangitis (195856) NA (NA%)	Chronic kidney disease stage 3 (443597) NA (NA%)	–	Complete trisomy 21 syndrome (439125) NA (NA%)
21	Cystitis (195588) 6 (3.2%)	Cyanosis (438555) NA (NA%)	Congenital stenosis of tricuspid valve (4263510) 11 (3.5%)	COVID-19 (37311061) NA (NA%)	–	Chronic atrial fibrillation (4141360) NA (NA%)	Chronic passive congestion of liver (200451) NA (NA%)	–	Complication associated with device (43021974) NA (NA%)
22	Dizziness and giddiness (433316) 6 (3.2%)	Diarrhea (196523) NA (NA%)	Respiratory distress syndrome in the newborn (258866) 11 (3.5%)	Cataract (375545) NA (NA%)	–	Congenital anomaly of pulmonary artery (435646) NA (NA%)	Colitis, enteritis and gastroenteritis presumed infectious (195453) NA (NA%)	–	Complication of surgical procedure (434547) NA (NA%)
23	Low back pain (194133)	Disorder of fetus and/or	Urinary tract infectious	Chest pain (77670)	–	Congenital atresia of pulmonary	Combined disorders of mitral,	–	Congenital anomaly of pulmonary

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	64/111

	CPRD GOLD (UK)								
	Underlying disease			Disease progression			Device received		
	Window								
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
	6 (3.2%)	newborn (441406) NA (NA%)	disease (81902) 11 (3.5%)	NA (NA%)		artery (4031766) NA (NA%)	aortic and tricuspid valves (4108235) NA (NA%)		artery (435646) NA (NA%)
24	Nutritional deficiency disorder (435227) 6 (3.2%)	Disorder of integument (4028387) NA (NA%)	Neonatal jaundice (435656) 10 (3.2%)	Cholelithiasis AND cholecystitis without obstruction (201070) NA (NA%)	–	Congenital heart disease (312723) NA (NA%)	Complete trisomy 21 syndrome (439125) NA (NA%)	–	Congenital insufficiency of aortic valve (321107) NA (NA%)
25	Open wound (444187) 6 (3.2%)	Disorder of muscle (137275) NA (NA%)	Neonatal jaundice after preterm delivery (440847) 10 (3.2%)	Cholelithiasis without obstruction (444367) NA (NA%)	–	Congenital hypothyroidism without goiter (4130017) NA (NA%)	Concussion injury of brain (4001336) NA (NA%)	–	Congenital insufficiency of pulmonary valve (4035467) NA (NA%)
Top 25 concepts by cohort/window. Values are count (%); <5 is suppressed.									

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	65/111

Table 21 Top 25 recorded medications concepts by cohort and time window for BIGAN. The table shows the most frequently recorded clinical concepts for the underlying disease, disease progression, and device received cohorts across three time windows: 365 to 31 days before index, 30 to 1 days before index, and on the index date. Values are presented as count (%). Counts below 5 were suppressed and are shown as NA

	BIGAN Medications								
	Underlying disease			Disease progression			Device received		
	Window								
Top	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
1	influenza virus vaccine, unspecified formulation (40213158) 56 (29.5%)	acetaminophen (1125315) 9 (3.9%)	acetaminophen (1125315) NA (NA%)	influenza virus vaccine, unspecified formulation (40213158) 8 (47.1%)	COVID-19 vaccine (35894915) NA (NA%)	albuterol (1154343) NA (NA%)	COVID-19 vaccine (35894915) 9 (37.5%)	acetaminophen (1125315) NA (NA%)	acetaminophen (1125315) NA (NA%)
2	COVID-19 vaccine (35894915) 29 (15.3%)	aspirin (1112807) 5 (2.2%)	–	pneumococcal conjugate vaccine, 13 valent (40213198) 5 (29.4%)	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate (Meningococcal Protein Conjugate), and Hepatitis B (Recombinant)	amoxicillin 50 MG/ML Oral Suspension (1713370) NA (NA%)	influenza virus vaccine, unspecified formulation (40213158) 7 (29.2%)	acetylcysteine (1139042) NA (NA%)	ferrous sulfate (1396131) NA (NA%)

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 66/111

	BIGAN Medications								
	Underlying disease			Disease progression			Device received		
	Window								
T op	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
					Vaccine. (40213284) NA (NA%)				
3	acetaminophen (1125315) 23 (12.1%)	COVID-19 vaccine (35894915) NA (NA%)	–	0.4 ML enoxaparin sodium 100 MG/ML Prefilled Syringe (40160973) NA (NA%)	acetaminophen (1125315) NA (NA%)	ibuprofen 20 MG/ML Oral Suspension (19019050) NA (NA%)	acetaminophen (1125315) 5 (20.8%)	azithromycin 500 MG Oral Tablet (1734134) NA (NA%)	folic acid 5 MG Oral Tablet (1387453) NA (NA%)
4	acetaminophen 100 MG/ML Oral Solution (1126750) 23 (12.1%)	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate (Meningococcal Protein Conjugate), and Hepatitis B (Recombinant) Vaccine. (40213284)	–	24 HR isosorbide mononitrate 60 MG Extended Release Oral Tablet (1383869) NA (NA%)	acetaminophen 100 MG/ML Oral Solution (1126750) NA (NA%)	prednisolone (1550557) NA (NA%)	12 HR timolol 5 MG/ML Ophthalmic Solution (793238) NA (NA%)	cloperastine (35201862) NA (NA%)	–

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 67/111

	BIGAN Medications								
	Underlying disease			Disease progression			Device received		
	Window								
T op	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
		NA (NA%)							
5	pneumococcal conjugate vaccine, 13 valent (40213198) 20 (10.5%)	acetaminophen 100 MG/ML Oral Solution (1126750) NA (NA%)	–	Bilastine (44012547) NA (NA%)	furosemide 40 MG Oral Tablet (957136) NA (NA%)	–	Bilastine (44012547) NA (NA%)	domperidone 10 MG Oral Tablet (19037834) NA (NA%)	–
6	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate (Meningococcal Protein Conjugate), and Hepatitis B (Recombinant) Vaccine. (40213284) 19 (10.0%)	acetaminophen 500 MG Oral Tablet (19020053) NA (NA%)	–	COVID-19 vaccine (35894915) NA (NA%)	ibuprofen (1177480) NA (NA%)	–	Human Papillomavirus 9-valent vaccine (40213322) NA (NA%)	folic acid 5 MG Oral Tablet (1387453) NA (NA%)	–
7	amoxicillin (1713332) 15 (7.9%)	acetaminophen 650 MG Oral Tablet (1125393)	–	Diphtheria and Tetanus Toxoids and	influenza virus vaccine, unspecified	–	acetaminophen 500 MG Oral Tablet	mupirocin (951511) NA (NA%)	–

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 68/111

	BIGAN Medications								
	Underlying disease			Disease progression			Device received		
	Window								
T op	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
		NA (NA%)		Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate (Meningococcal Protein Conjugate), and Hepatitis B (Recombinant) Vaccine. (40213284)	formulation (40213158)		(19020053)	NA (NA%)	
8	meningococcal C conjugate vaccine (40213176)	amoxicillin (1713332)	–	acetaminophen (1125315)	levothyroxine sodium 0.025 MG Oral Tablet (40175174)	–	allopurinol 100 MG Oral Tablet (1167323)	pyrilamine (1159811)	–
	15 (7.9%)	NA (NA%)		NA (NA%)	NA (NA%)		NA (NA%)	NA (NA%)	

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 69/111

	BIGAN Medications								
	Underlying disease			Disease progression			Device received		
	Window								
T op	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
9	methylprednisolone (1506270) 15 (7.9%)	amoxicillin 875 MG / clavulanate 125 MG Oral Tablet (19115197) NA (NA%)	–	acetaminophen 100 MG/ML Oral Solution (1126750) NA (NA%)	levothyroxine sodium 0.05 MG Oral Tablet (40175210) NA (NA%)	–	allopurinol 300 MG Oral Tablet (19018787) NA (NA%)	–	–
10	amoxicillin 50 MG/ML Oral Suspension (1713370) 14 (7.4%)	azithromycin 500 MG Oral Tablet (1734134) NA (NA%)	–	albuterol (1154343) NA (NA%)	meningococcal C conjugate vaccine (40213176) NA (NA%)	–	amoxicillin (1713332) NA (NA%)	–	–
11	codeine (1201620) 14 (7.4%)	bisoprolol fumarate 2.5 MG Oral Tablet (40166188) NA (NA%)	–	amlodipine 5 MG Oral Tablet (1332419) NA (NA%)	pneumococcal conjugate vaccine, 13 valent (40213198) NA (NA%)	–	azithromycin 500 MG Oral Tablet (1734134) NA (NA%)	–	–
12	meningococcal group B vaccine (45775636)	calcifediol (19035569) NA (NA%)	–	amoxicillin (1713332)	prednisolone (1550557)	–	betahistine 16 MG Oral Tablet	–	–

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 70/111

	BIGAN Medications								
	Underlying disease			Disease progression			Device received		
	Window								
T op	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
	14 (7.4%)			NA (NA%)	NA (NA%)		(19020127) NA (NA%)		
13	cholecalciferol (19095164) 13 (6.8%)	cholecalciferol (19095164) NA (NA%)	–	amoxicillin 50 MG/ML Oral Suspension (1713370) NA (NA%)	–	–	betamethasone 3 MG/ML / betamethasone acetate 3 MG/ML Injectable Suspension (19121383) NA (NA%)	–	–
14	albuterol (1154343) 12 (6.3%)	cloperastine (35201862) NA (NA%)	–	amoxicillin 875 MG / clavulanate 125 MG Oral Tablet (19115197) NA (NA%)	–	–	bromazepam (19030353) NA (NA%)	–	–
15	omeprazole 20 MG Delayed Release Oral	desloratadine 0.5 MG/ML Oral Solution (19123210)	–	aspirin (1112807)	–	–	budesonide 0.1 MG/ACT UAT Nasal	–	–

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 71/111

	BIGAN Medications								
	Underlying disease			Disease progression			Device received		
	Window								
T op	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
	Capsule (19019418) 12 (6.3%)	NA (NA%)		NA (NA%)			Spray (939301) NA (NA%)		
16	mupirocin 0.02 MG/MG Topical Ointment (19008723) 11 (5.8%)	dexketoprofen 25 MG Oral Tablet (19101779) NA (NA%)	–	azithromycin 40 MG/ML Oral Suspension (1734108) NA (NA%)	–	–	budesonide 0.16 MG/ACT UAT / formoterol fumarate 0.0045 MG/ACT UAT Metered Dose Inhaler (42902748) NA (NA%)	–	–
17	prednisolone (1550557) 11 (5.8%)	ferrous glycine sulfate (19000753) NA (NA%)	–	bisoprolol fumarate 2.5 MG Oral Tablet (40166188) NA (NA%)	–	–	calcifediol (19035569) NA (NA%)	–	–
18	ibuprofen (1177480)	furosemide 40 MG Oral	–	bromazepam	–	–	candesartan cilexetil 16 MG Oral	–	–

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 72/111

	BIGAN Medications								
	Underlying disease			Disease progression			Device received		
	Window								
T op	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
	10 (5.3%)	Tablet (957136) NA (NA%)		(19030353) NA (NA%)			Tablet (1351583) NA (NA%)		
19	tobramycin 3 MG/ML Ophthalmic Solution (902741) 10 (5.3%)	ibuprofen (1177480) NA (NA%)	–	budesonide (939259) NA (NA%)	–	–	capsaicin 0.75 MG/ML Topical Cream (939902) NA (NA%)	–	–
20	acetaminophen 650 MG Oral Tablet (1125393) 9 (4.7%)	ibuprofen 400 MG Oral Tablet (19019072) NA (NA%)	–	cefditoren (1747005) NA (NA%)	–	–	carbocysteine (19041843) NA (NA%)	–	–
21	ibuprofen 600 MG Oral Tablet (19019073) 9 (4.7%)	influenza virus vaccine, unspecified formulation (40213158) NA (NA%)	–	cefixime 20 MG/ML Oral Suspension (19074876) NA (NA%)	–	–	cefuroxime 500 MG Oral Tablet (19075002) NA (NA%)	–	–
22	measles, mumps and	lorazepam 1 MG Oral	–	cefuroxime 50	–	–	cloperastine	–	–

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 73/111

	BIGAN Medications								
	Underlying disease			Disease progression			Device received		
	Window								
T op	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
	rubella virus vaccine (40213183) 9 (4.7%)	Tablet (19019113) NA (NA%)		MG/ML Oral Suspension (1778225) NA (NA%)			(35201862) NA (NA%)		
23	rotavirus vaccine, unspecified formulation (40213219) 9 (4.7%)	meningococcal group B vaccine (45775636) NA (NA%)	–	cholecalciferol (19095164) NA (NA%)	–	–	codeine (1201620) NA (NA%)	–	–
24	bisoprolol fumarate 2.5 MG Oral Tablet (40166188) 8 (4.2%)	methylprednisolone (1506270) NA (NA%)	–	clonazepam 0.5 MG Oral Tablet (798875) NA (NA%)	–	–	desloratadine 5 MG Disintegrating Oral Tablet (19102483) NA (NA%)	–	–
25	cloperastine (35201862) 8 (4.2%)	nystatin 100000 UNT/ML Oral Suspension (19079119) NA (NA%)	–	cloperastine (35201862) NA (NA%)	–	–	dexamethasone 1 MG/ML / tobramycin 3 MG/ML Ophthalmic Suspension	–	–

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 74/111

	BIGAN Medications								
	Underlying disease			Disease progression			Device received		
	Window								
T op	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	0 to 0
							(19076134) NA (NA%)		
Top 25 concepts by cohort/window. Values are count (%); <5 is suppressed.									

Table 22 Top 25 recorded medications concepts by cohort and time window for CPRD Gold (UK). The table shows the most frequently recorded clinical concepts for the underlying disease, disease progression, and device received cohorts across three time windows: 365 to 31 days before index, 30 to 1 days before index, and on the index date. Values are presented as count (%). Counts below 5 were suppressed and are shown as NA.

	CPRD GOLD (UK) Medications							
	Underlying disease			Disease progression		Device received		
	Window							
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	-365 to -31	-30 to -1	0 to 0
I	diphtheria toxoid vaccine, inactivated (529303) 374 (21.9%)	Haemophilus influenzae type b vaccine, conjugate unspecified formulation (40213316) 221 (10.6%)	Haemophilus influenzae type b vaccine, conjugate unspecified formulation (40213316)	influenza virus vaccine, unspecified formulation (40213158) 54 (23.9%)	Haemophilus influenzae type b vaccine, conjugate unspecified formulation (40213316) 12 (5.3%)	influenza virus vaccine, unspecified formulation (40213158) 75 (40.1%)	aspirin 75 MG Disintegrating Oral Tablet (19004044) 9 (4.8%)	Paraffin 0.728 MG/MG Topical Gel [Oilatum] by Glaxosmith kline (36814221) NA (NA%)

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 75/111

	CPRD GOLD (UK) Medications							
	Underlying disease			Disease progression		Device received		
	Window							
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	-365 to -31	-30 to -1	0 to 0
			31 (1.4%)					
2	poliovirus vaccine, unspecified formulation (40213203) 374 (21.9%)	diphtheria toxoid vaccine, inactivated (529303) 218 (10.5%)	diphtheria toxoid vaccine, inactivated (529303) 31 (1.4%)	diphtheria toxoid vaccine, inactivated (529303) 40 (17.7%)	diphtheria toxoid vaccine, inactivated (529303) 12 (5.3%)	amoxicillin 500 MG Oral Capsule (19073187) 21 (11.2%)	simvastatin 20 MG Oral Tablet (1539411) 6 (3.2%)	amiodarone hydrochloride 200 MG Oral Tablet (1309992) NA (NA%)
3	tetanus toxoid vaccine, inactivated (529411) 374 (21.9%)	poliovirus vaccine, unspecified formulation (40213203) 218 (10.5%)	pertussis vaccine (19033193) 31 (1.4%)	poliovirus vaccine, unspecified formulation (40213203) 40 (17.7%)	pertussis vaccine (19033193) 12 (5.3%)	furosemide 40 MG Oral Tablet (957136) 18 (9.6%)	bisoprolol fumarate 2.5 MG Oral Tablet (40166188) 5 (2.6%)	aspirin 75 MG Delayed Release Oral Tablet (19003088) NA (NA%)
4	Haemophilus influenzae type b vaccine, conjugate unspecified formulation (40213316) 364 (21.3%)	tetanus toxoid vaccine, inactivated (529411) 218 (10.5%)	poliovirus vaccine, unspecified formulation (40213203) 31 (1.4%)	tetanus toxoid vaccine, inactivated (529411) 40 (17.7%)	poliovirus vaccine, unspecified formulation (40213203) 12 (5.3%)	aspirin 75 MG Disintegrating Oral Tablet (19004044) 17 (9.1%)	bisoprolol fumarate 5 MG Oral Tablet (40162878) 5 (2.6%)	bisoprolol fumarate 2.5 MG Oral Tablet (40166188) NA (NA%)
5	pertussis vaccine (19033193) 360 (21.0%)	pertussis vaccine (19033193) 215 (10.3%)	tetanus toxoid vaccine, inactivated (529411) 31 (1.4%)	pertussis vaccine (19033193) 38 (16.8%)	tetanus toxoid vaccine, inactivated (529411) 12 (5.3%)	bisoprolol fumarate 2.5 MG Oral Tablet (40166188) 5 (2.6%)	citalopram 20 MG Oral Tablet (19023636) 5 (2.6%)	codeine phosphate 30 MG Oral Tablet (40223099) NA (NA%)

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	76/111

	CPRD GOLD (UK) Medications							
	Underlying disease			Disease progression		Device received		
	Window							
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	-365 to -31	-30 to -1	0 to 0
			d (529411) 31 (1.4%)		12 (5.3%)	14 (7.5%)		NA (NA%)
6	influenza virus vaccine, unspecified formulation (40213158) 336 (19.6%)	Pneumococcal Conjugate, unspecified formulation (40213200) 130 (6.2%)	Pneumococcal Conjugate, unspecified formulation (40213200) 18 (0.8%)	Haemophilus influenzae type b vaccine, conjugate unspecified formulation (40213316) 32 (14.2%)	influenza virus vaccine, unspecified formulation (40213158) 10 (4.4%)	acetaminophen 500 MG Oral Tablet (19020053) 13 (7.0%)	influenza virus vaccine, unspecified formulation (40213158) 5 (2.6%)	propranolol hydrochloride 40 MG Oral Tablet (40163342) NA (NA%)
7	Pneumococcal Conjugate, unspecified formulation (40213200) 297 (17.4%)	meningococcal C conjugate vaccine (40213176) 94 (4.5%)	aspirin 75 MG Disintegrating Oral Tablet (19004044) 17 (0.8%)	Pneumococcal Conjugate, unspecified formulation (40213200) 29 (12.8%)	Pneumococcal Conjugate, unspecified formulation (40213200) 9 (4.0%)	amoxicillin 250 MG Oral Capsule (19073183) 11 (5.9%)	ramipril 2.5 MG Oral Capsule (1334459) 5 (2.6%)	sennoside B 7.5 MG Oral Tablet (19106119) NA (NA%)
8	meningococcal C conjugate vaccine (40213176) 228 (13.3%)	aspirin 75 MG Disintegrating Oral Tablet (19004044) 73 (3.5%)	rotavirus vaccine, unspecified formulation (40213219) 13 (0.6%)	amoxicillin 25 MG/ML Oral Suspension (1713520) 23 (10.2%)	meningococcal C conjugate vaccine (40213176) 6 (2.6%)	furosemide 20 MG Oral Tablet (19077546) 10 (5.3%)	0.3 ML lanreotide 300 MG/ML Injectable Solution (35785141) NA (NA%)	warfarin sodium 1 MG Oral Tablet (40163510) NA (NA%)

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	77/111

	CPRD GOLD (UK) Medications							
	Underlying disease			Disease progression		Device received		
	Window							
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	-365 to -31	-30 to -1	0 to 0
9	amoxicillin 25 MG/ML Oral Suspension (1713520) 136 (8.0%)	rotavirus vaccine, unspecified formulation (40213219) 68 (3.3%)	–	meningoccal C conjugate vaccine (40213176) 21 (9.3%)	aspirin 75 MG Disintegrating Oral Tablet (19004044) 5 (2.2%)	omeprazole 20 MG Delayed Release Oral Capsule (19019418) 10 (5.3%)	0.6 ML Enoxaparin 100 MG/ML Injectable Solution [Clexane] by Sanofi (43648309) NA (NA%)	warfarin sodium 3 MG Oral Tablet (40163540) NA (NA%)
10	rotavirus vaccine, unspecified formulation (40213219) 122 (7.1%)	alginate acid 225 MG / Magnesium Alginate 87.5 MG Powder for Oral Solution [Gaviscon Infant] by Forum Products (40744098) 50 (2.4%)	–	amoxicillin 50 MG/ML Oral Suspension (1713370) 19 (8.4%)	Albuterol 0.095 MG/ACTU AT Metered Dose Inhaler (589320) NA (NA%)	penicillin V potassium 250 MG Oral Tablet (19133873) 10 (5.3%)	1 ML Octreotide 0.1 MG/ML Injectable Solution (43608342) NA (NA%)	–
11	amoxicillin 500 MG Oral Capsule (19073187) 113 (6.6%)	amoxicillin 25 MG/ML Oral Suspension (1713520) 42 (2.0%)	–	Albuterol 0.095 MG/ACTU AT Metered Dose Inhaler (589320) 18 (8.0%)	Albuterol 0.1 MG/ACTU AT Inhalant Powder [Ventolin Evohaler] by Glaxosmithkline (40723359)	Albuterol 0.1 MG/ACTU AT Inhalant Powder [Ventolin Evohaler] by Glaxosmithkline (40723359)	1 ML medroxyprogesterone 150 MG/ML Injectable Suspension [Depo-Provera] by Pfizer (36054497) NA (NA%)	–

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 78/111

	CPRD GOLD (UK) Medications							
	Underlying disease			Disease progression		Device received		
	Window							
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	-365 to -31	-30 to -1	0 to 0
					NA (NA%)	9 (4.8%)		
12	aspirin 75 MG Disintegrating Oral Tablet (19004044) 113 (6.6%)	furosemide 40 MG Oral Tablet (957136) 40 (1.9%)	–	influenza nasal, unspecified formulation (40213327) 18 (8.0%)	Albuterol 0.1 MG/ACTU AT [Ventolin Evohaler] (36811920) NA (NA%)	citalopram 20 MG Oral Tablet (19023636) 8 (4.3%)	10 ML Insulin Lispro 100 UNT/ML Injectable Solution [Humalog] by Eli Lilly (36279643) NA (NA%)	–
13	measles virus vaccine (40213170) 109 (6.4%)	meningococcal B, unspecified formulation (40213175) 40 (1.9%)	–	chloramphenicol 5 MG/ML Ophthalmic Solution (19075115) 15 (6.6%)	Beclomethasone 0.1 MG/ACTU AT Inhalant Powder [Clenil Modulite] by Chiesi (40723026) NA (NA%)	diphtheria toxoid vaccine, inactivated (529303) 8 (4.3%)	1000 ML bicarbonate ion 0.017 MMOL/ML / POLYETHYLENE GLYCOL 3350 105 MG/ML / Potassium 0.0054 MMOL/ML / Sodium 0.065 MMOL/ML Oral Powder [Laxido] by Galen (40707728) NA (NA%)	–
14	rubella virus vaccine (40213223) 109 (6.4%)	hepatitis B vaccine, pediatric or pediatric/adol	–	measles virus vaccine (40213170)	Clotrimazole 0.01 MG/MG Topical	floxacin 500 MG Oral Capsule (19054961)	1000 ML bicarbonate ion 0.017 MMOL/ML / POLYETHYLE	–

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	79/111

	CPRD GOLD (UK) Medications							
	Underlying disease			Disease progression		Device received		
	Window							
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	-365 to -31	-30 to -1	0 to 0
		escent dosage (40213304) 37 (1.8%)		14 (6.2%)	Cream (44025887) NA (NA%)	8 (4.3%)	NE GLYCOL 3350 105 MG/ML / Potassium 0.0054 MMOL/ML / Sodium 0.065 MMOL/ML Oral Powder [Movicol] by Norgine (40707716) NA (NA%)	
15	meningococcal B, unspecified formulation (40213175) 108 (6.3%)	influenza virus vaccine, unspecified formulation (40213158) 37 (1.8%)	–	mumps virus vaccine (40213185) 14 (6.2%)	Influenza, split virus, trivalent, injectable, contains preservative (40213153) NA (NA%)	lansoprazole 30 MG Delayed Release Oral Capsule (929889) 8 (4.3%)	24 HR nicotine 0.875 MG/HR Transdermal System (19019307) NA (NA%)	–
16	mumps virus vaccine (40213185) 108 (6.3%)	warfarin sodium 1 MG Oral Tablet (40163510) 32 (1.5%)	–	rubella virus vaccine (40213223) 14 (6.2%)	Melatonin 2 MG Extended Release Oral Tablet [Circadin] by Flynn (21055709) NA (NA%)	poliovirus vaccine, unspecified formulation (40213203) 8 (4.3%)	3 ML Insulin Glargine 100 UNT/ML Injectable Solution (35779361) NA (NA%)	–
17	Albuterol 0.095	omeprazole 20 MG	–	rotavirus vaccine,	Paraffin 0.1 MG/MG /	prednisolone 5 MG	3 ML Insulin Glargine 100	–

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	80/111

	CPRD GOLD (UK) Medications							
	Underlying disease			Disease progression		Device received		
	Window							
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	-365 to -31	-30 to -1	0 to 0
	MG/ACTUAT Metered Dose Inhaler (589320) 84 (4.9%)	Delayed Release Oral Capsule (19019418) 31 (1.5%)		unspecified formulation (40213219) 13 (5.8%)	Petrolatum 0.132 MG/MG Topical Cream [Cetraben] by Thornton & Ross (40746551) NA (NA%)	Oral Tablet (1550560) 8 (4.3%)	UNT/ML Prefilled Syringe [Lantus] by Sanofi (21126853) NA (NA%)	
18	chloramphenicol 5 MG/ML Ophthalmic Solution (19075115) 73 (4.3%)	acetaminophen 500 MG Oral Tablet (19020053) 30 (1.4%)	–	aspirin 75 MG Disintegrating Oral Tablet (19004044) 12 (5.3%)	acetaminophen 24 MG/ML Oral Suspension (19063317) NA (NA%)	spironolactone 25 MG Oral Tablet (19079658) 8 (4.3%)	3 ML Insulin, Aspart, Human 100 UNT/ML Injectable Solution [Novorapid] by Novo Nordisk (40717353) NA (NA%)	–
19	warfarin sodium 1 MG Oral Tablet (40163510) 73 (4.3%)	ascorbic acid 66.7 MG/ML / ergocalciferol 667 UNT/ML / niacinamide 1.33 MG/ML / pyridoxine 1.33 MG/ML / riboflavin 1.33 MG/ML / thiamine 1.7 MG/ML / vitamin E 2220 UNT/ML Oral	–	Hydrocortisone 0.01 MG/MG Topical Cream (44097247) 11 (4.9%)	acetaminophen 50 MG/ML Oral Suspension (19063316) NA (NA%)	tetanus toxoid vaccine, inactivated (529411) 8 (4.3%)	500 MG Testosterone 0.02 MG/MG Topical Gel [Tostran] by Kyowa Kirin (40709655) NA (NA%)	–

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 81/111

	CPRD GOLD (UK) Medications							
	Underlying disease			Disease progression		Device received		
	Window							
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	-365 to -31	-30 to -1	0 to 0
		Solution [Abidec] by Omega (36061271) 29 (1.4%)						
20	omeprazole 20 MG Delayed Release Oral Capsule (19019418) 72 (4.2%)	simvastatin 40 MG Oral Tablet (1539407) 27 (1.3%)	–	meningococcal B, unspecified formulation (40213175) 11 (4.9%)	acetaminophen 500 MG Oral Tablet (19020053) NA (NA%)	warfarin sodium 1 MG Oral Tablet (40163510) 8 (4.3%)	Albuterol 0.1 MG/ACTUAT Inhalant Powder [Salamol Easi-Breathe] by TEVA (40723365) NA (NA%)	–
21	acetaminophen 500 MG Oral Tablet (19020053) 71 (4.2%)	bisoprolol fumarate 2.5 MG Oral Tablet (40166188) 25 (1.2%)	–	Beclomethasone 0.1 MG/ACTUAT Inhalant Powder [Clenil Modulite] by Chiesi (40723026) 9 (4.0%)	alginate acid 225 MG / Magnesium Alginate 87.5 MG Powder for Oral Solution [Gaviscon Infant] by Forum Products (40744098) NA (NA%)	amoxicillin 500 MG / clavulanate 125 MG Oral Tablet (1713694) 7 (3.7%)	Albuterol 0.1 MG/ACTUAT Inhalant Powder [Ventolin Evohaler] by Glaxosmithkline (40723359) NA (NA%)	–
22	acetaminophen 24 MG/ML Oral	warfarin sodium 3 MG Oral Tablet (40163540)	–	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2	amitriptyline hydrochloride 10 MG	bisoprolol fumarate 5 MG Oral	Benzalkonium 1 MG/ML / Chlorhexidine 1 MG/ML / isopropyl	–

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 82/111

	CPRD GOLD (UK) Medications							
	Underlying disease			Disease progression		Device received		
	Window							
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	-365 to -31	-30 to -1	0 to 0
	Suspension (19063317) 63 (3.7%)	25 (1.2%)		0.1 MG/ML Injectable Suspension (37003436) 9 (4.0%)	Oral Tablet (40162672) NA (NA%)	Tablet (40162878) 7 (3.7%)	myristate 25 MG/ML / Mineral Oil 25 MG/ML Topical Solution [Dermol] by Dermal (40750997) NA (NA%)	
23	hepatitis B vaccine, pediatric or pediatric/adolescent dosage (40213304) 63 (3.7%)	lactulose 670 MG/ML Oral Solution (19003454) 24 (1.1%)	–	acetaminophen 500 MG Oral Tablet (19020053) 9 (4.0%)	amoxicillin 25 MG/ML Oral Suspension (1713520) NA (NA%)	erythromycin stearate 250 MG Delayed Release Oral Tablet (1747454) 7 (3.7%)	Benzalkonium 5 MG/ML / isopropyl myristate 250 MG/ML / Mineral Oil 250 MG/ML Topical Solution [Dermol] by Dermal (40750987) NA (NA%)	–
24	lactulose 670 MG/ML Oral Solution (19003454) 63 (3.7%)	ranitidine 15 MG/ML Oral Solution (19126405) 23 (1.1%)	–	Albuterol 0.1 MG/ACTUAT Inhalant Powder [Ventolin Evohaler] by Glaxosmithkline (40723359) 8 (3.5%)	amoxicillin 500 MG Oral Capsule (19073187) NA (NA%)	simvastatin 40 MG Oral Tablet (1539407) 7 (3.7%)	Betamethasone 0.001 MG/MG / Fusidate 0.02 MG/MG Topical Cream [Fucibet] by Leo (36409523) NA (NA%)	–

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 83/111

	CPRD GOLD (UK) Medications							
	Underlying disease			Disease progression		Device received		
	Window							
To p	-365 to -31	-30 to -1	0 to 0	-365 to -31	-30 to -1	-365 to -31	-30 to -1	0 to 0
25	furosemide 40 MG Oral Tablet (957136) 58 (3.4%)	ramipril 2.5 MG Oral Capsule (1334459) 22 (1.1%)	–	Novel influenza-H1N1-09, injectable (40213186) 8 (3.5%)	ascorbic acid 66.7 MG/ML / ergocalciferol 667 UNT/ML / niacinamide 1.33 MG/ML / pyridoxine 1.33 MG/ML / riboflavin 1.33 MG/ML / thiamine 1.7 MG/ML / vitamin E 2220 UNT/ML Oral Solution [Abidec] by Omega (36061271) NA (NA%)	Influenza, split virus, trivalent, injectable, contains preservative (40213153) 6 (3.2%)	Budesonide 0.2 MG/ACTUAT / formoterol 0.006 MG/ACTUAT Inhalant Powder [Duoresp] by TEVA (35748401) NA (NA%)	–
Top 25 concepts by cohort/window. Values are count (%); <5 is suppressed.								

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	84/111

6 Discussion

6.1 Key results

This study estimated the incidence of underlying disease, disease progression, and pulmonary valve intervention cohorts using two European healthcare databases and extrapolated the results to the European population. The disease progression cohort was considered the most relevant population for orphan device designation because it represents individuals with evidence of progression to a clinically relevant state potentially requiring pulmonary valve intervention.

Across both databases, the estimated annual number of individuals in the disease progression cohort remained substantially below the European orphan medical device designation threshold of 12,000 affected individuals per year. Based on age-sex standardised incidence rates, the estimated annual number of device-eligible individuals in the European population ranged from 185 to 1,424 in BIGAN and from 688 to 1,691 in CPRD GOLD.

The annual incidence of disease progression remained low throughout the study period. In CPRD GOLD, incidence rates ranged from 0.12 to 0.32 per 100,000 person-years between 2006 and 2024. Similar estimates were obtained using incidence proportions. Extrapolated European population estimates derived from incidence proportions ranged from 145 to 1,047 individuals in BIGAN and from 551 to 1,352 individuals in CPRD GOLD.

Sensitivity analyses using alternative disease progression definitions produced similar results. Requiring evidence of underlying disease or prior intervention at any time before the progression event, at least 30 days before the event, or at least 365 days before the event resulted in comparable incidence estimates with overlapping confidence intervals. Estimates based on these alternative definitions remained well below the orphan device designation threshold.

External validation using data from the German National Quality Assurance Registry demonstrated good agreement with the study findings [6]. European population estimates derived from registry-reported pulmonary valve replacement activity overlapped with those obtained from both CPRD GOLD and BIGAN.

Clinical characterisation showed that the disease progression and device received cohorts were mainly for conditions directly related to RVOT and pulmonary valve dysfunction, including Tetralogy of Fallot, pulmonary artery stenosis, pulmonary valve stenosis and pulmonary valve regurgitation, supporting the cohort definitions used to identify the target population.

6.2 Comparison with Previous Literature

Published literature identified in this report mainly described congenital heart disease burden, specific congenital cardiac populations, or pulmonary valve replacement procedure activity. These studies provide clinical and epidemiological context, but most were not designed to estimate the annual device-eligible population for orphan device designation.

Population-level studies of congenital heart disease report estimates for congenital heart disease overall [13,18]. These estimates are broader than the target population in this study, which focused on individuals with underlying congenital or structural cardiac conditions who subsequently showed evidence of disease progression relevant to pulmonary valve intervention.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	85/111

Several studies described pulmonary valve replacement or transcatheter pulmonary valve implantation activity in specific registries or clinical cohorts [7–9]. These studies reported procedure counts or treated patient cohorts rather than annual population-based incidence of device eligibility. Therefore, they were not directly comparable with the disease progression cohort used as the primary population for orphan device estimation in this study.

The most directly comparable external benchmark was the German National Quality Assurance Registry, which reported pulmonary valve replacement activity with information on registry coverage [6]. After adjustment for reported registry coverage and extrapolation to the European population, the German benchmark overlapped with the European population estimates derived from CPRD GOLD and BIGAN.

Overall, previous literature supported of the study findings but did not provide a direct equivalent estimate of the annual TPVR-eligible population in Europe. The estimates from this study therefore provide additional evidence by applying a reproducible cohort definition to routinely collected healthcare data and extrapolating the disease progression cohort to the European population.

6.3 Limitations of the research methods

This study has several limitations. The analysis was based on routinely collected healthcare data, and cohort identification depended on the completeness and accuracy of coded diagnoses, procedures, and medication records. Misclassification may have occurred if relevant congenital heart disease, pulmonary valve disease, prior intervention, or device procedure records were missing, recorded outside the data source, or captured using codes not included in the phenotype definitions. This is possible either through a lack of recording or through a lack of linkage (e.g., to hospital data) that may better capture procedures or rare diagnoses, the impact of which would be to underestimate prevalence/incidence.

The disease progression cohort was used as a proxy for the device-eligible population. Although this cohort was designed to capture individuals with evidence of progression to clinically relevant pulmonary valve or right ventricular outflow tract dysfunction, routinely collected healthcare data do not contain all clinical information required to confirm device eligibility, such as imaging findings, haemodynamic measurements, anatomical suitability, symptom severity, or multidisciplinary clinical decision-making.

The cohorts were defined sequentially; limitations in earlier cohorts may carry forward into later cohorts. For example, incomplete capture of the underlying disease cohort could affect identification of the disease progression cohort, and incomplete capture of disease progression could affect interpretation of the device-received cohort. This cumulative dependency is important when interpreting the clinical accuracy of the final estimates. For a methodological study, it highlights the need for careful database selection, assessment of data quality, and sensitivity analyses using alternative cohort definitions.

The device received cohort may underestimate the total number of pulmonary valve interventions if procedures were incompletely captured in primary care records, hospital records, or source data. This limitation is particularly relevant for specialised congenital cardiac interventions, which may be delivered in tertiary centres and not fully reflected in all data sources.

Only two data sources were included in the current analysis. This limited the ability to formally explore between-data-source heterogeneity or to test methods for meta-analysis. It also limited the ability to compare alternative approaches for extrapolating estimates to the European population. For example, with more contributing data sources, it may be

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	86/111

possible to estimate incidence within each country, extrapolate data-source-level estimates to the corresponding national population, and then combine country-level estimates to produce an EU-level estimate. This approach could be compared with the direct extrapolation of age-sex standardised rates to the European population used in this study.

The available study periods differed between data sources. CPRD GOLD contributed data from 2006 onwards, whereas BIGAN contributed data from 2017 onwards. Estimates from BIGAN were affected by small counts in the disease progression and device-received cohorts, resulting in the suppression of some results and wider confidence intervals. To avoid including the 2020 and 2021 COVID-19 pandemic years in the main extrapolation, the primary European population estimates were based on the most recent three full years of data availability. Five-year pooled estimates were included in the Annex and showed similar results.

Although the study defined a broad underlying disease population, it did not present pre-specified incidence and prevalence estimates for specific congenital heart disease subtypes within that population, such as Tetralogy of Fallot. Tetralogy of Fallot is an important subtype because it is commonly represented among patients who later require pulmonary valve replacement. In contrast to the broader device-eligible population, published literature for specific underlying conditions, such as Tetralogy of Fallot, may be more available. Future analyses could therefore estimate incidence and prevalence for Tetralogy of Fallot as a subgroup within the broader underlying disease population and compare these estimates with published literature. This would help assess whether the data source captures a clinically expected underlying population before using it to estimate the smaller disease progression or device-eligible population.

The extrapolation to the European population required applying age-sex standardised rates from available data sources to external European population data. These estimates depend on assumptions about the representativeness of the contributing data sources and the availability and quality of population statistics. Differences in healthcare systems, coding practices, referral pathways, and access to specialist congenital cardiac services across European countries may affect generalisability.

Finally, this study represents initial evidence using currently available data sources. The analysis is expected to continue within the wider GREG programme, during which additional suitable data sources may be identified and included. Future analyses using more data sources, including different types of routinely collected healthcare data such as hospital data, insurance claims and health registries, could provide further evidence, allow comparison of alternative evidence synthesis and extrapolation methods, and improve the precision and generalisability of European population estimates.

6.4 Interpretation

A key requirement for orphan medical device designation in Europe is demonstrating that the device is intended for $\leq 12,000$ people in the EU per year. This study demonstrates a reproducible approach for estimating the size of device-eligible populations for rare conditions using routinely collected healthcare data. Importantly, the disease progression cohort enabled estimation of the potential device-eligible population without relying on observed device procedure data. This is particularly relevant for new or pre-market devices, where procedure records for the device may not yet exist in real-world data. This is particularly relevant for new or pre-market devices, where procedure records for the device may not yet exist in real-world data. However, incidence-based estimates represent new eligible individuals each year and may differ from prevalence-based estimates of the total number of people living with the condition during a year. In clinical scenarios where eligibility spans multiple years, incidence-based extrapolation alone may underestimate the total eligible population. Therefore, incidence and prevalence measures should be considered together when selecting the most appropriate measure for estimating the orphan device population.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	87/111

Rather than relying solely on published procedure counts or disease registry estimates, the proposed approach defines sequential cohorts representing the underlying disease population, disease progression population, and device received population, and then uses incidence estimation, age-sex standardisation, and population extrapolation to estimate the annual number of potentially eligible individuals.

For orphan device designation, the disease progression cohort may be particularly useful because it aims to approximate the population that has moved beyond the underlying condition and developed clinical features relevant to device eligibility. In the TPVR use case, this cohort produced estimates that were consistently below the European orphan medical device designation threshold of 12,000 individuals per year. However, the main value of the approach is that it provides a transparent framework for generating and testing these estimates across data sources and cohort definitions.

The use case also illustrates how sensitivity analyses can be incorporated into orphan device population estimation. Alternative disease progression definitions, incidence proportions, longer pooled time windows, and external registry benchmarks can be used to assess whether conclusions are sensitive to phenotype definitions, epidemiological measures, or data source selection.

More broadly, this study suggests that routinely collected healthcare data may support evidence generation for orphan medical device population estimation where direct population estimates are unavailable. However, the approach has been applied to two databases and one clinical use case, and the results may be influenced by database size, coding completeness, procedure capture, and cohort-definition choices. Further testing across additional clinical scenarios, data sources, and device areas is needed before wider recommendations can be made. With further validation, the use of common data models, standardised cohort definitions, and reproducible analytic code may help generate more transparent and comparable evidence on rare device-eligible populations.

6.5 Key methodology learning for future guidance

This study generated several methodological lessons that can inform future guidance on using real-world data for orphan medical device designation.

First, published literature may be insufficient to estimate the annual device-eligible population, even for devices that have been available for many years. In this case study, TPVI/PPVI has been used in clinical practice since the mid-2000s, but the available literature mainly describes the overall burden of congenital heart disease, specific clinical cohorts, registry procedure counts, or treated populations. These sources provide important clinical context but often lack the denominator information needed to estimate the annual population-based incidence of device eligibility. Future guidance should therefore recommend reviewing external evidence, while recognising that published literature alone may not be sufficient to assess the orphan designation threshold.

Also, when the device-eligible population cannot be directly observed, a disease-progression cohort can serve as a practical proxy for potential eligibility. For TPVI/PPVI, the broad underlying congenital heart disease population is too inclusive, while the device-received population may be too narrow because it only captures people who have already undergone pulmonary valve intervention. The disease progression cohort sits between these two groups. It identifies patients with underlying disease who later develop pulmonary valve or right ventricular outflow tract dysfunction that may warrant intervention. This approach is useful when the aim is to estimate the number of people who may be eligible for a device, rather than only the number who have already received it. Future guidance should therefore encourage

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	88/111

investigators to define and justify an intermediate disease progression or clinically eligible population where direct eligibility is not observable in routine data.

The population at risk, start of follow-up, end of follow-up, available study period, and handling of historical events should be clearly specified. In this study, estimates from BIGAN were less stable and had wider uncertainty, partly because BIGAN only contributed data from 2017 to 2025, and event counts were small. This suggests that future guidance should recommend reporting the available calendar years of data for each data source, the period used for analysis, the number of observed events, and the uncertainty around estimates. Where available data history is short, or event counts are very small, longer pooled time windows or additional data sources may be needed to produce more stable estimates.

Also, the size of the data sources is an important consideration in estimating the orphan device population. In this use case, annual estimates from BIGAN for the disease progression and device-received cohorts were often suppressed because event counts were fewer than five. This highlights the need to prioritise large population-based data sources, or to pool estimates across multiple years, when estimating populations for rare conditions.

Furthermore, sensitivity analyses should be considered essential rather than optional. In this study, alternative definitions of disease progression, different prior history requirements, incidence rates, and incidence proportions were used to assess the robustness of the conclusions. Future guidance should recommend testing whether estimates are sensitive to phenotype definitions, prior history requirements, and the choice between incidence rate and incidence proportion. In this case study, incidence proportions produced lower extrapolated estimates than incidence rates. For orphan device designation, incidence rates may be preferable as the primary measure because they use person-time and can better account for differences in follow-up time across individuals and data sources. Incidence proportions can still be useful as a sensitivity analysis because they provide a simpler, complementary estimate over a defined period.

Lastly, extrapolation to the European population requires transparent reporting of assumptions. In this study, data-source-level incidence estimates were age- and sex-standardised and extrapolated to the European population. This provided a practical way to estimate whether the annual population was likely to fall below the orphan medical device designation threshold. However, extrapolation depends on assumptions about how representative the contributing data sources are of the wider European population. These assumptions should be clearly stated. External evidence, such as registry data, published literature, or national statistics, can be used to contextualise the extrapolated estimates.

6.6 Generalisability

The findings from this study should be interpreted in the context of the contributing data sources and the cohort definitions used. Although CPRD GOLD and BIGAN represent different European healthcare settings, they may not fully capture differences in disease coding, referral pathways, clinical practice, and access to specialist congenital cardiac services across all European countries. However, the methodological framework developed in this study is designed to be transferable to other databases and healthcare systems using comparable routinely collected healthcare data. As additional data sources become available, the approach can be applied more broadly to improve the representativeness and precision of estimates of the orphan device population.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	89/111

7 Conclusion

In conclusion, this use case suggests that future guidance should set out a clear sequence of steps for estimating orphan device populations using real-world data. These steps should include: first, reviewing whether existing literature or registry evidence provides a usable estimate of the annual device-eligible population; second, defining the target population in terms of clinically meaningful disease stages rather than relying only on procedure records; third, reporting the available calendar years of data, observed event counts, denominators, and uncertainty for each data source; fourth, using sensitivity analyses to test alternative cohort definitions and incidence measures; and fifth, clearly stating the assumptions used when extrapolating estimates to the European population. This would make the evidence behind orphan device population estimates more transparent, reproducible, and comparable across future device submissions.

8 References

1. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: Executive Summary. *Journal of the American College of Cardiology*. 2019;73:1494–563. <https://doi.org/10.1016/j.jacc.2018.08.1028>
2. Saluja S, Contractor H, Wiltshire R, Mannan F, Hussain N, Abidin N, et al. An evaluation of patient outcomes following transcatheter pulmonary valve implantation: a meta-analysis. *European Heart Journal*. 2021;42:ehab724.2228. <https://doi.org/10.1093/eurheartj/ehab724.2228>
3. Shibbani K, Das T, Amin E. Past, Present, and Future of Transcatheter Pulmonary Valves. *American College of Cardiology* [Internet]. American College of Cardiology; 2025 [cited 2026 June 2]; <https://www.acc.org/latest-in-cardiology/articles/2025/05/05/17/03/http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2farticles%2f2025%2f05%2f05%2f17%2f03%2fpast-present-and-future-of-transcatheter-pulmonary-valves>. Accessed 2 June 2026
4. Kahn MG, Callahan TJ, Barnard J, Bauck AE, Brown J, Davidson BN, et al. A Harmonized Data Quality Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data. *eGEMs*. 2016;4:18. <https://doi.org/10.13063/2327-9214.1244>
5. Zimmerman MS, Smith AGC, Sable CA, Echko MM, Wilner LB, Olsen HE, et al. Global, regional, and national burden of congenital heart disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Child & Adolescent Health*. 2020;4:185–200. [https://doi.org/10.1016/S2352-4642\(19\)30402-X](https://doi.org/10.1016/S2352-4642(19)30402-X)
6. Hofbeck M, Arenz C, Bauer UMM, Horke A, Kerst G, Meyer R, et al. German Registry for Cardiac Operations and Interventions in Congenital Heart Disease: Annual Report 2022. *Thorac Cardiovasc Surg*. 2024;72:e16–29. <https://doi.org/10.1055/a-2350-7374>
7. Ballesteros Tejerizo F, Coserría Sánchez F, Jurado-Román A, Cruz-González I, Álvarez-Fuente M, Amat-Santos IJ, et al. Spanish cardiac catheterization in congenital heart diseases registry. Third official report from the ACI-SEC and the GTH-SECPC (2022). *RECICE*. 2024;13961. <https://doi.org/10.24875/RECICE.M24000456>
8. Hascoët S, Bentham JR, Giugno L, Betrián-Blasco P, Kempny A, Houeijeh A, et al. Outcomes of transcatheter pulmonary SAPIEN 3 valve implantation: an international registry. *European Heart Journal*. 2024;45:198–210. <https://doi.org/10.1093/eurheartj/ehad663>

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	90/111

9. Fraisse A, Aldebert P, Malekzadeh-Milani S, Thambo J-B, Piéchaud J-F, Aucoururier P, et al. Melody® transcatheter pulmonary valve implantation: Results from a French registry. *Archives of Cardiovascular Diseases*. 2014;107:607–14. <https://doi.org/10.1016/j.acvd.2014.10.001>
10. Belahnech Y, Martí-Aguasca G, Dos-Subirà L, Betrian-Blasco P, García Del Blanco B, Calvo-Barceló M, et al. Mid-term outcomes of percutaneous pulmonary valve replacement with Edwards-Sapien bioprosthesis in native right ventricular outflow tract. *Sci Rep*. 2025;15:3977. <https://doi.org/10.1038/s41598-024-82336-4>
11. Bokma JP, Geva T, Sleeper LA, Lee JH, Lu M, Sompolinsky T, et al. Improved Outcomes After Pulmonary Valve Replacement in Repaired Tetralogy of Fallot. *Journal of the American College of Cardiology*. 2023;81:2075–85. <https://doi.org/10.1016/j.jacc.2023.02.052>
12. Oosterhof T. Long-term follow-up of homograft function after pulmonary valve replacement in patients with tetralogy of Fallot. *European Heart Journal*. 2005;27:1478–84. <https://doi.org/10.1093/eurheartj/ehl033>
13. Dorobantu DM, Sharabiani MTA, Taliotis D, Parry AJ, Tulloh RMR, Bentham JR, et al. Age over 35 years is associated with increased mortality after pulmonary valve replacement in repaired tetralogy of Fallot: results from the UK National Congenital Heart Disease Audit database. *European Journal of Cardio-Thoracic Surgery*. 2020;58:825–31. <https://doi.org/10.1093/ejcts/ezaa069>
14. Gröning M, Smerup MH, Munk K, Andersen H, Nielsen DG, Nissen H, et al. Pulmonary Valve Replacement in Tetralogy of Fallot. *JACC: Cardiovascular Interventions*. 2024;17:217–27. <https://doi.org/10.1016/j.jcin.2023.10.070>
15. Pilati M, D’Aiello FA, Chessa M, Santoro G, Donti A, Mariucci E, et al. Percutaneous implantation of self-expanding pulmonary valves: results from real-life experience of the Venus-P valve Registry of the Italian Society of Pediatric Cardiology (SICPED). *International Journal of Cardiology Congenital Heart Disease*. 2025;21:100609. <https://doi.org/10.1016/j.ijcchd.2025.100609>
16. Protopapas E, Padalino M, Tobota Z, Ebels T, Speggorin S, Horer J, et al. The European Congenital Heart Surgeons Association congenital cardiac database: A 25-year summary of congenital heart surgery outcomes. *European Journal of Cardio-Thoracic Surgery*. 2025;67:ezaf119. <https://doi.org/10.1093/ejcts/ezaf119>
17. Huasheng L, Sun F, Ma W, Chen Y. Sex differences in global burden of Congenital Heart Anomalies in children under five from 1990 to 2021. Tran NN, editor. *PLoS One*. 2026;21:e0348351. <https://doi.org/10.1371/journal.pone.0348351>
18. Zimmerman MS, Smith AGC, Sable CA, Echko MM, Wilner LB, Olsen HE, et al. Global, regional, and national burden of congenital heart disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Child & Adolescent Health*. 2020;4:185–200. [https://doi.org/10.1016/S2352-4642\(19\)30402-X](https://doi.org/10.1016/S2352-4642(19)30402-X)
- 19 Medical Device Coordination Group (MDCG) 2024-10 Clinical evaluation of orphan medical devices June 2024.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	91/111

Annexes

Annex I: Results for Annual Period Prevalence

In CPRD GOLD, annual period prevalence of the underlying disease increased from 15.2 per 100,000 persons in 2006 to 27.1 per 100,000 persons in 2024 (**Figure 7**). In BIGAN, prevalence estimates were available from 2017 onwards and increased from 2.5 per 100,000 persons in 2017 to 15.1 per 100,000 persons in 2025.

In CPRD GOLD, annual period prevalence of disease progression ranged from 1.1 to 3.2 per 100,000 persons between 2006 and 2024 (**Figure 8**). The corresponding prevalence of device receipt ranged from 0.6 to 2.5 per 100,000 persons. In 2024, the prevalence of disease progression was 3.2 per 100,000 persons and the prevalence of device receipt was 2.4 per 100,000 persons. The count for BIGAN were all less than 5 hence is suppressed and cannot be reported.

For disease progression, three sensitivity analyses were conducted using different requirements for prior evidence of the underlying disease or initial intervention before the progression event. In the least restrictive definition, individuals were required to have any prior record of the underlying disease or initial intervention before the progression event. In the second definition, this prior record was required to occur at least 30 days before the progression event. In the most restrictive definition, the prior record was required to occur at least 365 days before the progression event.

Annual period prevalence estimates varied according to the definition applied (**Figure 9**). Across the study period, prevalence estimates based on any prior record ranged from 1.1 to 3.2 per 100,000 persons. Estimates requiring a record at least 30 days before the progression event ranged from 1.0 to 2.9 per 100,000 persons. Estimates requiring a record at least 365 days before the progression event ranged from 0.6 to 2.2 per 100,000 persons. In 2024, the prevalence estimates were 3.2, 2.9, and 2.2 per 100,000 persons for the any prior, ≥ 30 days prior, and ≥ 365 days prior definitions, respectively.

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	92/111

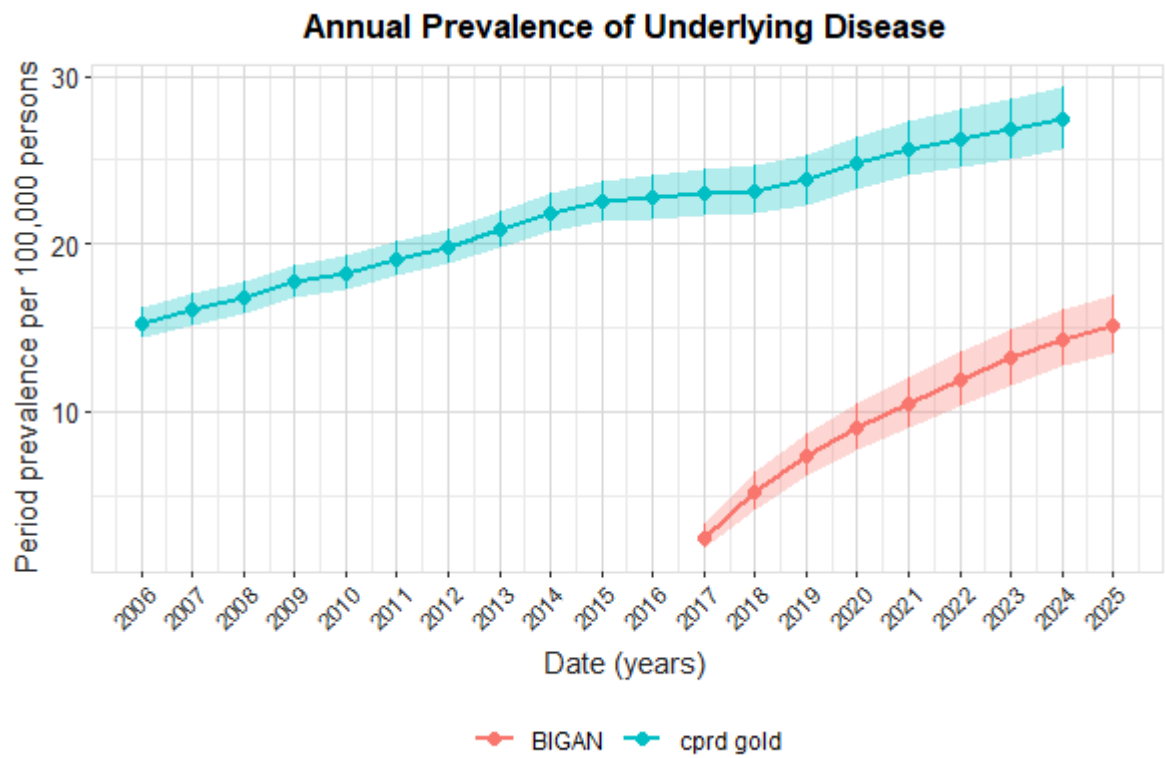


Figure 7 Annual prevalence of the underlying disease in CPRD GOLD (UK) and BIGAN, 2006-2025. Period prevalence estimates are presented per 100,000 persons. Points represent annual prevalence estimates and shaded areas indicate 95% confidence intervals. CPRD GOLD co

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	93/111

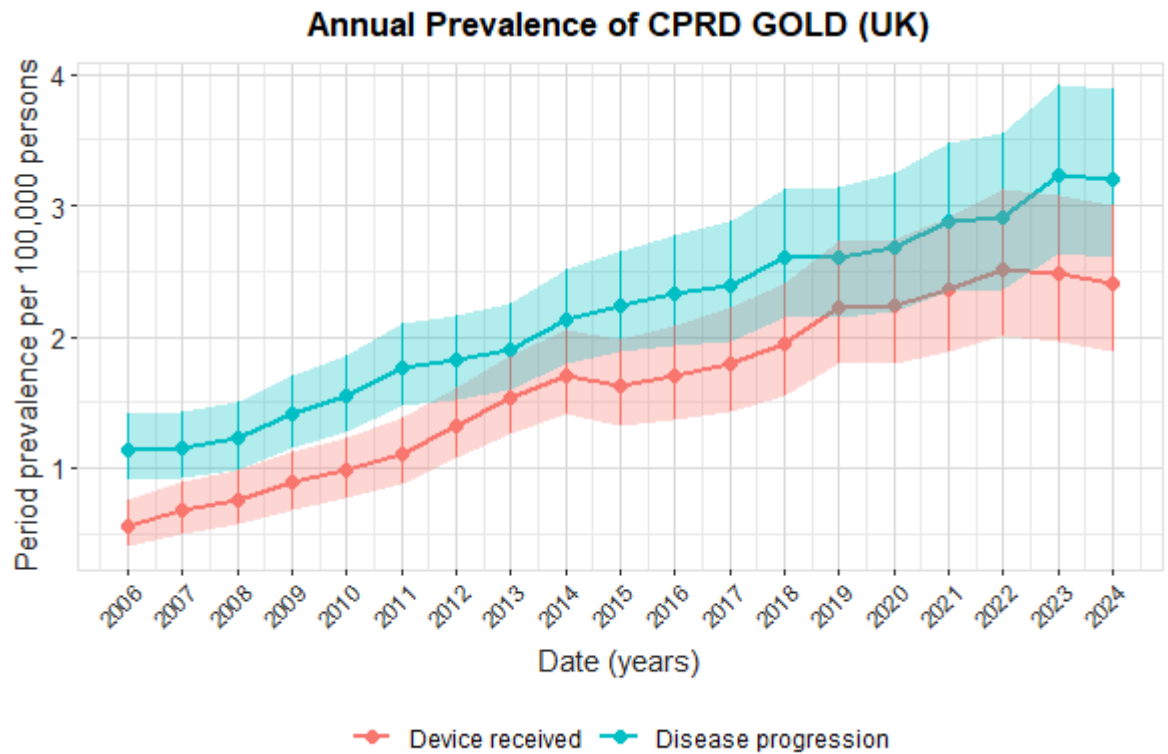


Figure 8 Annual prevalence of disease progression and device receipt in CPRD GOLD (UK), 2006–2024. Period prevalence estimates are presented per 100,000 persons. Disease progression refers to individuals with the underlying disease who progressed to the intervention-eligible population, while device receipt refers to individuals who received the device of interest. Points represent annual prevalence estimates and shaded areas indicate 95% confidence intervals.

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	94/111

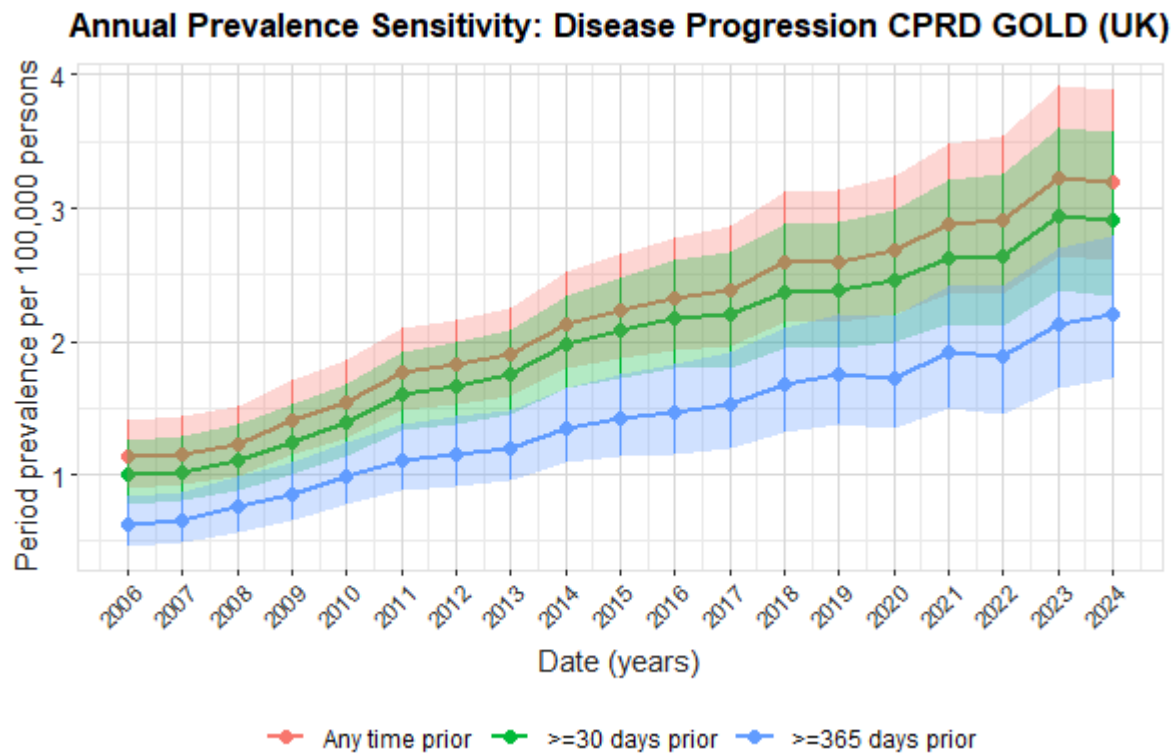


Figure 9 Annual prevalence sensitivity analysis for disease progression definitions in CPRD GOLD (UK), 2006–2024. Period prevalence estimates per 100,000 persons are presented using three alternative disease progression definitions based on the minimum time between the underlying disease diagnosis (or initial intervention) and the progression event: any prior record, ≥ 30 days prior, and ≥ 365 days prior. Points represent annual prevalence estimates and shaded areas represent 95% confidence intervals.

Annex II: Incidence Proportion

This section shows the annual incidence proportion results for the study.

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	95/111

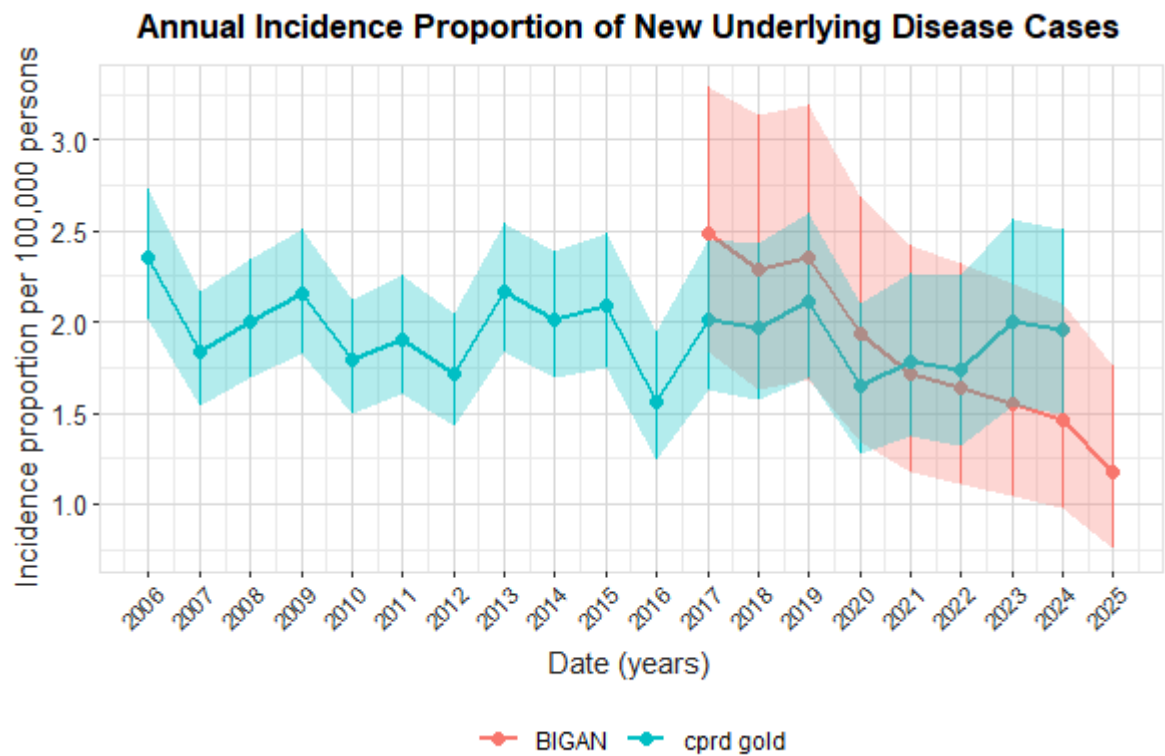


Figure 10 Annual incidence proportion of new underlying disease cases in BIGAN and CPRD GOLD, 2006–2025. Incidence rates are presented per 100,000 person-years. Points represent annual incidence estimates and shaded areas indicate 95% confidence intervals. CPRD GOLD contributed data from 2006 onwards, while BIGAN contributed data from 2017 onwards.

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	96/111

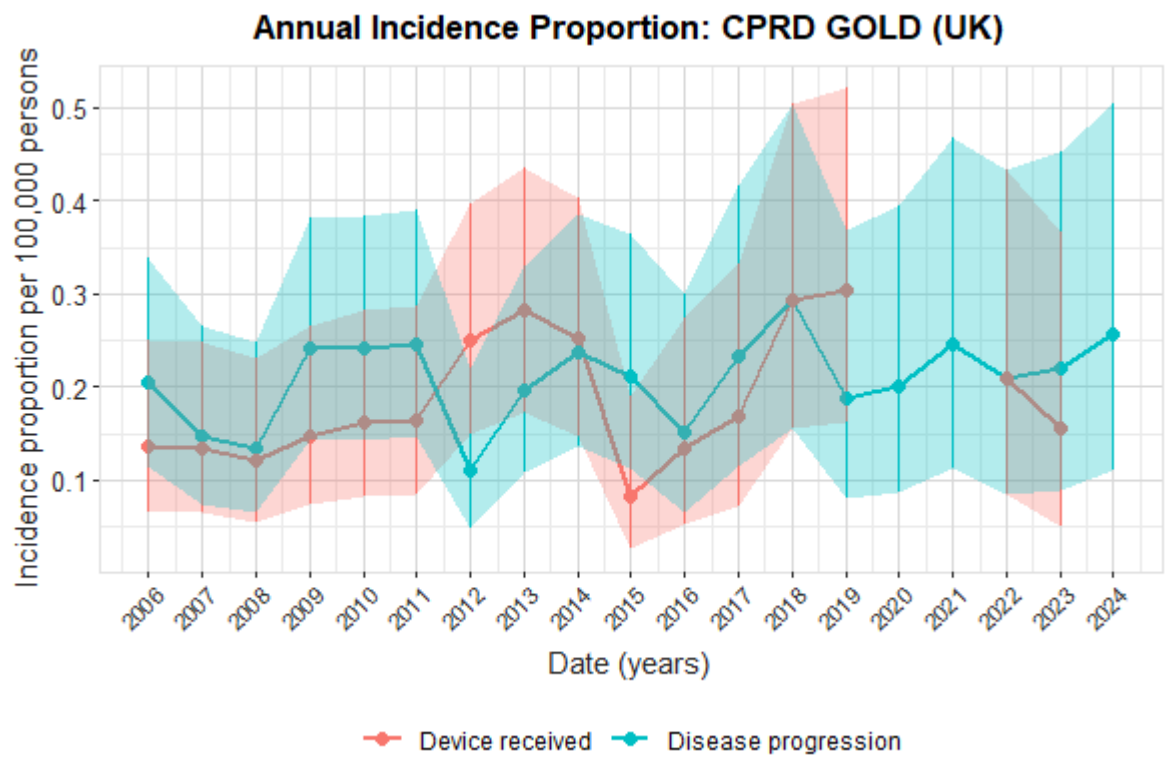


Figure 11 Annual incidence proportion of disease progression and device receipt in CPRD GOLD (UK), 2006–2024. Annual incidence rates are presented per 100,000 person-years. Disease progression refers to patients with the underlying disease who progressed to require intervention, while device received refers to patients receiving the device of interest. Points represent annual incidence estimates and shaded areas indicate 95% confidence intervals.

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	97/111

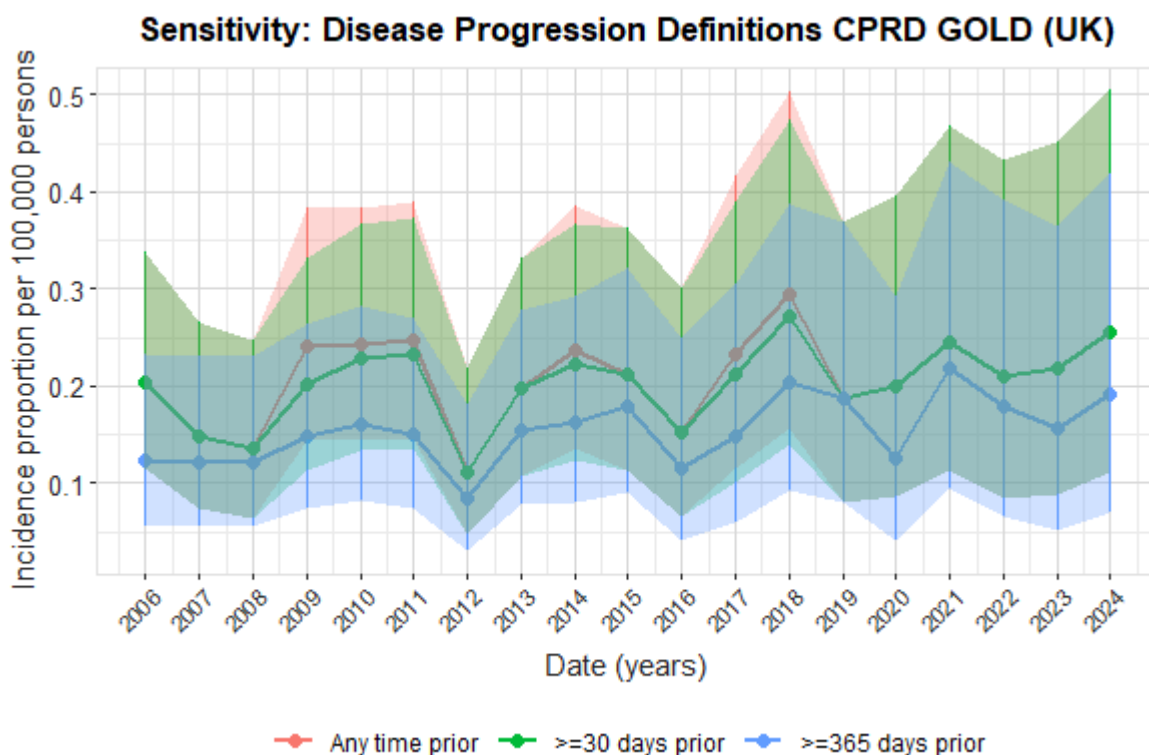


Figure 12 Annual incidence proportion sensitivity analysis for disease progression definitions in CPRD GOLD (UK), 2006–2024. Annual incidence rates per 100,000 person-years are shown using three alternative disease progression definitions based on the minimum time between the underlying disease diagnosis (or initial intervention) and the disease progression event: any prior record, ≥ 30 days prior, and ≥ 365 days prior.

Annex III: Extrapolation results

The section presents supplementary extrapolations results for using 5 year pool rate and other definitions of disease progression cohort..

Table 23 Incidence rates and estimated annual numbers of individuals in the European population for the underlying disease, disease progression, and device received cohorts. Results are based on the most recent five years of available data from BIGAN and CPRD GOLD

Database name	Incidence last 5 years					
	BIGAN			CPRD Gold		
	Crude	Standardised	EU total, extrapolation	Crude	Standardised	EU total, extrapolation
Underlying Disease	1.53 (1.29-1.80)	2.30 (1.91-2.70)	8,589-12,151	1.99 (1.78-2.23)	2.22 (1.97-2.47)	8,877-11,112
Disease Progression	0.12 (0.06-0.21)	0.16 (0.06-0.26)	270-1,187	0.25 (0.18-0.34)	0.26 (0.18-0.34)	800-1,539

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU 98/111

Database name	Incidence last 5 years					
	BIGAN			CPRD Gold		
Rate	Crude	Standardise d	EU total, extrapolatio n	Crude	Standardise d	EU total, extrapolatio n
Device received	0.13 (0.06- 0.22)	0.14 (0.06- 0.22)	270-983	0.15 (0.09- 0.22)	0.15 (0.09- 0.21)	392-937

Crude and age-sex standardised incidence rates are presented per 100,000 person-years with 95% confidence intervals. Estimated annual numbers of individuals in the European population were obtained by applying age-sex standardised incidence rates to the European population. Ranges represent the corresponding 95% confidence intervals.

Table 24 Incidence proportion and estimated annual numbers of individuals in the European population for the underlying disease, disease progression, and device received cohorts.

Database name	Incidence proportion last 5 years					
	BIGAN			CPRD Gold		
Proportion	Crude	Standardise d	EU total, extrapolatio n	Crude	Standardise d	EU total, extrapolatio n
Underlying Disease	1.50 (1.27- 1.77)	1.49 (1.24- 1.74)	5,602-7,816	1.82 (1.62- 2.03)	1.60 (1.42- 1.78)	6,387-8,003
Disease Progression	0.11 (0.06- 0.20)	0.12 (0.04- 0.19)	202-848	0.23 (0.16- 0.31)	0.21 (0.14- 0.27)	634-1,221
Device received	0.12 (0.06- 0.22)	0.11 (0.05- 0.18)	222-807	0.13 (0.08- 0.20)	0.13 (0.08- 0.19)	349-835

Results are based on the most recent five years of available data from BIGAN and CPRD GOLD. Crude and age-sex standardised incidence rates are presented per 100,000 person-years with 95% confidence intervals. Estimated annual numbers of individuals in the European population were obtained by applying age-sex standardised incidence rates to the European population. Ranges represent the corresponding 95% confidence intervals.

Table 25 Disease progression incidence rate and extrapolated European population estimates using the same alternative disease progression definitions as the incidence sensitivity analysis.

Database name	Disease progression incidence last 3 years					
	BIGAN			CPRD Gold		
Rate	Crude	Standardise d	EU total, extrapolatio n	Crude	Standardise d	EU total, extrapolatio n
Any time prior	0.12 (0.05- 0.25)	0.18 (0.04- 0.32)	185-1,424	0.25 (0.16- 0.38)	0.26 (0.15- 0.38)	688-1,691
>=30 days prior	0.12 (0.05- 0.25)	0.18 (0.04- 0.32)	185-1,424	0.25 (0.16- 0.38)	0.26 (0.15- 0.38)	688-1,691
>=365 days prior	0.09 (0.03- 0.20)	0.11 (0.01- 0.21)	50-934	0.19 (0.11- 0.31)	0.19 (0.10- 0.29)	457-1,291

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device		Version: v3.0
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	99/111

Disease progression incidence last 3 years						
Database name	BIGAN			CPRD Gold		
Rate	Crude	Standardise d	EU total, extrapolatio n	Crude	Standardise d	EU total, extrapolatio n
Crude and age-sex standardised incidence proportions are reported per 100,000 persons with 95% confidence intervals. Disease progression was defined using the same three prior-history requirements as in the incidence sensitivity analysis: any prior record of the underlying disease or initial intervention before the progression event, a record at least 30 days before the progression event, and a record at least 365 days before the progression event. European population estimates were derived by extrapolating age-sex standardised incidence proportions to the European population. Ranges represent the lower and upper bounds of the 95% confidence intervals.						

Table 26 Disease progression incidence proportions and extrapolated European population estimates using the same alternative disease progression definitions as the incidence sensitivity analysis.

Disease progression incidence proportion last 3 years						
Database name	BIGAN			CPRD Gold		
Proportion	Crude	Standardise d	EU total, extrapolatio n	Crude	Standardise d	EU total, extrapolatio n
Any time prior	0.12 (0.05-0.24)	0.13 (0.03-0.23)	145-1,047	0.23 (0.14-0.35)	0.21 (0.12-0.30)	551-1,352
>=30 days prior	0.12 (0.05-0.24)	0.13 (0.03-0.23)	145-1,047	0.23 (0.14-0.35)	0.21 (0.12-0.30)	551-1,352
>=365 days prior	0.08 (0.03-0.20)	0.09 (0.01-0.17)	43-758	0.18 (0.10-0.28)	0.17 (0.09-0.25)	402-1,133
Crude and age-sex standardised incidence proportions are reported per 100,000 persons with 95% confidence intervals. Disease progression was defined using the same three prior-history requirements as in the incidence sensitivity analysis: any prior record of the underlying disease or initial intervention before the progression event, a record at least 30 days before the progression event, and a record at least 365 days before the progression event. European population estimates were derived by extrapolating age-sex standardised incidence proportions to the European population. Ranges represent the lower and upper bounds of the 95% confidence intervals.						

Annex IV: Codelist for the underlying disease, initial surgery, disease progression and device received phenotype

Table 27 Codelist for the underlying disease phenotype Congenital heart disease involving the right ventricular outflow tract/pulmonary valve pathway.

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
312728	Congenital tricuspid atresia and stenosis	Condition	SNOMED	standard
313005	Congenital stenosis of pulmonary valve	Condition	SNOMED	standard
313867	Double outlet right ventricle	Condition	SNOMED	standard
316226	Complete transposition of great vessels	Condition	SNOMED	standard
319921	Congenital pulmonary valve abnormality	Condition	SNOMED	standard
320206	Congenital atresia of pulmonary valve	Condition	SNOMED	standard
320835	Tetralogy of Fallot	Condition	SNOMED	standard

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	100/111

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
432431	Discordant ventriculoarterial connection	Condition	SNOMED	standard
435646	Congenital anomaly of pulmonary artery	Condition	SNOMED	standard
441385	Corrected transposition of great vessels	Condition	SNOMED	standard
441950	Common arterial trunk (truncus arteriosus)	Condition	SNOMED	standard
3654955	Double outlet right ventricle with subaortic ventricular septal defect without pulmonary stenosis	Condition	SNOMED	standard
3656077	Double outlet right ventricle with subaortic or doubly committed ventricular septal defect and pulmonary stenosis Fallot type	Condition	SNOMED	standard
3656079	Double outlet right ventricle with subaortic ventricular septal defect and pulmonary stenosis Fallot type	Condition	SNOMED	standard
3656081	Transposition of great arteries with concordant atrioventricular connections and ventricular septal defect	Condition	SNOMED	standard
3656083	Transposition of great arteries with concordant atrioventricular connections and ventricular septal defect and left ventricular outflow tract obstruction	Condition	SNOMED	standard
3656120	Common arterial trunk with pulmonary dominance	Condition	SNOMED	standard
3656123	Common arterial trunk with pulmonary dominance and aortic coarctation	Condition	SNOMED	standard
3656128	Tricuspid atresia with absent right atrioventricular connection	Condition	SNOMED	standard
4006983	Truncus arteriosus, Edwards' type IV	Condition	SNOMED	standard
4030427	Congenital coronary artery fistula to pulmonary artery	Condition	SNOMED	standard
4030676	Prune belly syndrome with pulmonic stenosis, mental retardation and deafness	Condition	SNOMED	standard
4031766	Congenital atresia of pulmonary artery	Condition	SNOMED	standard
4035467	Congenital insufficiency of pulmonary valve	Condition	SNOMED	standard
4061819	Aortopulmonary window	Condition	SNOMED	standard
4066746	Ebstein's anomaly with atrial septal defect	Condition	SNOMED	standard
4068833	Atresia of pulmonary artery with septal defect	Condition	SNOMED	standard
4069090	Incomplete great vessel transposition	Condition	SNOMED	standard
4069180	Supernumerary pulmonary valve cusps	Condition	SNOMED	standard
4069182	Ebstein's anomaly	Condition	SNOMED	standard
4069184	Infundibular pulmonic stenosis	Condition	SNOMED	standard
4070297	Pentalogy of Fallot	Condition	SNOMED	standard
4070795	Congenital fusion of pulmonic cusps	Condition	SNOMED	standard
4070821	Hypoplasia of pulmonary valve	Condition	SNOMED	standard
4070914	Congenital fusion of pulmonary valve segment	Condition	SNOMED	standard
4070916	Fallot's trilogy	Condition	SNOMED	standard
4097984	Coarctation of pulmonary artery	Condition	SNOMED	standard
4100005	Transposition of aorta	Condition	SNOMED	standard
4100121	Double outlet right ventricle with noncommitted ventricular septal defect	Condition	SNOMED	standard
4100143	Absent tricuspid leaflet	Condition	SNOMED	standard
4100877	Accessory tissue on tricuspid leaflet	Condition	SNOMED	standard
4100879	Fused tricuspid papillary muscle	Condition	SNOMED	standard
4101011	Double outlet right ventricle with doubly committed ventricular septal defect	Condition	SNOMED	standard
4101013	Solitary aortic trunk with pulmonary atresia	Condition	SNOMED	standard
4101035	Tricuspid annulus hypoplasia	Condition	SNOMED	standard
4101036	Overriding tricuspid valve	Condition	SNOMED	standard

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	101/111

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
4101160	Straddling tricuspid valve	Condition	SNOMED	standard
4101162	Double orifice of tricuspid valve	Condition	SNOMED	standard
4101164	Absent tricuspid papillary muscle	Condition	SNOMED	standard
4101618	Tetralogy of Fallot with pulmonary stenosis	Condition	SNOMED	standard
4101619	Tetralogy of Fallot with pulmonary atresia	Condition	SNOMED	standard
4101620	Ventricular septal defect in Fallot's tetralogy	Condition	SNOMED	standard
4101625	Right ventricular outflow tract obstruction	Condition	SNOMED	standard
4102836	Double outlet right ventricle with subaortic ventricular septal defect	Condition	SNOMED	standard
4102838	Solitary arterial trunk	Condition	SNOMED	standard
4102857	Dilatation of tricuspid annulus	Condition	SNOMED	standard
4102862	Parachute malformation of tricuspid valve	Condition	SNOMED	standard
4102863	Hypoplastic tricuspid papillary muscle	Condition	SNOMED	standard
4103131	Dextraposition of aorta in Fallot's tetralogy	Condition	SNOMED	standard
4103292	Congenital absence of left pulmonary artery	Condition	SNOMED	standard
4108587	Right ventricular fibromuscular infundibular stenosis	Condition	SNOMED	standard
4108723	Congenital abnormality of arterial valves	Condition	SNOMED	standard
4108725	Pulmonary valve cusp hypoplasia	Condition	SNOMED	standard
4108726	Pulmonary valve ring hypoplasia	Condition	SNOMED	standard
4108727	Absent pulmonary valve syndrome	Condition	SNOMED	standard
4108728	Quadricuspid pulmonary valve	Condition	SNOMED	standard
4108735	Pulmonary trunk atresia	Condition	SNOMED	standard
4108736	Pulmonary atresia with absent pulmonary artery	Condition	SNOMED	standard
4108737	Pulmonary trunk absent with confluent pulmonary arteries	Condition	SNOMED	standard
4108738	Pulmonary trunk absent with non-confluent pulmonary arteries	Condition	SNOMED	standard
4108740	Anomalous origin of right pulmonary artery from ascending aorta	Condition	SNOMED	standard
4108751	Major aortopulmonary collateral artery	Condition	SNOMED	standard
4109200	Pulmonary valve dysplasia	Condition	SNOMED	standard
4109201	Bicuspid pulmonary valve	Condition	SNOMED	standard
4109203	Abnormal origin of left pulmonary artery	Condition	SNOMED	standard
4109204	Anomalous origin of left pulmonary artery from ductus arteriosus	Condition	SNOMED	standard
4109314	Anomalous origin of left pulmonary artery from ascending aorta	Condition	SNOMED	standard
4109315	Anomalous origin of left pulmonary artery from right pulmonary artery	Condition	SNOMED	standard
4109330	Stenosis of systemic to pulmonary artery collateral artery	Condition	SNOMED	standard
4109331	Bronchopulmonary collateral artery	Condition	SNOMED	standard
4109336	Commissural fusion of pulmonary valve	Condition	SNOMED	standard
4109337	Pulmonary atresia with ventricular septal defect	Condition	SNOMED	standard
4109338	Accessory tissue on pulmonary valve cusp	Condition	SNOMED	standard
4109339	Unicuspid pulmonary valve	Condition	SNOMED	standard
4109345	Abnormal origin of right pulmonary artery	Condition	SNOMED	standard
4109346	Anomalous origin of right pulmonary artery from ductus arteriosus	Condition	SNOMED	standard
4109478	Collaterals to pulmonary arteries	Condition	SNOMED	standard
4109479	Systemic to pulmonary collateral artery	Condition	SNOMED	standard
4112085	Pulmonary atresia with intact ventricular septum	Condition	SNOMED	standard
4112086	Pulmonary valve atresia without ventricular outflow tract	Condition	SNOMED	standard
4112087	Imperforate pulmonary valve	Condition	SNOMED	standard
4112088	Muscular pulmonary atresia	Condition	SNOMED	standard
4112094	Pulmonary trunk stenosis	Condition	SNOMED	standard

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	102/111

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
4112095	Pulmonary trunk hypoplasia	Condition	SNOMED	standard
4112096	Pulmonary atresia with confluent pulmonary arteries	Condition	SNOMED	standard
4112097	Pulmonary trunk absent with absent pulmonary artery	Condition	SNOMED	standard
4123286	Abnormal number of pulmonary valve cusps	Condition	SNOMED	standard
4126122	Pulmonic stenosis and congenital nephrosis	Condition	SNOMED	standard
4145158	Right hypoplastic heart syndrome	Condition	SNOMED	standard
4149211	Congenital pulmonary artery aneurysm	Condition	SNOMED	standard
4152172	Congenital abnormality of thoracic aorta and pulmonary arteries	Condition	SNOMED	standard
4161005	L - transposition of the great vessels	Condition	SNOMED	standard
4161304	D - transposition of the great vessels	Condition	SNOMED	standard
4163292	Tetralogy of Fallot with absent pulmonary valve	Condition	SNOMED	standard
4182602	Congenital hypoplasia of tricuspid valve	Condition	SNOMED	standard
4184499	Congenital anomaly of tricuspid valve	Condition	SNOMED	standard
4184599	Congenital hypoplasia of pulmonary artery	Condition	SNOMED	standard
4199318	Congenital supra-ventricular pulmonary stenosis	Condition	SNOMED	standard
4218874	Scimitar syndrome	Condition	SNOMED	standard
4220169	Congenital absence of right pulmonary artery	Condition	SNOMED	standard
4225420	Common arterial trunk and widely separate origin of pulmonary arteries	Condition	SNOMED	standard
4239048	Anomalous origin of pulmonary artery	Condition	SNOMED	standard
4244027	Congenital hypertrophy of pulmonary valve	Condition	SNOMED	standard
4244184	Congenital hypoplasia of pulmonary valve	Condition	SNOMED	standard
4244193	Congenital malposition of pulmonary artery	Condition	SNOMED	standard
4245104	Combined valvular-subvalvular pulmonic stenosis	Condition	SNOMED	standard
4245227	Congenital abnormal shape of pulmonary valve	Condition	SNOMED	standard
4245433	Congenital dilatation of pulmonary artery	Condition	SNOMED	standard
4245443	Congenital hypertrophy of tricuspid valve	Condition	SNOMED	standard
4245803	Congenital abnormal shape of tricuspid valve	Condition	SNOMED	standard
4245811	Congenital absence of tricuspid valve	Condition	SNOMED	standard
4246492	Common arterial trunk and separate origin of pulmonary arteries	Condition	SNOMED	standard
4246514	Cleft leaflet of tricuspid valve	Condition	SNOMED	standard
4251327	Double outlet left ventricle	Condition	SNOMED	standard
4252111	Common arterial trunk and common origin of pulmonary arteries	Condition	SNOMED	standard
4253217	Coronary artery arising from main pulmonary artery	Condition	SNOMED	standard
4263510	Congenital stenosis of tricuspid valve	Condition	SNOMED	standard
4269199	Congenital atresia of tricuspid valve	Condition	SNOMED	standard
4289152	Congenital absence of pulmonary valve	Condition	SNOMED	standard
4305961	Congenital insufficiency of tricuspid valve	Condition	SNOMED	standard
4311400	Agenesis of pulmonary artery	Condition	SNOMED	standard
4316070	Right-sided pulmonary arterial trunk	Condition	SNOMED	standard
4317288	Pulmonary artery stenosis	Condition	SNOMED	standard
4354052	Right ventricular muscular infundibular stenosis	Condition	SNOMED	standard
35607996	Retinal arterial macroaneurysm with supra-ventricular pulmonic stenosis	Condition	SNOMED	standard
35624311	Pulmonary valve agenesis, tetralogy of Fallot, absence of ductus arteriosus syndrome	Condition	SNOMED	standard
36714644	Atresia of pulmonary valve	Condition	SNOMED	standard
37109597	Fallot complex with intellectual disability and growth delay syndrome	Condition	SNOMED	standard

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	103/111

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
37205075	Pulmonary valve agenesis, intact ventricular septum, persistent ductus arteriosus syndrome	Condition	SNOMED	standard
40486040	Discontinuous pulmonary arteries	Condition	SNOMED	standard
40486042	Ventricular septal defect with anterior malaligned outlet septum with overriding pulmonary valve	Condition	SNOMED	standard
40486045	Ventricular septal defect with posterior malaligned outlet septum with overriding pulmonary valve	Condition	SNOMED	standard
40486055	Continuity between mitral valve and pulmonary valve	Condition	SNOMED	standard
40486057	Discontinuity between mitral valve and pulmonary valve	Condition	SNOMED	standard
40486072	Unicommissural unicuspid pulmonary valve	Condition	SNOMED	standard
40486075	Distal aortopulmonary window with minimal superior rim	Condition	SNOMED	standard
40486078	Intermediate aortopulmonary window with adequate superior and inferior rim	Condition	SNOMED	standard
40486079	Confluent aortopulmonary window with minimal superior and inferior rim	Condition	SNOMED	standard
40486553	Proximal aortopulmonary window with minimal inferior rim	Condition	SNOMED	standard
40486615	Congenital abnormality of tricuspid chordae tendinae	Condition	SNOMED	standard
40486616	Congenital abnormality of tricuspid leaflet	Condition	SNOMED	standard
40486625	Pulmonary atresia and ventricular septal defect with aorta from left ventricle	Condition	SNOMED	standard
40486626	Pulmonary atresia and ventricular septal defect with aorta from right ventricle	Condition	SNOMED	standard
40486627	Stenosis of right pulmonary artery	Condition	SNOMED	standard
40486701	Pulmonary artery with absent proximal arterial connection	Condition	SNOMED	standard
40486706	Hypoplasia of pulmonary cusps of absent pulmonary valve type	Condition	SNOMED	standard
40487068	Aortopulmonary window with tubular connection	Condition	SNOMED	standard
40487070	Coarctation of right pulmonary artery	Condition	SNOMED	standard
40487083	Ebstein's anomaly of left sided tricuspid valve with discordant atrioventricular connections	Condition	SNOMED	standard
40487158	Diffuse stenosis of left pulmonary artery	Condition	SNOMED	standard
40487182	Abnormal attachment of tricuspid chordae tendinae	Condition	SNOMED	standard
40487195	Diffuse stenosis of right pulmonary artery	Condition	SNOMED	standard
40487527	Common arterial trunk with pulmonary arteries arising from trunk and unobstructed aortic arch	Condition	SNOMED	standard
40487547	Acommissural unicuspid pulmonary valve	Condition	SNOMED	standard
40487572	Supravalvar pulmonary trunk stenosis	Condition	SNOMED	standard
40487649	Obstructed interchordal space of tricuspid chordae tendinae	Condition	SNOMED	standard
40487663	Right pulmonary artery with absent proximal arterial connection	Condition	SNOMED	standard
40487668	Single stenosis of left pulmonary artery	Condition	SNOMED	standard
40487963	Pulmonary trunk absent with absent left pulmonary artery	Condition	SNOMED	standard
40487964	Pulmonary trunk absent with absent right pulmonary artery	Condition	SNOMED	standard
40487979	Congenital abnormality of tricuspid papillary muscle	Condition	SNOMED	standard
40487980	Ebstein's anomaly with functional tricuspid stenosis	Condition	SNOMED	standard
40487984	Vascular ring with right aortic arch and right arterial ligament with absent left pulmonary artery	Condition	SNOMED	standard
40487985	Vascular ring with right aortic arch and right patent arterial duct with absent left pulmonary artery	Condition	SNOMED	standard
40487991	Absent pulmonary trunk	Condition	SNOMED	standard
40487993	Atresia of pulmonary trunk with absent left pulmonary artery	Condition	SNOMED	standard

	D5.1 Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	104/111

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
40487994	Atresia of pulmonary trunk with absent right pulmonary artery	Condition	SNOMED	standard
40488015	Anomalous origin of pulmonary artery from patent arterial duct	Condition	SNOMED	standard
40488027	Multiple stenoses of left pulmonary artery	Condition	SNOMED	standard
40488028	Multiple stenoses of right pulmonary artery	Condition	SNOMED	standard
40488046	Left pulmonary artery with absent proximal arterial connection	Condition	SNOMED	standard
40488060	Single stenosis of right pulmonary artery	Condition	SNOMED	standard
40488398	Common arterial trunk with crossed over pulmonary arteries	Condition	SNOMED	standard
40488437	Pulmonary atresia with ventricular septal defect of Fallot type	Condition	SNOMED	standard
40489968	Congenital abnormality of pulmonary trunk	Condition	SNOMED	standard
40489971	Absent pulmonary valve syndrome with ventricular septal defect of non Fallot type	Condition	SNOMED	standard
40489974	Systemic to pulmonary collateral artery from coronary artery	Condition	SNOMED	standard
40490010	Stenosis of left pulmonary artery	Condition	SNOMED	standard
40490417	Double outlet right ventricle with doubly committed ventricular septal defect and pulmonary stenosis	Condition	SNOMED	standard
40490504	Scimitar syndrome with additional anomalous pulmonary venous connection	Condition	SNOMED	standard
40490515	Congenital abnormality of pulmonary valve cusp	Condition	SNOMED	standard
40490959	Coarctation of left pulmonary artery	Condition	SNOMED	standard
40491482	Common arterial trunk with pulmonary origin from truncal valve sinus	Condition	SNOMED	standard
40491893	Double outlet right ventricle with intact ventricular septum	Condition	SNOMED	standard
40491939	Double outlet right ventricle with subpulmonary ventricular septal defect	Condition	SNOMED	standard
40491956	Common arterial trunk with obstruction of aortic arch	Condition	SNOMED	standard
40492434	Common arterial trunk with isolated pulmonary artery	Condition	SNOMED	standard
40492500	Anterior-posterior orientation of bicuspid pulmonary valve	Condition	SNOMED	standard
40493416	Pulmonary artery connecting to coronary artery via collateral artery	Condition	SNOMED	standard
40493460	Eccentric opening of tricuspid pulmonary valve	Condition	SNOMED	standard
40493461	Congenital stenosis of pulmonary artery	Condition	SNOMED	standard
40493470	Absence of pulmonary valve cusp	Condition	SNOMED	standard
40493477	Right-left orientation of bicuspid pulmonary valve	Condition	SNOMED	standard
40493497	Ebstein's anomaly of tricuspid valve with atrialization of right ventricular chamber	Condition	SNOMED	standard
42538529	Double outlet right ventricle with subaortic or doubly committed ventricular septal defect without pulmonary stenosis - ventricular septal defect type	Condition	SNOMED	standard
42538530	Common arterial trunk with aortic dominance	Condition	SNOMED	standard
42538671	Tetralogy of Fallot with pulmonary atresia and systemic-to-pulmonary collateral artery	Condition	SNOMED	standard
42539142	Common arterial trunk with pulmonary dominance and interrupted aortic arch	Condition	SNOMED	standard
42873056	Major systemic to pulmonary collateral artery supplying both lungs	Condition	SNOMED	standard
42873057	Major systemic to pulmonary collateral artery supplying entire right lung	Condition	SNOMED	standard
42873058	Major systemic to pulmonary collateral artery supplying entire left lung	Condition	SNOMED	standard
42873059	Major systemic to pulmonary collateral artery supplying part of right lung	Condition	SNOMED	standard
42873060	Major systemic to pulmonary collateral artery supplying part of left lung	Condition	SNOMED	standard
42873061	Major systemic to pulmonary collateral artery supplying unknown zone of distribution	Condition	SNOMED	standard

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	105/111

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
43020499	Dextrotransposition of the great arteries	Condition	SNOMED	standard
43020559	Systemic to pulmonary collateral artery contributing to dual lung supply	Condition	SNOMED	standard
43021052	Systemic to pulmonary collateral artery from descending thoracic aorta	Condition	SNOMED	standard
43021053	Systemic to pulmonary collateral artery from abdominal aorta	Condition	SNOMED	standard
43021059	Infective endarteritis at site of aortopulmonary window	Condition	SNOMED	standard
43021180	Systemic to pulmonary collateral artery from right carotid artery	Condition	SNOMED	standard
43021181	Systemic to pulmonary collateral artery from left carotid artery	Condition	SNOMED	standard
43021188	Systemic to pulmonary collateral artery from right renal artery	Condition	SNOMED	standard
43021189	Systemic to pulmonary collateral artery connecting with artery	Condition	SNOMED	standard
43021190	Systemic to pulmonary collateral artery from right brachiocephalic artery	Condition	SNOMED	standard
43021191	Systemic to pulmonary collateral artery from left brachiocephalic artery	Condition	SNOMED	standard
43021321	Systemic to pulmonary collateral artery connecting with central pulmonary arteries	Condition	SNOMED	standard
43021322	Systemic to pulmonary collateral artery connecting with isolated intraparenchymal pulmonary arteries	Condition	SNOMED	standard
43021323	Systemic to pulmonary collateral artery connecting with tracheobronchial arteries	Condition	SNOMED	standard
43021626	Major systemic to pulmonary collateral artery with pulmonary artery proximal to hilar bifurcation	Condition	SNOMED	standard
43021871	Progression of fetal right ventricular outflow tract obstruction	Condition	SNOMED	standard
43021911	Major systemic to pulmonary collateral artery	Condition	SNOMED	standard
43021972	Systemic to pulmonary collateral artery from left renal artery	Condition	SNOMED	standard
43022039	Major systemic to pulmonary collateral artery with absent pulmonary arteries proximal to hilar bifurcation	Condition	SNOMED	standard
45766266	Anomalous origin of pulmonary artery from ascending aorta	Condition	SNOMED	standard
45768850	Congenital stenosis of right pulmonary artery	Condition	SNOMED	standard
45772930	Congenital stenosis of left pulmonary artery	Condition	SNOMED	standard

Table 28 Codelist for the initial intervention/surgery phenotype Initial repair of RVOT

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
927089	Replacement, aortic valve; by translocation of autologous pulmonary valve and transventricular aortic annulus enlargement of the left ventricular outflow tract with valved conduit replacement of pulmonary valve (Ross-Konno procedure)	Procedure	CPT4	standard
2001453	Open and other replacement of pulmonary valve with tissue graft	Procedure	ICD9Proc	standard
2001454	Open and other replacement of pulmonary valve	Procedure	ICD9Proc	standard
2107137	Replacement, aortic valve; by translocation of autologous pulmonary valve with allograft replacement of pulmonary valve (Ross procedure)	Procedure	CPT4	standard
2107192	Replacement, pulmonary valve	Procedure	CPT4	standard
2107193	Right ventricular resection for infundibular stenosis, with or without commissurotomy	Procedure	CPT4	standard
2107194	Outflow tract augmentation (gusset), with or without commissurotomy or infundibular resection	Procedure	CPT4	standard

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	106/111

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
2107264	Repair of complex cardiac anomaly other than pulmonary atresia with ventricular septal defect by construction or replacement of conduit from right or left ventricle to pulmonary artery	Procedure	CPT4	standard
2107267	Repair of double outlet right ventricle with intraventricular tunnel repair; with repair of right ventricular outflow tract obstruction	Procedure	CPT4	standard
2107306	Complete repair tetralogy of Fallot with pulmonary atresia including construction of conduit from right ventricle to pulmonary artery and closure of ventricular septal defect	Procedure	CPT4	standard
2107379	Total repair, truncus arteriosus (Rastelli type operation)	Procedure	CPT4	standard
2107461	Repair of pulmonary atresia with ventricular septal defect, by construction or replacement of conduit from right or left ventricle to pulmonary artery	Procedure	CPT4	standard
2726896	Replacement of Pulmonary Valve with Zooplastic Tissue, Open Approach	Procedure	ICD10PCS	standard
4017746	Correction of tetralogy of Fallot using valved right ventricular outflow conduit	Procedure	SNOMED	standard
4017748	Correction of tetralogy of Fallot using right ventricular outflow patch	Procedure	SNOMED	standard
4018926	Repair of pulmonary artery	Procedure	SNOMED	standard
4019100	Implantation of outflow tract prosthesis in pulmonary valvuloplasty	Procedure	SNOMED	standard
4019929	Repair of tetralogy of Fallot	Procedure	SNOMED	standard
4020080	Homograft pulmonary valve replacement	Procedure	SNOMED	standard
4020093	Infundibulectomy of heart using patch	Procedure	SNOMED	standard
4020515	Xenograft pulmonary valve replacement	Procedure	SNOMED	standard
4020516	Mechanical prosthetic pulmonary valve replacement	Procedure	SNOMED	standard
4036615	Total repair of truncus arteriosus, Rastelli type operation	Procedure	SNOMED	standard
4049979	Repair of double outlet right ventricle	Procedure	SNOMED	standard
4051805	Construction of a cardiac conduit	Procedure	SNOMED	standard
4066169	Right ventricular resection for infundibular stenosis with commissurotomy	Procedure	SNOMED	standard
4077745	Rastelli operation in repair of transposition of great vessels	Procedure	SNOMED	standard
4137534	Repair of tetralogy of Fallot with absent pulmonary valve	Procedure	SNOMED	standard
4145119	Heart valve replacement	Procedure	SNOMED	standard
4166459	Disc valve pulmonary valve replacement	Procedure	SNOMED	standard
4169960	Ball valve pulmonary valve replacement	Procedure	SNOMED	standard
4169962	Bileaflet pulmonary valve replacement	Procedure	SNOMED	standard
4173643	Single leaflet pulmonary valve replacement	Procedure	SNOMED	standard
4175022	Infundibulectomy of ventricle in total repair of tetralogy of Fallot	Procedure	SNOMED	standard
4178794	Construction of left ventricle to aorta tunnel with right ventricle to pulmonary trunk direct anastomosis	Procedure	SNOMED	standard
4179509	Removal of obstruction of right ventricular outflow tract	Procedure	SNOMED	standard
4184741	Creation of conduit of right ventricle and pulmonary artery in repair of pulmonary artery atresia	Procedure	SNOMED	standard
4196823	Correction of transposition of great vessels	Procedure	SNOMED	standard
4202319	Porcine pulmonary valve replacement	Procedure	SNOMED	standard
4203901	Repair of pulmonary valve with tissue graft	Procedure	SNOMED	standard
4207328	Direct anastomosis of right ventricle to pulmonary trunk	Procedure	SNOMED	standard
4225412	Formation of conduit of right ventricle and pulmonary artery in repair of pulmonary artery atresia in truncus arteriosus	Procedure	SNOMED	standard
4244731	Augmentation of outflow tract of pulmonary valve	Procedure	SNOMED	standard
4259143	Creation of conduit between right ventricle and pulmonary artery	Procedure	SNOMED	standard

	D5.I Results of prevalence and characterisation			
	WP5 – Medical Device		Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph		Security: PU	107/111

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
4264274	Repair of truncus arteriosus	Procedure	SNOMED	standard
4286184	Creation of conduit of right ventricle and pulmonary artery in repair of transposition of great vessels	Procedure	SNOMED	standard
4293017	Open heart valvuloplasty of pulmonary valve without replacement	Procedure	SNOMED	standard
4299720	Repair of pulmonary valve	Procedure	SNOMED	standard
4304923	Rastelli operation for repair of pulmonary artery atresia	Procedure	SNOMED	standard
4308136	Complete repair of tetralogy of Fallot with transannular patch	Procedure	SNOMED	standard
4322960	Augmentation of outflow tract in total repair of tetralogy of Fallot	Procedure	SNOMED	standard
4323509	Replacement of aortic root using pulmonary valve autograft with right ventricle to pulmonary artery valved conduit	Procedure	SNOMED	standard
4324899	Construction of left ventricle to aorta tunnel with right ventricle to pulmonary artery valved conduit	Procedure	SNOMED	standard
4327798	Implantation of outflow tract prosthesis in total repair of tetralogy of Fallot	Procedure	SNOMED	standard
4336901	Right ventricular outflow tract myotomy	Procedure	SNOMED	standard
4336903	Construction of conduit - right ventricle to left pulmonary artery	Procedure	SNOMED	standard
4338292	Right ventricular outflow tract muscle resection	Procedure	SNOMED	standard
4338618	Construction of conduit - right ventricle to pulmonary trunk	Procedure	SNOMED	standard
4338619	Construction of conduit - right ventricle to right pulmonary artery	Procedure	SNOMED	standard
4339184	Replacement of pulmonary valve	Procedure	SNOMED	standard
4339836	Replacement of implanted pulmonary valve	Procedure	SNOMED	standard
4339972	Operation on the right ventricular outflow tract	Procedure	SNOMED	standard
4339974	Patch enlargement of right ventricular outflow tract	Procedure	SNOMED	standard
4339975	Construction of conduit - right ventricle to both pulmonary arteries	Procedure	SNOMED	standard
40486688	Replacement of aortic root using pulmonary valve autograft and replacement of pulmonary valve	Procedure	SNOMED	standard
40488996	Repair of tetralogy of Fallot using right ventricular outflow conduit	Procedure	SNOMED	standard
40491526	Procedure on right ventricular outflow tract	Procedure	SNOMED	standard
40493448	Anastomosis of superior vena cava to pulmonary artery and reconstruction of right ventricular outflow tract	Procedure	SNOMED	standard
44783274	Mechanical heart valve replacement	Procedure	SNOMED	standard
44789859	Left ventricle to aorta tunnel with right ventricle to pulmonary artery valved conduit	Procedure	SNOMED	standard
44790090	Relief of right ventricular outflow tract obstruction	Procedure	SNOMED	standard
44790415	Aortic root replacement using pulmonary valve autograft with right ventricle to pulmonary artery valved conduit and aortoventriculoplasty	Procedure	SNOMED	standard
45766375	Repair of double outlet right ventricle with anastomosis of left ventricle to aorta via ventricular septal defect and right ventricle to pulmonary trunk conduit	Procedure	SNOMED	standard
45771338	Rastelli creation of conduit between right ventricle and pulmonary artery	Procedure	SNOMED	standard

Table 29 Codelist for the disease progression phenotype

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
317296	Rheumatic disease of pulmonary valve	Condition	SNOMED	standard
3654792	Mild pulmonary valve stenosis	Condition	SNOMED	standard

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	108/111

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
3654793	Moderate pulmonary valve stenosis	Condition	SNOMED	standard
3654794	Severe pulmonary valve stenosis	Condition	SNOMED	standard
3654795	Mild pulmonary valve regurgitation	Condition	SNOMED	standard
3654796	Moderate pulmonary valve regurgitation	Condition	SNOMED	standard
3654797	Severe pulmonary valve regurgitation	Condition	SNOMED	standard
3656098	Acquired stenosis of subpulmonary area	Condition	SNOMED	standard
4101625	Right ventricular outflow tract obstruction	Condition	SNOMED	standard
4101627	Right ventricular outflow obstruction - tubular	Condition	SNOMED	standard
4103134	Right ventricular outflow obstruction - localized	Condition	SNOMED	standard
4108233	Pulmonary stenosis, non-rheumatic	Condition	SNOMED	standard
4108739	Peripheral pulmonary artery stenosis	Condition	SNOMED	standard
4108819	Pulmonary valve stenosis with insufficiency	Condition	SNOMED	standard
4111416	Pulmonary incompetence, non-rheumatic	Condition	SNOMED	standard
4112094	Pulmonary trunk stenosis	Condition	SNOMED	standard
4119957	Functional pulmonary regurgitation	Condition	SNOMED	standard
4143607	Rheumatic pulmonary valve insufficiency	Condition	SNOMED	standard
4156427	Dynamic right ventricular outflow tract obstruction	Condition	SNOMED	standard
4209011	Pulmonic valve stenosis	Condition	SNOMED	standard
4237202	Pulmonic valve regurgitation	Condition	SNOMED	standard
4238914	Rheumatic pulmonary valve stenosis	Condition	SNOMED	standard
4245104	Combined valvular-subvalvular pulmonic stenosis	Condition	SNOMED	standard
4312621	Rheumatic pulmonary valve stenosis with insufficiency	Condition	SNOMED	standard
4317288	Pulmonary artery stenosis	Condition	SNOMED	standard
4354070	Pulmonary valve stenosis with doming	Condition	SNOMED	standard
4354071	Pulmonary valve stenosis with narrow jet	Condition	SNOMED	standard
40486627	Stenosis of right pulmonary artery	Condition	SNOMED	standard
40486704	Right ventricular outflow tract obstruction due to abnormal cardiac muscle bands	Condition	SNOMED	standard
40487158	Diffuse stenosis of left pulmonary artery	Condition	SNOMED	standard
40487195	Diffuse stenosis of right pulmonary artery	Condition	SNOMED	standard
40487543	Right ventricular outflow tract obstruction due to aneurysm of membranous septum	Condition	SNOMED	standard
40487572	Supravalvar pulmonary trunk stenosis	Condition	SNOMED	standard
40487633	Right ventricular outflow tract obstruction due to septoparietal trabeculation	Condition	SNOMED	standard
40487668	Single stenosis of left pulmonary artery	Condition	SNOMED	standard
40487989	Right ventricular outflow tract obstruction due to prolapse of Eustachian valve	Condition	SNOMED	standard
40487990	Right ventricular outflow tract obstruction due to prolapsed arterial valve	Condition	SNOMED	standard
40488027	Multiple stenoses of left pulmonary artery	Condition	SNOMED	standard
40488028	Multiple stenoses of right pulmonary artery	Condition	SNOMED	standard
40488060	Single stenosis of right pulmonary artery	Condition	SNOMED	standard
40489397	Right ventricular outflow tract obstruction due to common atrioventricular valve	Condition	SNOMED	standard
40489398	Right ventricular outflow tract obstruction due to fibromuscular shelf	Condition	SNOMED	standard
40489399	Right ventricular outflow tract obstruction due to malaligned outlet septum	Condition	SNOMED	standard
40489972	Subpulmonary stenosis	Condition	SNOMED	standard

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	109/111

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
40490010	Stenosis of left pulmonary artery	Condition	SNOMED	standard
40490955	Right ventricular outflow tract obstruction due to atrioventricular valve	Condition	SNOMED	standard
40491516	Obstruction of right ventricular outflow tract due to aortico-left ventricular tunnel	Condition	SNOMED	standard
40493475	Right ventricular outflow tract obstruction due to septal hypertrophy	Condition	SNOMED	standard
43020902	Subneopulmonary valve stenosis	Condition	SNOMED	standard
43020918	Subpulmonary stenosis as complication of procedure	Condition	SNOMED	standard
43020919	Acquired subpulmonary stenosis associated with functionally univentricular heart	Condition	SNOMED	standard
43020920	Acquired subpulmonary stenosis due to restrictive ventricular defect associated with functionally univentricular heart	Condition	SNOMED	standard
43020922	Subpulmonary stenosis associated with functionally univentricular heart as complication of procedure	Condition	SNOMED	standard
44804775	Subaortic right ventricular outflow tract obstruction	Condition	SNOMED	standard
44813206	Subpulmonary right ventricular outflow tract obstruction	Condition	SNOMED	standard
45766087	Non-rheumatic pulmonary valve stenosis with regurgitation	Condition	SNOMED	standard
45766089	Postprocedural pulmonary valve regurgitation	Condition	SNOMED	standard
45766092	Neopulmonary valve regurgitation	Condition	SNOMED	standard
45766093	Neopulmonary valve stenosis	Condition	SNOMED	standard
45766094	Prosthetic pulmonary valve failure requiring replacement	Condition	SNOMED	standard
45766096	Endocarditis of prosthetic pulmonary valve	Condition	SNOMED	standard
45766097	Postprocedural pulmonary valve stenosis	Condition	SNOMED	standard
45766143	Acquired stenosis of left pulmonary artery	Condition	SNOMED	standard
45766144	Acquired stenosis of right pulmonary artery	Condition	SNOMED	standard
45766180	Prosthetic pulmonary valve stenosis	Condition	SNOMED	standard
45766182	Prosthetic pulmonary valve regurgitation	Condition	SNOMED	standard
45768937	Stenosis of right pulmonary artery as complication of procedure	Condition	SNOMED	standard
45768938	Stenosis of left pulmonary artery as complication of procedure	Condition	SNOMED	standard
45768939	Pulmonary trunk stenosis as complication of procedure	Condition	SNOMED	standard
45773076	Prosthetic pulmonary valve failure requiring revision	Condition	SNOMED	standard
45773168	Prosthetic pulmonary valve failure	Condition	SNOMED	standard
45773174	Acquired pulmonary trunk stenosis	Condition	SNOMED	standard

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	110/111

Table 30 Device Recived codelist PPVII surgical PVR

Concept Id	Concept Name	Domain Id	Vocabulary Id	Standard Concept
2001453	Open and other replacement of pulmonary valve with tissue graft	Procedure	ICD9Proc	standard
2001454	Open and other replacement of pulmonary valve	Procedure	ICD9Proc	standard
2107192	Replacement, pulmonary valve	Procedure	CPT4	standard
2726896	Replacement of Pulmonary Valve with Zooplastic Tissue, Open Approach	Procedure	ICD10PCS	standard
4020080	Homograft pulmonary valve replacement	Procedure	SNOMED	standard
4020515	Xenograft pulmonary valve replacement	Procedure	SNOMED	standard
4020516	Mechanical prosthetic pulmonary valve replacement	Procedure	SNOMED	standard
4166459	Disc valve pulmonary valve replacement	Procedure	SNOMED	standard
4169960	Ball valve pulmonary valve replacement	Procedure	SNOMED	standard
4169962	Bileaflet pulmonary valve replacement	Procedure	SNOMED	standard
4173643	Single leaflet pulmonary valve replacement	Procedure	SNOMED	standard
4178623	Percutaneous transluminal replacement of pulmonary valve	Procedure	SNOMED	standard
4202319	Porcine pulmonary valve replacement	Procedure	SNOMED	standard
4336902	Transluminal right ventricular outflow tract laser operation	Procedure	SNOMED	standard
4339184	Replacement of pulmonary valve	Procedure	SNOMED	standard
4339836	Replacement of implanted pulmonary valve	Procedure	SNOMED	standard
4339973	Balloon dilatation of right ventricular outflow tract	Procedure	SNOMED	standard
37206820	Percutaneous pulmonary valve implantation	Procedure	SNOMED	standard
40481952	Percutaneous insertion of stent into right ventricular outflow tract using fluoroscopic guidance	Procedure	SNOMED	standard
40482389	Percutaneous insertion of pulmonary valve using fluoroscopic guidance	Procedure	SNOMED	standard
40483634	Percutaneous replacement of pulmonary valve using fluoroscopic guidance	Procedure	SNOMED	standard
40756772	Endovascular replacement of pulmonary valve	Procedure	ICD9Proc	standard
40756793	Transapical replacement of pulmonary valve	Procedure	ICD9Proc	standard
42628056	Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed	Procedure	CPT4	standard
42742455	Implantation of catheter-delivered prosthetic pulmonary valve, endovascular approach	Procedure	CPT4	standard
44793497	Fluoroscopy guided percutaneous pulmonary valve replacement	Procedure	SNOMED	standard
46257454	Echocardiography, transesophageal (TEE) for guidance of a transcatheter intracardiac or great vessel(s) structural intervention(s) (eg, TAVR, transcatheter pulmonary valve replacement, mitral valve repair, paravalvular regurgitation repair, left atrial ap	Procedure	CPT4	standard

	D5.I Results of prevalence and characterisation		
	WP5 – Medical Device	Version: v3.0	
	Author(s): M. Du, A. Kim, A. Perramon-Malavez, A. Prats-Urbe, A. Rudolph	Security: PU	III/III

Table 31 EU-27 + EFTA standard population from www.ec.europa.eu/eurostat

Proposed EU-27 + EFTA standard population

Age Group (years)	Standard Population
0-0	1 000
1-4	4 000
5-9	5 500
10-14	5 500
15-19	5 500
20-24	6 000
25-29	6 000
30-34	6 500
35-39	7 000
40-44	7 000
45-49	7 000
50-54	7 000
55-59	6 500
60-64	6 000
65-69	5 500
70-74	5 000
75-79	4 000
80-84	2 500
85-89	1 500
90-94	800
95+	200
Total	100 000