Study Protocol P2-C1-010

06/12/2023

Version 2.1

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DOCUMENT HISTORY

Version	Date	Description
V1.0	20/10/2023	**Submission to EMA**
V2.0	21/11/2023	**Submission of updated version to EMA**
V2.1	06/12/2023	**Submission of updated version to EMA for archiving purposes**

Study Title	DARWIN EU® - Characterization of patients with chronic hepatitis B and C
Protocol version identifier	V2.1
Date of last version of protocol	6th December 2023
EU PAS register number	To be completed after study approval by the EMA.

Active substance

No.	Therapeutic Drug Class	ATC Code
1.	**Peginterferon**	
	Cepeginterferon alfa-2b	L03AB14
	Peginterferon -α-2a	L03AB11, L03AB61
	Peginterferon -α-2b	L03AB10, L03AB60
	Peginterferon alfacon-2	L03AB16
	Interferon alfa-2a	L03AB04
	interferon alfa-2b	L03AB05
2.	**Antivirals for treatment of HCV infections**	
	Ribavirin	J05AP01
	Telaprevir	J05AP02
	Boceprevir	J05AP03
	Faldaprevir	J05AP04
	Simeprevir	J05AP05
	Asunaprevir	J05AP06
	Daclatasvir	J05AP07
	Sofosbuvir	J05AP08
	Dasabuvir	J05AP09
	Elbasvir	J05AP10
	Grazoprevir	J05AP11
	Coblopasvir	J05AP12
	Sofosbuvir and ledipasvir	J05AP51
	Dasabuvir, ombitasvir, paritaprevir and ritonavir	J05AP52
	Ombitasvir, paritaprevir and ritonavir	J05AP53
	Elbasvir and grazoprevir	J05AP54
	Sofosbuvir and velpatasvir	J05AP55
	Sofosbuvir, velpatasvir and voxilaprevir	J05AP56
	Glecaprevir and pibrentasvir	J05AP57
	Daclatasvir, asunaprevir and beclabuvir	J05AP58
3.	**Antivirals for treatment of HBV infections**	
	Adefovir dipivoxil	J05AF08
	Entecavir	J05AF10

		Telbivudine	J05AF11
		Tenofovir alafenamide	J05AF13
		Tenofovir disoproxil fumarate	J05AF07
		Lamivudine	J05AF05
		Bulevirtide	J05AX28

Medicinal product	N/A
Research question and objectives	Research question What are the characteristics of patients with chronic hepatitis B and hepatitis C? Study objectives 1. To report the number and percentage of patients diagnosed with chronic HBV/HCV infection who initiate treatment with interferon or any specified antivirals, stratified by age, sex, calendar year, and country/database throughout the study period (2012 - 2022). 2. To report the number and percentage of patients diagnosed with chronic HBV/HCV infection who are undergoing treatment with any specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022). 3. To characterize patients with chronic HBV/HCV infection at the initiation of treatment with interferon or specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022). 4. To estimate the proportion of all patients with chronic HBV/HCV infection, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).
Country(-ies) of study	Estonia, France, Germany, Netherlands, Spain, and the United Kingdom
Author	Johnmary T. Arinze (j.arinze@darwin-eu.org) Katia Verhamme (k.verhamme@darwin-eu.org)

LIST OF ABBREVIATIONS

Acronyms/term	Description
ATC	Anatomical Therapeutic Chemical Classification
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization Study
EBB	Estonian Biobank
ECDC	The European Centre for Disease Prevention and Control
EGCUT	Estonian Genome Center at the University of Tartu
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
GP	General Practitioner
HBV	Hepatitis B viral infection
HCV	Hepatitis C viral infection
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
IP	Inpatient
IPCI	Integrated Primary Care Information Project
OHDSI	Observational Health Data Sciences and Informatics
OP	Outpatient
OMOP	Observational Medical Outcomes Partnership
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organization

1 TITLE

DARWIN EU® - Characterization of patients with chronic hepatitis B and C

2 RESPONSIBLE PARTIES – STUDY TEAM

Table 1 shows a description of the Study team by role, name and organization.

Table 1: Description of Study Team

Study team Role	Names	Organisation
Principal Investigator/ Clinical Epidemiologists	Katia Verhamme Johnmary Arinze Dina Vojinovic-Dees	Erasmus MC Erasmus MC IQVIA
Data Scientist(s)	Cesar Barboza Gutierrez	Erasmus MC
Data Partner*	**Names**	**Organization**
Local Study Coordinator/ Data Analyst	Antonella Delmestri James Brash Vianney Jouhet Verdy Guillaume Mees Mosseveld Miguel-Angel Mayer Angela Leis Juan Ramirez Raivo Kolde	University of Oxford – CPRD IQVIA - DA Germany CHUBX – France CHUBX – France Erasmus MC – IPCI PSMAR – IMASIS PSMAR – IMASIS PSMAR – IMASIS University of Tartu - Estonian Biobank

*Data partners' role is only to execute code at their data source. These people do not have an investigator role.

3 ABSTRACT (STAND ALONE SUMMARY OF THE STUDY PROTOCOL)

Title

DARWIN EU® - Characterization of patients with chronic hepatitis B and C

Rationale and Background

In 2015, UN Member States adopted Sustainable Development Goals (SDGs) for 2030 (1) with an 'urgent call to action' comprised of 17 goals/179 targets. EU/EEA countries are committed to monitoring progress towards these goals. Specifically, Target 3.3 states: 'By 2030, end the epidemics of AIDS, tuberculosis, malaria

and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases'. The 2016 WHO Global Health Sector Strategy (GHSS) (2) aims to eliminate viral hepatitis by 2030, and WHO EU has developed a hepatitis action plan to steer the implementation of the GHSS in Europe (3).

The European Centre for Disease Prevention and Control (ECDC) has developed a monitoring system for Hepatitis B Viral Infection (HBV) and Hepatitis C Viral Infection (HCV) aligned with indicators and targets of the GHSS and the WHO European Region Action Plan (4). Comprehensive data on the prevalence of chronic HBV/HCV infections and utilisation of antiviral treatments for chronic HBV/HCV infections are important to monitor progress towards the elimination targets related to treatment, to adjust prevalence estimates over time, and to support effective planning of prevention and control activities by countries.

To date, data collected by EU Member States and reported to ECDC come from a range of heterogeneous sources with different levels of quality and completeness. Several reasons contribute to this heterogeneous data collection including as the lack of standardised or electronic data systems in countries. Therefore, robust and timely data at national or subnational level generated through DARWIN EU will add to the available body of evidence and/or will help address current evidence gaps.

Research question and Objectives

Research question

What are the characteristics of patients with chronic HBV and HCV?

Study objectives

1. To report the number and percentage of patients diagnosed with chronic HBV/HCV infection who initiate treatment with interferon or any specified antivirals, stratified by age, sex, calendar year, and country/database throughout the study period (2012 - 2022).
2. To report the number and percentage of patients diagnosed with chronic HBV/HCV infection who are undergoing treatment with any specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).
3. To characterize patients with chronic HBV/HCV infection at the initiation of treatment with interferon or specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).
4. To estimate the proportion of all patients with chronic HBV/HCV infection, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).

Research Methods

Study design

- Population-level drug utilisation study: Population level drug utilisation study to estimate the number and percentage of individuals initiating (Objective 1) or undergoing (Objective 2) treatment with interferon or any of the specific antivirals of interests among patients with chronic HBV/HCV infection.
- New drug user cohort study (Objective 3): Patient-level drug utilisation analyses to provide large scale characterization of chronic HBC/HCV infections at the time of treatment initiation with interferon or any of the specific antivirals of interests).
- Population-level cohort study (Objective 4): Population-level descriptive epidemiology to estimate the proportion of all patients with chronic HBV/HCV infection in the general population.

Population

Population level drug utilisation: This will include all patients diagnosed with chronic HBV/HCV infection in the respective databases from 2012 to 2022 (or the latest available date if earlier).

Patient-level drug utilization: This will include all patients with chronic HBV/HCV infection who are new users of interferon or any of the specific antivirals of interests in the respective databases from 2012 to 2022 (or the latest available date if earlier).

Population-level descriptive epidemiology: Population-level descriptive epidemiology analyses will include all individuals in the respective databases from 2012 to 2022 (or the latest available date if earlier. Within this population, we will estimate the proportion of all patients diagnosed with chronic HBV/HCV infection.

Variables

Therapeutic drug classes of interest:

- Interferon: Cepeginterferon alfa-2b, Peginterferon -α-2a, Peginterferon -α-2b, Peginterferon alfacon-2, Interferon alpha-2a, and Interferon alpha-2b.
- Antivirals for treatment of HBV infections: Adefovir dipivoxil, Entecavir, Telbivudine, Tenofovir alafenamide, Tenofovir disoproxil fumarate, Lamivudine, and Bulevirtide
- Antivirals for treatment of HCV infections: Asunaprevir, Beclabuvir, Boceprevir, Coblopasvir, Daclatasvir, Dasabuvir, Elbasvir, Faldaprevir, Glecaprevir, Grazoprevir, Ledipasvir, Ombitasvir, Paritaprevir, Pibrentasvir, Ribavirin, Ritonavir, Simeprevir, Sofosbuvir, Telaprevir, Velpatasvir and Voxilaprevir

Conditions of interest:

- Chronic Hepatitis B Viral Infection (HBV)
- Chronic Hepatitis C Viral Infection (HCV)

Data sources

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Estonian Biobank (EBB), Estonia
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
6. Integrated Primary Care Information Project (IPCI), The Netherlands

Sample size

No sample size was calculated for this study, as our primary focus is to describe characteristics of patients with chronic HBV/HCV infection, regardless of the sample size. Based on a preliminary feasibility assessment, the expected number of person counts with chronic HBV/HCV infection range from 200 (CPRD GOLD) to 14,700 (IQVIA DA Germany) for HBV and from 200 (IPCI) to 17,000 (IQVIA DA Germany) for HCV infection.

Data analyses

Population-level drug utilization analyses: The the number and percentage of patients who are prescribed each of the pre-specified drugs from the designated list for the treatment of HBV/HCV infections will be estimated in patients with chronic HBV/HCV infections (Objective 1 and 2). The statistical analyses will be performed based on OMOP-CDM mapped data using the *PatientProfile* R package, and stratified by age, sex, calendar year and data sources.

Patient-level drug utilisation analyses: Large-scale patient-level characterisation will be conducted at time of treatment initiation, following the diagnosis of chronic HBV/HCV infections, to describe patient demographics and medical history including the presence of co-morbidities and concurrent medication use (Objective 3). The index date will be determined as the date of the first prescription of the specific therapeutic drug class for each individual. The statistical analyses will be conducted using the *"DrugUtilization"* R package based on OMOP-CDM mapped data, and be stratified by age, sex, calendar year and data sources.

Population-level descriptive epidemiology: The number and proportion (expressed as a percentage) of patients with chronic HBV infection or chronic HCV infection in the overall eligible population will be estimated (Objective 4). The statistical analyses will be performed based on OMOP-CDM mapped data using the *"PatientProfile"* R package, and stratified by age, sex, calendar year and data sources.

For all analyses, results will be reported with a minimum cell count of 5, and any counts smaller than 5 will be obscured to ensure privacy and confidentiality.

4 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	20/11/2023	All	Update	Inclusion of additional drugs of interest. Clarification of terminologies
2.	06/12/2023	3	Update	The study team was updated to incorporate the recently added study team member (DV and GI) and additional members of the database partners.

5 MILESTONES

Additional study specific deliverables (e.g. results of validation of new disease concepts, statistical analysis plan, etc.) might be requested but this will be on an individual basis

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	19th October 2023
Final Study Protocol	6th December 2023
Creation of Analytical code	6th November 2023

Execution of Analytical Code on the data	December 2023
Interim Study Report (if applicable)	Not applicable
Draft Study Report	18th December 2023
Final Study Report	To be confirmed

6 RATIONALE AND BACKGROUND

Viral hepatitis is a major public health concern, affecting millions of people worldwide; with hepatitis B and hepatitis C resulting in chronic infections. The World Health Organization (WHO) estimates that 354 million people worldwide live with hepatitis B or C,(5) and that in 2019 1.5 million people were newly infected with chronic hepatitis B, and 1.5 million people were newly infected with chronic hepatitis C.(6) In 2021, 16,187 cases of hepatitis B virus (HBV) and 14,560 cases of hepatitis C infections were reported in EU/EEA Member States, corresponding to a crude rate of 4.7 cases per 100 000 population and 4.1 cases per 100 000 population respectively.(7, 8) WHO estimates that 1.1 million deaths occurred in 2019 due to these infections and their complications including liver cancer, cirrhosis, and other conditions.(6)

HBV infection is primarily transmitted through percutaneous inoculation or mucosal exposure to infectious body fluids. Most immunocompetent adults infected with HBV can clear the virus, but some develop chronic infection. HCV infection mainly transmitted through contact with infected blood and, less commonly, through sexual intercourse and perinatal transmission. About 30% of individuals who are acutely infected with HCV spontaneously clear the virus within 6 months, while the rest develop chronic infection. Chronic HBV/HCV infections are often asymptomatic but can lead to severe complications including cirrhosis and/or hepatocellular carcinoma if untreated.

Diagnosis of chronic HBV/HCV infections requires appropriate history and laboratory testing for serological markers. Specifically, the presence of antibodies to HBeAg denotes a possible chronic HBV infection, while the diagnosis of HCV infection includes detection of antibodies to HCV which indicate if someone has ever been exposed to the virus as well as direct testing for HCV RNA to identify active cases of infection. (9, 10)

Treatment of chronic HBV/HCV infection aims to suppress viral replication, reduce liver inflammation, and prevent disease progression. Antiviral therapies, including nucleoside analogues and interferons, are available. The choice of treatment depends on various factors, such as the severity of liver disease, and differs for each infection. The mainstay of therapy for HCV infection was injectable pegylated interferon and ribavirin, with a modest cure rate ranging from 40% to 60% and high rates of adverse events. However, the introduction of highly effective Direct-Acting Antivirals (DAAs) for chronic HCV treatment showed improvement in cure rates to 90% – 97%.(9, 10)

WHO's global hepatitis strategy, endorsed by all WHO Member States, set global targets of achieving 90% reduction in new chronic hepatitis B and C infections, a 65% reduction in deaths from hepatitis B and hepatitis C, and treatment of 80% of people living with these infections by 2023.(5) The 2016 WHO Global Health Sector Strategy (GHSS) aims to eliminate viral hepatitis by 2030,(11) and WHO EU has developed a hepatitis action plan to steer the implementation of the GHSS in Europe(3). The European Centre for Disease Prevention and Control (ECDC) has developed a monitoring system for HBV/HCV aligned with indicators and targets of the GHSS and the WHO European Region Action Plan.(4) Nevertheless, comprehensive data on the prevalence of chronic HBV/HCV infections and utilization of antiviral treatments for chronic HBV/HCV infections are important to monitor progress towards the elimination targets related to treatment and to support effective planning of prevention and control activities by countries.

To date, data collected by EU Member States and reported to ECDC come from different sources with different levels of quality and completeness. Several reasons contribute to this heterogeneous data collection such as the lack of standardised or electronic systems to collect data across countries. Thus, robust, and

timely data at national or subnational level generated through DARWIN EU will add to the available body of evidence and/or address current evidence gap.

7 RESEARCH QUESTION AND OBJECTIVES

Research question:

What are the characteristics of patients with chronic HBV and HCV?

Study objectives

1. To report the number and percentage of patients diagnosed with chronic HBV/HCV infection who initiate treatment with interferon or any specified antivirals, stratified by age, sex, calendar year, and country/database throughout the study period (2012 - 2022).
2. To report the number and percentage of patients diagnosed with chronic HBV/HCV infection who are undergoing treatment with any specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).
3. To characterize patients with chronic HBV/HCV infection at the initiation of treatment with interferon or specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).
4. To estimate the proportion of all patients with chronic HBV/HCV infection, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022).

Table 2: Primary and secondary research questions and objective

Objectives:	To estimate the number and percentage of individuals initiating (Objective 1) or undergoing (Objective 2) treatment with interferon or any of the specific antivirals of interests among patients with chronic HBV/HCV infection, stratified by age, sex, calendar year and country/database during the study period (2012 - 2022). To characterize patients with chronic HBV/HCV infection at the initiation of treatment with interferon or specified antivirals, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022) (objective 3). To estimate the proportion of patients with chronic HBV/HCV infection, stratified by age, sex, calendar year, and country/database during the study period (2012 - 2022) (objective 4).
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	Population level drug utilisation: all patients with chronic HBV/HCV infection in the respective databases from 2012 to 2022 (or the latest available date if earlier. Patient-level drug utilization: all patients diagnosed with chronic HBV/HCV infection who are new users of interferon or any of the specific antivirals of interests in the respective databases from 2012 to 2022 (or the latest available date if earlier).

	Population level descriptive epidemiology: all individuals in the respective databases from 2012 to 2022 (or the latest available date if earlier).
Exposure:	Therapeutic drug classes of interest: • Peginterferon: Cepeginterferon alfa-2b, Peginterferon -α-2a, Peginterferon -α-2b,Peginterferon alfacon-2, Interferon alpha-2a, and Interferon alpha-2b. • Antivirals for treatment of HBV infections: Adefovir dipivoxil, Entecavir, Telbivudine, Tenofovir alafenamide, Tenofovir disoproxil fumarate, Lamivudine, and Bulevirtide • Antivirals for treatment of HCV infections: Asunaprevir, Beclabuvir, Boceprevir, Coblopasvir, Daclatasvir, Dasabuvir, Elbasvir, Faldaprevir, Glecaprevir, Grazoprevir, Ledipasvir, Ombitasvir, Paritaprevir, Pibrentasvir, Ribavirin, Ritonavir, Simeprevir, Sofosbuvir, Telaprevir, Velpatasvir and Voxilaprevir
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Population level drug utilisation: Follow-up will start on the date of diagnosis of chronic HBV/HCV infection during the study period. Patient-level drug utilization: Follow-up will start on the date of incident prescription of interferon or any of the specific antivirals of interests. Population-level descriptive epidemiology: Follow-up will start when patients fulfil inclusion criteria (i.e., present in the database between 1st of January 2012 and 31st of December). End of follow-up will be defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 6 data sources: CHUBX (France), CPRD GOLD (UK), EBB (Estonia), IQVIA DA Germany (Germany), IMASIS (Spain) and IPCI (the Netherlands).
Main measure of effect:	The number and percentage of users of peginterferon or any of the specific antivirals of interests in patients with chronic HBV/HCV. Large scale characterization of patients with HBV/HCV initiating treatment with interferon or any of the specific antivirals of interests. Number and proportion of patients with chronic HBV/HCV in the general population.

8 RESEARCH METHODS

8.1 Study type and Study Design

A cohort study will be conducted using routinely collected health data from 6 databases. The study will comprise three consecutive parts:

- Cohort analysis will be used to estimate the number and percentage of individuals initiating (Objective 1) or undergoing (Objective 2) treatment with interferon or any of the specific antivirals of interests among patients with chronic HBV/HCV infection.
- New drug user cohort study will be used to characterize patients with chronic HBV/HCV infections at the time of treatment initiation with interferon or any of the specific antivirals of interests (Objective 3).
- Population-level cohort study will be conducted to assess the proportion of patients with chronic HBV/HCV infection in the general population (Objective 4).

Table 3. Description of Potential Study Types and Related Study Designs

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Population level DUS	Population-level cohort	Off the shelf (C1)
Patient Level DUS	New drug/s user cohort	Off the shelf (C1)
Population-level descriptive epidemiology	Population-level cohort	Off the shelf (C1)

8.2 Study Setting and Data Sources

This study will be conducted using routinely collected data from 6 databases in 6 European countries (5 EU countries and United Kingdom). All databases were previously mapped to the OMOP Common Data Model (CDM).

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Estonian Biobank (EBB), Estonia
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
6. Integrated Primary Care Information Project (IPCI), The Netherlands

For this study, we have selected six databases from ten databases available in the DARWIN EU® Database Catalogue. The selection process was based on two primary criteria: data reliability and relevance to the research question at hand. These selected databases demonstrate substantial record counts for both chronic HBV/HCV infection and the drugs of interest. Moreover, they offer a good geographical spread, ensuring representation from diverse regions of Europe.

These suggested databases meet the requirements for conducting a patient-level characterization, patient-level drug utilization study and population-level descriptive epidemiology, enabling is to characterize chronic HBV/HCV infection. Additionally, by including databases from different settings, we can capture both inpatient and outpatient drug prescriptions. The estimation of proportion of patients with chronic HBV/HCV

disease will be confined to primary care databases exclusively. Therefore, Objective 4 of the study will not be investigated within the hospital databases IMASIS and CHUBX.

Information on data source(s) planned to be used with a justification for their choice in terms of ability to capture the relevant data is described in a **Table 4**.

When it comes to assessing the reliability of data sources, the data partners are asked to describe their internal data quality process on the source data as part of the DARWIN EU onboarding procedure. To further ensure data quality, we utilize the Achilles tool, which systematically characterizes the data and presents it in a dashboard format that is inspected. The generated data characteristics such as age distribution, condition prevalence per year, data density, measurement value distribution can be compared against expectations for the data.

Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility consistently across the data sources. In terms of relevance, a more general-purpose diagnostic tool, CohortDiagnostics, has been developed. This package evaluates phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture including data generation. It provides additional insights into cohort characteristics, record counts and index event misclassification. Furthermore, timeliness is guarded by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have clear understanding of the time period covered by each released database, as this can vary across different domains. To facilitate this, the CdmOnboarding (and Achilles) packages contain a 'data density' plot. This plot displays the number of records per OMOP domain on a monthly basis. This allows to get insights when data collection started, when new sources of data were added and when until when data was included.

Table 4. Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
France	CHUBX	Database covers hospital care settings where medication with prokinetic properties may be prescribed/dispensed.	Secondary care (in and outpatients)	EHR	2.1 million	05/05/2023
UK	CPRD GOLD	Database covers primary care where medication with prokinetic properties may be prescribed/dispensed.	Primary care	EHR	3 million	20/03/2023
Estonia	EBB	Database covers information from primary care and secondary care setting (insurance claims, digital prescriptions) where ERAs/ PDE-5is prescriptions are issued.	Biobank	Claims data	0.2 million	20/03/2023
Germany	IQVIA DA Germany	Databases covers primary care / outpatient specialist care setting where medication with prokinetic properties may be prescribed/dispensed.	Primary care and outpatient specialist care	EHR	8.5 million	13/03/2023
Spain	IMASIS	Database covers hospital care settings where medication with prokinetic properties may be prescribed/dispensed.	Secondary care (in and outpatient)	EHR	0.6 million	31/12/2022
The Netherlands	IPCI	Database covers primary care where medication with prokinetic properties may be prescribed/dispensed.	Primary care	EHR	1.4 million	21/03/2023

Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).(12)

Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom (University of Oxford)

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(13) 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). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data is available for 20 million patients, including 3.2 million currently registered patients.

Access to CPRD GOLD data requires approval via the Research Data Governance Process. CPRD GOLD will be onboarded as Data Partner for DARWIN EU® in 2023.

Estonian Biobank – University of Tartu (Estonia)

The Estonian Biobank (EBB) is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT). Its cohort size is currently close to 200,000 participants (“gene donors” >= 18 years of age) which closely reflects the age, sex and geographical distribution of the Estonian adult population. Genomic GWAS analysis has been performed on all gene donors. The database also covers health insurance claims, digital prescriptions, discharge reports, information about incident cancer cases and causes of death from national sources for each donor.

IQVIA Disease Analyser (DA) Germany, Germany

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings.(14) Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patients visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals

(Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymized relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry.

Integrated Primary Care Information Project (IPCI), The Netherlands

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.(15) The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996.(15) The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g., exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board.(15)

8.3 Study Period

The study period will be from 1st of January 2012 until the earliest of 31st December 2022 or the respective data lock for the last database update (see Table 4 for more details on each database's latest data).

8.4 Follow-up

To calculate the number and percentage of users of interferon or any of the specific antivirals of interests, follow-up with start on the date of new diagnosis of chronic HBV/HCV infection until the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whatever comes first.

For the patient-level utilization, study participants will be followed up from the date of incident prescription of interferon or any of the specific antivirals of interests (index date) until the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whatever comes first.

For the population-level descriptive epidemiology, follow up will start when patients fulfil inclusion criteria i.e., present in the database between 1st of January 2012 and 31st of December 2022. End of follow-up will be defined as the earliest loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whatever comes first.

The operational definition of start of follow-up is described in Table 5.

Table 5: Operational Definition of Time 0 (index date) and 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[1]	Code Type[2]	Diagnosis position	Incident with respect to…[3]	Measurement characteristics/ validation	Source of algorithm
All patients from the database eligible for the study (i.e., present in the database during study period) and diagnosed with chronic HBV/HCV infection. – analysis of incident use of interferon or any of the specific antivirals of interests	Date of diagnosis of chronic HBV/HCV infection	Multiple	Incident	[-Inf., ID]	IP and OP	RxNorm	n/a	Use of interferon or any of the specific antivirals of interests	n/a	n/a
All patients from the database eligible for the study (i.e., present in the database during study period) and diagnosed with chronic HBV/HCV infection.– analysis of prevalent use of interferon or any of the specific antivirals of interests	Date of diagnosis of chronic HBV/HCV infection	Multiple	Prevalent	None	IP and OP	RxNorm	n/a	n/a	n/a	n/a

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…[3]	Measurement characteristics/ validation	Source of algorithm
All patients from the database eligible for the study and diagnosed with chronic HBV/HCV infection initiating treatment with interferon or any of the specific antivirals of interests – Large scale characterisation	Initiation of treatment with interferon or any of the specific antivirals of interests in patients diagnosed with chronic HBV/HCV	Single entry	Incident	[-∞, ID]	IP and OP	SNOMED and RxNorm	n/a	Use of interferon or any of the specific antivirals of interests	n/a	n/a
All patients from the database eligible for the study – analysis to estimate the proportion of patients with chronic HBV/HCV infection	Patients present in the database from 2012 to 2022 (or the latest available date if earlier.	Multiple entries	Prevalent	n/a	IP and OP	SNOMED	n/a	n/a	n/a	n/a

[1] IP = inpatient, [3]Incident with respect to = provide a brief text description of what the patient is required to be incident to (e.g. incident user of Drug X), OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

8.5 Study Population with inclusion and exclusion criteria

For population level drug utilization (Objective 1 and 2), study population will include all patients with chronic HBV/HCV infection in the respective databases from 2012 to 2022 (or the latest available date if earlier).

For patient-level drug utilization (Objective 3), the study population will include all patients with chronic HBV/HCV infection who are new users of interferon or any of the specific antivirals of interests in the respective databases from 2012 to 2022 (or the latest available date if earlier), and no record of using the respective drugs in the year preceding the index date.

For population-level descriptive epidemiology (Objective 4), the study population will include all individuals identified in the database from 2012 to 2022.

Table 6. 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
Chronic HBV/HCV infection	Patients diagnosed with chronic HBV/HCV infection during the study period.	After	[-∞,0]	IP and OP	SNOMED	primary and secondary diagnosis code	All individuals within selected databases	n/a	n/a
Washout period	New users will be required to have no used interferon or any of the specific antivirals of interests 1 year before a "new" prescription	After	1 year	IP and OP	n/a	n/a	All patients with chronic HBV/HCV infection	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable. Order of application – after (i.e., the first possible study entry date is first selected and then inclusion criteria are applied)

[2] For hospital databases and the EBB, both primary and secondary diagnosis codes will be used. (thus, not only primary code for reason of admission)

8.6 Variables

8.6.1. Exposure

For this study, exposure of interest is use (during study period) of interferon or any of the specific antivirals of interests:

- Interferon: Cepeginterferon alfa-2b, Peginterferon -α-2a, Peginterferon -α-2b, Peginterferon alfacon-2, Interferon alpha-2a, and Interferon alpha-2b.
- Antivirals for treatment of HBV infections: Adefovir dipivoxil, Entecavir, Telbivudine, Tenofovir alafenamide, Tenofovir disoproxil fumarate, Lamivudine, and Bulevirtide
- Antivirals for treatment of HCV infections: Asunaprevir, Beclabuvir, Boceprevir, Coblopasvir, Daclatasvir, Dasabuvir, Elbasvir, Faldaprevir, Glecaprevir, Grazoprevir, Ledipasvir, Ombitasvir, Paritaprevir, Pibrentasvir, Ribavirin, Ritonavir, Simeprevir, Sofosbuvir, Telaprevir, Velpatasvir and Voxilaprevir

Details of exposure are described in Table 7.

Table 7. Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Incident with respect to…[3]	Measurement characteristics/ validation	Source of algorithm
Interferon or any of the specific antivirals of interest	Preliminary list provided in 8.6.1 section.	[-Inf., ID]	Calendar year	Biobank, primary and secondary care	RxNorm	n/a	All patients diagnosed with chronic HBV/HCV infection in the database during the study period	Previous use of interferon or any of the specific antivirals of interests	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable; [2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter); [3] Provide brief description on what patients is required to be incident to (e.g. when identifying incident users of drug, requirement may be that the patient is incident with respect to that drug).

8.6.2. Outcome/s (where relevant)

n/a

8.6.3. Other covariates, including confounders, effect modifiers and other variables (where relevant)

The study covariates for stratification will include:

- Calendar year
- Age categories:
  - Children and adolescents: 1-17
  - Young adults: 18-44
  - Middle aged adults: 45-64
  - Older adults: 65 and over
- Sex: male of female

A list of pre-specified comorbidities and comedication will be used for large-scale patient characterisation, identified as concept codes/descendants.

The following conditions will be of interest (i.e., frequency of comorbidities will be assessed at index date):

- Liver cirrhosis
- Alcoholic fatty liver
- Human immunodeficiency virus infection
- Sexually transmitted disease
- Diabetes mellitus
- Cardiovascular disease
- Hypertension
- Chronic kidney disease (CKD)
- Alcoholism

The following medication will be of interest: Top 10 prevalent drugs in each data source.

Large-scale characterisation of baseline characteristics: the operational definition of the covariates is described in the Table 8 below. Index date is the start of the (first) incident prescription during the study period. From this large-scale characterisation, we will report the top 10 of most frequent comorbidities.

Table 8. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Comorbidities	Large-scale patient-level characterisation of new users with regard to underlying comorbidities	Counts	At index date (ID) and 365 days before ID	Primary care, secondary care and biobank	SNOMED	n/a	Persons with new use during the study period	n/a	n/a
Concomitant medication	Large-scale patient-level characterisation of new users with regard to concomitant medication	Counts	At index date (ID) and 365 days before ID	Primary care, secondary care and biobank	RxNorm	n/a	Persons with new use during the study period	n/a	n/a

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

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

8.6.1 Study size

No sample size has been calculated for this study, as our primary focus is to describe characteristics of patients with chronic HBV/HCV infection, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of person counts with chronic HBV/HCV infection range from 200 (CPRD GOLD) to 14,700 (IQVIA DA Germany) for HBV and from 200 (IPCI) to 17,000 (IQVIA DA Germany) for HCV infection.

8.7 Analysis

This section will describe the details of the analysis approach and rationale for the choice of analysis, with reference to the Draft Catalogue of Data Analysis which describes the type of analysis in function of the study type.

Table 9. Description of Study Types and Type of analysis

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Population level DUS	Off-the-shelf (C1)	- number and percentage of users of Peginterferon or any of the specific antivirals of interest
Patient Level DUS	Off-the-shelf (C1)	- Characterisation of patient-level features
Population-level descriptive epidemiology	Off-the-shelf (C1)	- Proportion of patients with chronic HBV/HCV infection

8.7.1 Federated Network Analyses

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics are performed on a subset of the data sources or on a simulated set of patients and quality control checks are performed. Once all the tests are passed, the final package is released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally execute the analytics against the OMOP-CDM in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

The study results of all data sources are checked after which they are made available to the team in the Digital Research Environment (DRE) and the Study Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

8.7.2 Patient privacy protection

Cell suppression will be applied as required by databases to protect people's privacy. Cell counts < 5 will be masked.

8.7.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package "*DrugUtilization*" for the patient-level drug utilization analyses including patient-level characterization, and "*PatientProfile"* package for the population-level estimation of drug utilization and the proportion of chronic HBV/HCV infections.

Drug exposure calculations

Drug eras will be defined as follows: Exposure starts at date of the first prescription, e.g., the index date the person entered the cohort. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 30 days. The time between the two joined eras will be considered as exposed by the first era as shown in **Figure 1**, first row. Note: dose is not considered for this study.

Gap era joint mode	**Schematics**	**Dose in between**	**Cumulative dose**	**Cumulative time**
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

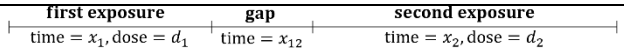

Figure 1: Gap era joint mode

New user cohorts

New users will be selected based on their first prescription of the respective drug of interest after the start of the study. New users will be required to not have been exposed to the drug of interest anytime prior to the current prescription. If the start date of a prescription does not fulfil the exposure washout criteria of 365days of no use, the whole exposure is eliminated.

8.7.4 Methods to derive parameters of interest

Calendar time

Calendar time will be based on the calendar year of the index prescription.

Age

Age at index date (date of diagnosis of chronic HBV/HCV or date of new prescribing of the drug of interest) will be calculated using January 1st of the year of birth as proxy for the actual birthday. Age categories are as following:

- Children and adolescents: 1-17
- Young adults: 18-44
- Middle aged adults: 45-64
- Older adults: 65 and over

Sex

Results for population-level analyses will be presented stratified by sex.

Characterization of patient-level features

Objective 3: Large scale patient characterisation before/on index date (= date of prescription) will be provided for patients with chronic HBV/HCV infection initiating treatment with interferon or any of the specific antivirals of interest. In these patients, the number and proportion of patients with the comorbidities and drugs of interest (see section on covariates) will be described at index date and in the one year prior to the index date (-365 to -1 day before index date).

8.7.5 Methods to derive parameters of interest

8.7.5.1 Proportion calculation

Proportion calculations will be conducted separately for interferon or any of the specific antivirals of interest.

Proportion calculations

Objective 1: Proportion will be calculated by dividing the number of patients with chronic HBV/HCV infection who initiate treatment with interferon or any specified antivirals by the total number of patients with chronic HBV/HCV infection at a particular time point.

Methodology for Proportion Calculation:

Numerator: the number of patients with chronic HBV/HCV infection who initiate treatment with interferon or the specified antivirals during the specified time period.

Denominator: the total number of patients with chronic HBV/HCV infection at the same particular time point.

Proportion (%) = (Number of Patients Initiating Treatment / Total Number of Patients with Chronic HBV/HCV Infection) * 100

Objective 2: Proportion will be calculated by dividing the number of patients with chronic HBV/HCV infection that underwent treatment with interferon or any specified antivirals by the total number of patients with chronic HBV/HCV infection at a particular time point.

Methodology for Proportion Calculation:

Numerator: the number of patients with chronic HBV/HCV infection that underwent treatment with interferon or the specified antivirals during the specified time period.

Denominator: the total number of patients with chronic HBV/HCV infection at the same particular time point.

Proportion (%) = (Number of Patients That Underwent Treatment / Total Number of Patients with Chronic HBV/HCV Infection) * 100

Objective 4: Proportion will be calculated by dividing the number of patients with chronic HBV/HCV infection by the total number of individuals present in each data source at a particular time point.

Methodology for Proportion Calculation:

Numerator: the number of patients with chronic HBV/HCV infection during the specified time period.

Denominator: the total number of individuals present in each data source at the same particular time point.

Proportion (%) = (Total Number of Patients with Chronic HBV/HCV Infection / Total Number of Individuals present in each data source) * 100.

8.7.5.2 Minimum cell count of 5

For all analyses, results will be reported with a minimum cell count of 5, and any counts smaller than 5 will be obscured to ensure privacy and confidentiality.

8.8 Sensitivity analyses

None

8.9 Missing data

For this study, data from real world databases are used implying that data as available within the database is collected as part of patient management and covariates such as medical comorbidity are not systematically recorded in the same way for each individual patient. Also there might be differences in recording of data between the different databases, for instance where details of recording might depend on reimbursement criteria. This will be explored by comparing the proportion of comorbidity and use of concomitant drugs between databases.

The population as included within these real-world databases is dynamic meaning that patients might enter and leave the database at every moment in time. Differences in follow-up time will be explored by providing the median follow-up time, by database, of individuals diagnosed with chronic HBV/HCV.

8.10 Evidence synthesis

Results from analyses described in section 8.7 **Error! Reference source not found.** will be presented s eparately for each database and no meta-analysis of results will be conducted.

9 DATA MANAGEMENT

9.1 Data management

All databases are mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org .

The analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain

aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.2 Data storage and protection

For this study, participants from various EU member states will process personal data from patients which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.
All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.
The output files are stored in the DARWIN Digital Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

10 QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining cohorts for drugs, a systematic search of possible codes for inclusion will be identified using *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, *DrugExposureDiagnostics* (19) will be run if needed to assess the use of different codes across the databases contributing to the study.

The study code will be based on two R packages namely the *PatientProfile* package and the *DrugUtilisation* Package. These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

11 LIMITATIONS OF THE RESEARCH METHODS

The study will be informed by routinely collected health care data and several considerations should be mentioned. The data is sourced from specific clinical databases in different countries, potentially limiting the generalizability of findings to a broader population. Therefore, the study population may not be entirely representative of the entire population of individuals with chronic HBV/HCV infections. Differences in healthcare systems, guidelines, and access to treatments across countries may impact the choice of treatment modalities. This could potentially introduce variability in treatment initiation. Additionally, changes in treatment guidelines and practices over time may impact the interpretation of trends in treatment initiation and characteristics of patients.

12 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analyzed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfill the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices.

13 GOVERNANCE BOARD ASPECTS

All data sources require approval from their respective IRB board, with the exception of IQVIA DA Germany which will not require any further specific approvals to undertake this study.

A PDF report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

14 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

14.1 Study Report

A study report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the study report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

15 OTHER ASPECTS

n/a

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ANNEXES

Appendix I: List of Stand-Alone documents (e.g. lists with concept definitions (conditions & drugs), validation procedures, questionnaires etc.)

Appendix II: ENCePP checklist for study protocols

17 APPENDIX I – LIST WITH PRELIMINARY CONCEPT DEFINITIONS

Preliminary list – list to be reviewed once protocol approved and prior to parametrisation of study code (using phenotype deck)

Peginterferon or any of the specific antivirals of interests

Concept ID	Therapeutic Drug Class	ATC Code
	Peginterferon	
45893501	Cepeginterferon alfa-2b	L03AB14
21603868, 21603870	Peginterferon -α-2a	L03AB11, L03AB61
21603867, 21603869	Peginterferon -α-2b	L03AB10, L03AB60
-	Peginterferon alfacon-2	L03AB16
21603861	Interferon alfa-2a	L03AB04
21603862	interferon alfa-2b	L03AB05
	Antivirals for treatment of HCV infections	
1501793	Ribavirin	J05AP01
1501770	Telaprevir	J05AP02
1501762	Boceprevir	J05AP03
1502088	Faldaprevir	J05AP04
1501782	Simeprevir	J05AP05
1501772	Asunaprevir	J05AP06
1501785	Daclatasvir	J05AP07
1501783	Sofosbuvir	J05AP08
1501880	Dasabuvir	J05AP09
715916	Elbasvir	J05AP10
715917	Grazoprevir	J05AP11
-	Coblopasvir	J05AP12
1501784	Sofosbuvir and ledipasvir	J05AP51
1502013	Dasabuvir, ombitasvir, paritaprevir and ritonavir	J05AP52
1501771	Ombitasvir, paritaprevir and ritonavir	J05AP53
1502105	Elbasvir and grazoprevir	J05AP54
1502106	Sofosbuvir and velpatasvir	J05AP55
1501776	Sofosbuvir, velpatasvir and voxilaprevir	J05AP56
715779	Glecaprevir and pibrentasvir	J05AP57
715845	Daclatasvir, asunaprevir and beclabuvir	J05AP58
	Antivirals for treatment of HBV infections	
21603167	Adefovir dipivoxil	J05AF08
21603169	Entecavir	J05AF10
21603170	Telbivudine	J05AF11

1123612	Tenofovir alafenamide	J05AF13
21603166	Tenofovir disoproxil fumarate	J05AF07
21603164	Lamivudine	J05AF05
947866	Bulevirtide	J05AX28

Chronic HBV infection (SNOMED-CT code list)

Concept ID	Concept name
192240	Chronic viral hepatitis B with hepatitis D
4009793	Chronic aggressive type B viral hepatitis
4173584	Chronic active type B viral hepatitis
4296554	Chronic persistent type B viral hepatitis
37017654	Occult chronic type B viral hepatitis
439674	Chronic viral hepatitis B without delta-agent
	Congenital viral hepatitis B infection
194574	Chronic type B viral hepatitis
4308946	Hepatic coma due to chronic hepatitis B
4308946	Hepatic coma due to viral hepatitis B
4340379	Hepatitis B carrier
	Hepatitis B screening positive
197493	Hepatitis D superinfection of hepatitis B carrier
198683	Viral hepatitis B without hepatic coma
4281232	Type B viral hepatitis
40483136	Hepatitis B and C

Chronic HCV infection (SNOMED-CT code list)

Concept id	Concept name
45769525	Chronic active hepatitis C
3654685	Chronic hepatitis B co-occurrent with hepatitis C and hepatitis D
198964	Chronic hepatitis C
35625141	Chronic hepatitis C caused by Hepatitis C virus genotype 1
35625296	Chronic hepatitis C caused by Hepatitis C virus genotype 1a
35625295	Chronic hepatitis C caused by Hepatitis C virus genotype 1b
35625139	Chronic hepatitis C caused by Hepatitis C virus genotype 2
35625040	Chronic hepatitis C caused by Hepatitis C virus genotype 3
35625140	Chronic hepatitis C caused by Hepatitis C virus genotype 4
35624867	Chronic hepatitis C caused by hepatitis C virus genotype 5
35624866	Chronic hepatitis C caused by hepatitis C virus genotype 6
3654682	Chronic hepatitis C co-occurrent with human immunodeficiency virus infection
45766656	Chronic hepatitis C with stage 2 fibrosis
45757726	Chronic hepatitis C with stage 3 fibrosis

Concept id	Concept name
763021	Chronic viral hepatitis C with hepatic coma
43531723	Cirrhosis of liver due to chronic hepatitis C
4268705	Finding of Hepatitis C status
45757360	Glomerulonephritis due to hepatitis C
46270142	Hepatic coma due to chronic hepatitis C
439672	Hepatic coma due to viral hepatitis C
40483136	Hepatitis B and hepatitis C
4154688	Hepatitis C antibody positive with elevated ALT
4196134	Hepatitis C antibody test positive
4340380	Hepatitis C carrier
44809233	Hepatitis C genotype 1
44809234	Hepatitis C genotype 2
44809236	Hepatitis C genotype 3
44809237	Hepatitis C genotype 4
44809238	Hepatitis C genotype 5
44809239	Hepatitis C genotype 6
44805040	Hepatitis C resolved
44792611	Hepatitis C screening positive
4234024	Hepatitis C viral ribonucleic acid polymerase chain reaction negative
44813294	Hepatitis C viral ribonucleic acid polymerase chain reaction positive
4227247	Hepatitis C virus enzyme-linked immunosorbent assay test positive
4153375	PCR positive for hepatitis C viral RNA (genotype 1A)
46273598	Polymerase chain reaction test for Hepatitis C positive
45773146	Reactivation of hepatitis C viral hepatitis

Hypertension (SNOMED-CT code list)

Concept ID	Concept name
320128	Essential hypertension

Cardiovascular disease (SNOMED-CT code list)

concept_id	concept_name
134057	Disorder of cardiovascular system

Diabetes mellitus (SNOMED-CT code list)

concept_id	concept_name
201820	Diabetes mellitus
4322638	Diabetes mellitus AND insipidus with optic atrophy AND deafness
4143529	Diabetes mellitus associated with cystic fibrosis
4245270	Diabetes mellitus associated with genetic syndrome
4240589	Diabetes mellitus associated with hormonal etiology

concept_id	concept_name
4178452	Diabetes mellitus associated with pancreatic disease
4178790	Diabetes mellitus associated with receptor abnormality
42537681	Diabetes mellitus caused by chemical
765478	Diabetes mellitus caused by drug without complication
4144583	Diabetes mellitus due to cystic fibrosis
43531011	Diabetes mellitus due to genetic defect in beta cell function
43531642	Diabetes mellitus due to genetic defect in insulin action
4192852	Diabetes mellitus due to insulin receptor antibodies
45757077	Diabetes mellitus due to pancreatic injury
4237068	Diabetes mellitus due to structurally abnormal insulin
443012	Diabetes mellitus during pregnancy - baby delivered
192691	Diabetes mellitus during pregnancy - baby not yet delivered
4058243	Diabetes mellitus during pregnancy, childbirth and the puerperium
45757129	Diabetes mellitus in mother complicating childbirth
194700	Diabetes mellitus in mother complicating pregnancy, childbirth AND/OR puerperium
4079850	Diabetes mellitus in neonate small for gestational age
45766050	Diabetes mellitus in remission
4062685	Diabetes mellitus in the puerperium - baby delivered during current episode of care
4062686	Diabetes mellitus in the puerperium - baby delivered during previous episode of care
4235410	Diabetes mellitus induced by non-steroid drugs
4136889	Diabetes mellitus induced by non-steroid drugs without complication
45757674	Diabetes mellitus type 1 without retinopathy
36684827	Diabetes mellitus type 2 with periodontal disease
45757474	Diabetes mellitus type 2 without retinopathy
44793113	Diabetes mellitus with multiple complications
4008576	Diabetes mellitus without complication
43531645	Diabetes mellitus, transient neonatal 1
43531019	Diabetes mellitus, transient neonatal 2
43531020	Diabetes mellitus, transient neonatal 3
4129516	Diabetes-deafness syndrome maternally transmitted
4046332	Diabetic acute painful polyneuropathy
37312019	Diabetic cardiomyopathy
35625719	Diabetic cataract of bilateral eyes
4033942	Diabetic dermopathy
4087682	Diabetic foot
4159742	Diabetic foot ulcer
4137220	Diabetic glomerulonephritis

concept_id	concept_name
4114426	Diabetic hand syndrome
37018912	Diabetic hand syndrome due to type 2 diabetes mellitus
4164175	Diabetic intraretinal microvascular anomaly
443727	Diabetic ketoacidosis
4009303	Diabetic ketoacidosis without coma
37110068	Diabetic mastopathy
4048028	Diabetic mononeuropathy
4262282	Diabetic mononeuropathy multiplex
4234742	Diabetic neuropathy with neurologic complication
4151453	Diabetic optic papillopathy
4311708	Diabetic peripheral neuropathy
44805628	Diabetic retinopathy detected by national screening programme
4082347	Diabetic thick skin syndrome
4047906	Insulin dependent diabetes mellitus type 1A
4102018	Insulin dependent diabetes mellitus type 1B
45769875	Insulin reactive hypoglycemia due to type 2 diabetes mellitus
4129524	Insulin resistance - type A
4129525	Insulin resistance - type B
4130162	Insulin treated type 2 diabetes mellitus
43531006	Maturity onset diabetes of the young, type 1
4130164	Maturity onset diabetes of the young, type 2
43531640	Maturity-onset diabetes of the young
43531017	Maturity-onset diabetes of the young, type 10
43531018	Maturity-onset diabetes of the young, type 11
43531012	Maturity-onset diabetes of the young, type 3
43531013	Maturity-onset diabetes of the young, type 4
43531014	Maturity-onset diabetes of the young, type 5
43531643	Maturity-onset diabetes of the young, type 6
43531015	Maturity-onset diabetes of the young, type 7
43531644	Maturity-onset diabetes of the young, type 8
43531016	Maturity-onset diabetes of the young, type 9
37204818	Myopathy and diabetes mellitus
193323	Neonatal diabetes mellitus
44793114	Pre-existing diabetes mellitus
45757079	Pre-existing diabetes mellitus in mother complicating childbirth
43531007	Pre-existing diabetes mellitus in pregnancy
4062687	Pre-existing malnutrition-related diabetes mellitus
606039	Pre-existing malnutrition-related diabetes mellitus in pregnancy
4063042	Pre-existing type 1 diabetes mellitus
43531008	Pre-existing type 1 diabetes mellitus in pregnancy

concept_id	concept_name
4063043	Pre-existing type 2 diabetes mellitus
43531010	Pre-existing type 2 diabetes mellitus in pregnancy
201254	Type 1 diabetes mellitus
4099215	Type 1 diabetes mellitus maturity onset
40484648	Type 1 diabetes mellitus uncontrolled
40484649	Type 1 diabetes mellitus well controlled
4152858	Type 1 diabetes mellitus with arthropathy
4099214	Type 1 diabetes mellitus with ulcer
443412	Type 1 diabetes mellitus without complication
201826	Type 2 diabetes mellitus
45757508	Type 2 diabetes mellitus controlled by diet
4230254	Type 2 diabetes mellitus in nonobese
4304377	Type 2 diabetes mellitus in obese
40485020	Type 2 diabetes mellitus well controlled
4200875	Type 2 diabetes mellitus with peripheral angiopathy
4099651	Type 2 diabetes mellitus with ulcer
4193704	Type 2 diabetes mellitus without complication
45766051	Type I diabetes mellitus in remission
45766052	Type II diabetes mellitus in remission
40482801	Type II diabetes mellitus uncontrolled

Liver Cirrhosis (SNOMED-CT code list)

concept_id	concept_name
4048083	Advanced cirrhosis
196463	Alcoholic cirrhosis
4055212	Bacterial portal cirrhosis
192675	Biliary cirrhosis
4059289	Biliary cirrhosis of children
4058681	Capsular portal cirrhosis
4049282	Cholangiolitic cirrhosis
44805713	Cirrhosis associated with cystic fibrosis
194692	Cirrhosis - non-alcoholic
4064161	Cirrhosis of liver
37111265	Cirrhosis of liver caused by amiodarone
37117933	Cirrhosis of liver caused by methotrexate
37111266	Cirrhosis of liver caused by methyldopa
43531723	Cirrhosis of liver due to chronic hepatitis C
45772057	Cirrhosis of liver due to hepatitis B
42539566	Cirrhosis of liver with primary sclerosing cholangitis
4153294	Cirrhosis secondary to cholestasis

concept_id	concept_name
4292401	Clonorchiasis with biliary cirrhosis
4163687	Cruveilhier-Baumgarten syndrome
4232955	Cryptogenic cirrhosis
37396401	Decompensated cirrhosis of liver
4055210	Diffuse nodular cirrhosis
4143008	Drug-induced cirrhosis of liver
4159158	Early cirrhosis
4058680	Fatty portal cirrhosis
4294539	Florid cirrhosis
4203601	Glissonian cirrhosis
4340946	Hypoxia-associated cirrhosis
37396157	Idiopathic copper associated cirrhosis of liver
4268006	Indian childhood cirrhosis
4340393	Infectious cirrhosis
4144116	Juvenile portal cirrhosis
4340392	Laennec's cirrhosis, non-alcoholic
4049419	Latent cirrhosis
605193	Liver cirrhosis due to classical cystic fibrosis
3185452	Liver cirrhosis secondary to nonalcoholic steatohepatitis
4184779	Macronodular cirrhosis
4071022	Micronodular cirrhosis
4050640	Mixed micro and macronodular cirrhosis
4148254	Multilobular portal cirrhosis
44783142	North American Indian childhood cirrhosis
4048057	Nutritional cirrhosis
4003673	Obstructive biliary cirrhosis
4140536	Parasitic cirrhosis
4059285	Pigmentary portal cirrhosis
4300060	Pigment cirrhosis
4304584	Portal cirrhosis
4098583	Posthepatitic cirrhosis
4313567	Postnecrotic cirrhosis
3183806	Postviral gastroparesis
4135822	Primary biliary cholangitis
37399445	Reynolds syndrome
4046123	Secondary biliary cirrhosis
4053079	Syphilitic cirrhosis
4058682	Syphilitic portal cirrhosis
4046016	Toxic cirrhosis
4059287	Toxic portal cirrhosis

concept_id	concept_name
4055209	Unilobular portal cirrhosis

Chronic kidney disease (CKD) (SNOMED-CT code list)

Concept id	Name
36717349	Chronic kidney disease due to systemic infection
36716455	Chronic kidney disease due to traumatic loss of kidney
36716947	Chronic renal insufficiency
36716184	Chronic kidney disease following donor nephrectomy
36717534	Chronic kidney disease following excision of renal neoplasm
37017104	Chronic kidney disease mineral and bone disorder
764011	Benign hypertensive heart disease and chronic renal disease
45773688	Chronic kidney disease due to type 1 diabetes mellitus
44782429	Chronic kidney disease due to hypertension
43531578	Chronic kidney disease due to type 2 diabetes mellitus
443597	Chronic kidney disease stage 3
443601	Chronic kidney disease stage 2
443614	Chronic kidney disease stage 1
443612	Chronic kidney disease stage 4
443611	Chronic kidney disease stage 5
198185	Chronic renal failure

Human immunodeficiency virus infection (SNOMED-CT code list)

concept_id	concept_name
439727	Human immunodeficiency virus infection

Alcoholic fatty liver disease (SNOMED-CT code list)

concept_id (and descendents)	concept_name
193256	Alcoholic fatty liver

Sexually transmitted disease (SNOMED-CT code list)

concept_id (and descendants)	concept_name
440647	Sexually transmitted infectious disease

Alcoholism (SNOMED-CT code list)

concept_id (and descendants)	concept_name
4218106	Alcoholism

18 APPENDIX II – ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:
DARWIN EU® - Characterization of patients with chronic hepatitis B and C

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6, 7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

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

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, proportion)	☒	☐	☐	8.8
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2/8.5
4.2	Is the planned study population defined in terms of:				8.5
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	8.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorized according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☐	☒	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	8.6
6.2	Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	

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

Comments:

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

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.6
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	8.6
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.6
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	8.6
	9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.6
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.6
	9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	8.6

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	8.7
10.3 Are descriptive analyses included?	☒	☐	☐	8.8
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	10.0
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.1 Selection bias?	☒	☐	☐	11
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	12, 13
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.2

Comments:

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

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	14

Comments:

Name of the main author of the protocol: Katia Verhamme

Date: 6th December 2023

Signature: