



Clinical Study Protocol

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Title: Real-World Evidence on Diagnosed Gastroparesis in Europe: Multi-database observational epidemiological study

Study Number: TAK-906-5003

Document Version and Date: Version 1.0, 31 July 2020

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**NON-INTERVENTIONAL STUDY
PROTOCOL**

Study title: Real-World Evidence on Diagnosed Gastroparesis in Europe: Multi-Database Observational Study

Study number: TAK-906-5003

Version number: 1.0 (31 July 2020)

Ethics statement: This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

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Signature page

Study title: Real-World Evidence on Diagnosed Gastroparesis in Europe: Multi-database observational epidemiological study

Study number: TAK-906-5003

Version number: 1.0 (31 July 2020)

Sponsor - Takeda Pharmaceuticals

Signature and Date (DD/Month/YYYY)

_____, GI Global Evidence and Outcomes

_____, GI-Motility Global Evidence and Outcomes

08 / 10 / 2020

Vendor Investigator

RWI Nordics, IQVIA

08 / 13 / 2020

STUDY INFORMATION

Title	Real-World Evidence on Diagnosed Gastroparesis in Europe: Multi-database observational epidemiological study
Protocol version identifier	1.0
Date of last version of protocol	31 July 2020
Marketing authorisation holder(s)	Takeda Pharmaceuticals International Co. 40 Landsdowne Street Cambridge, MA, 02139
Objectives	Information on the occurrence and characteristics of patients with gastroparesis in Europe is scarce and additional investigations are needed. The primary objectives of this study are: • To assess the incidence and prevalence of gastroparesis in the adult, pediatric, and overall populations in countries of interest. • To describe patients with gastroparesis in terms of characteristics and natural history of disease, including socio-demographic characteristics, etiologic factors, clinical characteristics, diagnostic practices, and treatment practices.
Country(-ies) of study	Finland and Spain
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TABLE OF CONTENTS

1.0	LIST OF ABBREVIATIONS	7
2.0	RESPONSIBLE PARTIES	9
3.0	AMENDMENTS AND UPDATES.....	10
4.0	MILESTONES	11
5.0	RATIONALE AND BACKGROUND.....	12
6.0	OBJECTIVES	14
7.0	RESEARCH METHODS	15
7.1	Study design.....	15
7.2	Setting	15
7.2.1	Study population	15
7.2.2	Study time frames	16
7.2.3	Source population	17
7.2.4	Analysis population	17
7.3	Variables	19
7.3.1	Case definitions.....	19
7.3.2	Demographic and clinical characteristics	22
7.4	Data sources	23
7.5	Study size	25
7.6	Data management.....	26
7.7	Data analysis	26
7.7.1	Incidence	27
7.7.2	Prevalence	27
7.7.3	Descriptive analysis of cases of gastroparesis	27
7.7.4	Validation of cases of gastroparesis.....	27
7.7.5	Sensitivity analyses	29
7.8	Quality control	29
7.9	Limitations of the research methods	30
8.0	PROTECTION OF HUMAN SUBJECTS	34
9.0	MANAGEMENT AND REPORTING OF ADVERSE EVENTS	35
9.1	Definitions.....	35
9.2	Collection and notifying of Adverse Events, Special Situation Reports and Product Quality Issues to Takeda Pharmacovigilance.....	36
10.0	PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	38
11.0	REFERENCES	39
Annex 1	List of stand-alone documents	42
Annex 2	ENCePP checklist	42

1.0 LIST OF ABBREVIATIONS

AE	Adverse event
ADR	Adverse drug reaction
ATC	The Anatomical Therapeutic Chemical Classification System
AvoHILMO	Register of Primary Health Care Visits (Finland)
CI	Confidence interval
EGG	Cutaneous electrogastrography
EHR	Electronic Health Records
EMR	Electronic Medical Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
HILMO	Care Register for Health Care (Finland)
HUS	The Hospital District of Helsinki and Uusimaa, including Helsinki University Hospital
GEBT	Gastric Emptying Breath Test
GES	Gastric Emptying Scintigraphy
GI	Gastrointestinal
GVP	Guideline on Good Pharmacovigilance Practices
IBD	Inflammatory bowel disease
ICD-9-CM	International Statistical Classification of Diseases and Related Health Problems, 9 th revision, Clinical modification
ICD-9-PCS	International Classification of Diseases, 9 th Revision, Procedure Coding System
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10 th revision
ICPC-2	International Classification of Primary Care, Second edition
ICH	International Conference on Harmonisation
IBD	Inflammatory bowel disease
ISPE GPP	Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology
KOL	Key Opinion Leader
KUH	Kuopio University Hospital
LOC	Local Operating Company
LPD	QuintilesIMS Longitudinal Health Search Database (Spain)
MBDS	Spanish Minimum Basic Dataset
MRI	Magnetic Resonance Imaging
NCSP	NOMESCO Classification of Surgical Procedures
NOMESCO	Nordic Medico-Statistical Committee
NOS	Not otherwise specified
NPV	Negative predictive value
PPV	Positive predictive value
PSSHHP	Hospital District of North Savo
PQI	Product Quality Issue
RWE	Real World Evidence
SAE	Serious adverse event
SPAT	Finnish classification of functions in outpatient primary health care
SPECT	Single-Photon Emission Computed Tomography
SSR	Special situation report

THL	National Institute for Health and Welfare
UK	United Kingdom
U.S.	United States
WMC	Wireless motility capsule

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2.0 RESPONSIBLE PARTIES

The Market Authorization Holder has contracted the management of this study to IQVIA.

Principal Investigator: [REDACTED], [REDACTED], RWI Nordics, IQVIA

Co-investigators who substantially contributed to the study concept and design:

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3.0 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	<date>	<text>	<text>	<text>
2	<date>	<text>	<text>	<text>
...	<date>	<text>	<text>	<text>

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4.0 MILESTONES

Milestone	Planned date	Actual date	Comments
Study Protocol finalization	Q3 2020	TBC	
SAP finalization	Q4 2020	TBC	
Registration in the EU-PAS register	Q3-Q4 2020	TBC	After protocol finalization and approval
Start of data collection	Q2 2021	TBC	NA
End of data collection	Q3 2021	TBC	NA
Study Report I ready	Q1 2022	TBC	
Full-scale study report	Q2 2022	TBC	Primary objectives
<i>Optional exploratory objectives</i>			
Start of data collection	Q3 2022	TBC	Following assessment of primary objective outcome and approval to proceed
End of data collection	Q3 2023	TBC	NA
Final report of study results	Q4 2023 ^a	TBC	Study Report 2 (optional exploratory objectives)

^a To be finally defined following optional exploratory objective study approval

5.0 RATIONALE AND BACKGROUND

Gastroparesis is a chronic motility disorder characterized by delayed gastric emptying in the absence of mechanical obstruction (1). The main symptoms include early satiety, nausea, vomiting, bloating, and upper abdominal pain (2). In severe cases, gastroparesis may be associated with prominent dehydration, malnutrition, and weight loss (3,4). Gastroparesis may result from several different etiologies, the most common being idiopathic causes and diabetes, followed by Parkinson's disease, collagen vascular disorders, and intestinal pseudo-obstruction (3,5). Other etiologies are known to include medical intervention (iatrogenic or surgical) and viral or bacterial infection (6). Gastroparesis is a serious disorder associated with impaired quality of life and a substantially increased risk of morbidity and mortality (4,7,8).

The occurrence of symptoms, test finding of delayed gastric emptying, and the absence of other explanations for the symptoms are central for the clinical diagnosis of gastroparesis (9). Because the main symptoms of gastroparesis in large part overlap with those of other dyspeptic disorders (e.g. peptic ulcer and functional dyspepsia), definite diagnosis of gastroparesis can only be made after thorough clinical evaluation, including documentation of delayed gastric emptying (6). Gastric emptying scintigraphy following a standardized meal is commonly recognized as the gold-standard in evidence required for diagnosis of gastroparesis (10,11). Accordingly, given the thorough clinical assessment typically required for diagnosis, the epidemiological evidence on the occurrence and natural history of gastroparesis has primarily been restricted to case-series and studies in small hospital-based cohorts, with a paucity of studies conducted in the community setting. Consequently, the prevalence, incidence, and natural history of gastroparesis in the general unselected population is largely unknown (12).

Among the few population-based investigations that have been published, a recent United States (U.S.) study based on electronic health records (EHR) data reported a prevalence of 0.16%, without standardization for demographic variables (13). Notably, however, the vast majority of patients (85.8%) with gastroparesis did not have documentation of diagnostic testing, which may indicate potential for misclassification (13,14). Another U.S. study based on linked medical records from one county in Minnesota observed a prevalence of cases classified as definite gastroparesis of 24.2 per 100,000 (0.02%) persons and an incidence of 6.3 per 100,000 person-years (8). The study limitations included potential for disease misclassification, lack of ethnic representativeness (approximately 90% of the study population were white), and other potential sources of non-representativeness that may accompany the use of regional medical center data. Another small population-based study conducted in the same U.S. county observed a prevalence of gastroparesis of 5.2% in patients with type 1 diabetes, 1.0% in patients with type 2 diabetes, and 0.2% among selected control patients (15). In a study conducted to assess the prevalence of hidden gastroparesis in the community, delayed gastric emptying was observed in 1.8% of the participants, which was substantially higher than the observed prevalence of diagnosed gastroparesis (0.02%), indicating that a large proportion of patients with gastroparesis may not be diagnosed (15,16). The evidence on the occurrence of gastroparesis in Europe (EU) is limited. However, in a recent study in the Clinical Practice Research Datalink (CPRD), the age- and sex-standardized prevalence of gastroparesis based on general practice records in the UK was 13.8 per 100,000 persons and the corresponding incidence rate 1.5 to 1.9 per 100,000 person-years (17). The evidence on natural history and occurrence of gastroparesis in the pediatric population is similarly very limited.

Given the sparsity of epidemiological data, there is an urgent need to improve the understanding of gastroparesis in Europe, both in terms of occurrence and patient population characteristics. Therefore, we will conduct a bi-national, multi-database, retrospective study to investigate the prevalence, incidence, and natural history of gastroparesis in Finland and Spain. An optional

exploratory set of objectives may be addressed to assess the validity of the ascertainment of cases of gastroparesis at later time.

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6.0 OBJECTIVES

Primary objectives

The primary objectives are:

- To assess the incidence and prevalence of gastroparesis in the adult, pediatric, and overall populations in countries of interest.
- To describe patients with gastroparesis in terms of characteristics and natural history of disease, including socio-demographic characteristics, etiologic factors, clinical characteristics, diagnostic practices, and treatment practices.

The optional exploratory objectives are:

- To assess the validity of ascertainment of gastroparesis using the study case definition, with EMR chart review as the reference standard.
- To describe patients with gastroparesis identified in EMR chart review in terms of characteristics and natural history of disease, including socio-demographic characteristics, etiologic factors, clinical characteristics, diagnostic practices, and treatment practices and patterns.
- To assess the incidence and prevalence of gastroparesis, in the adult, pediatric, and overall population, adjusted for validation results from the EMR chart review.

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7.0 RESEARCH METHODS

7.1 Study design

This will be a real world evidence observational, bi-national, retrospective study using data from multiple structured secondary databases in Finland and Spain, to investigate the incidence and prevalence of gastroparesis and to describe the characteristics of patients with gastroparesis. The analyses will be conducted in the adult, pediatric, and overall patient populations. The primary objectives will be investigated separately in each database and patient population.

Cases of gastroparesis will be identified based on information on diagnoses and other clinical records, records of conducted tests and test results, procedures, and recorded pharmacological and non-pharmacological treatment. Potential cases will be classified into three categories, defined according to the likelihood of true gastroparesis: *definite*, *likely*, and *possible*. Separate analyses including cases identified using each definition will be conducted.

The optional explorative objectives – to assess the validity of case ascertainment – will be addressed provided that a sufficient number of cases are identified in the analyses of the primary objectives, to ensure that the validation is reliable and with adequate precision.

7.2 Setting

7.2.1 Study population

The study will be conducted based on routinely-collected secondary data from large healthcare databases in Finland and Spain. The study countries were selected based on a feasibility assessment including input from the Key Opinion Leaders (KOLs) and availability of data sources with (regional or national) representative coverage in different parts of Europe. In addition, the study databases were selected based on linkage capability (to other secondary data sources) and the availability of structured data on healthcare contacts, treatment, and other relevant information for the identification and characterization of patients with gastroparesis.

In Finland, the study will be conducted in a regional setting, based on hospital discharge electronic medical record (EMR) data from the Hospital District of Helsinki and Uusimaa (HUS) and the Hospital District of North Savo (PSSHP). Together, the two regions cover approximately 50% of the Finnish population. Regional hospital discharge EMR data will be linked to the national administrative and health registers, to create a study-specific database. The regional EMR data have complete coverage of secondary care for the respective hospital areas. The Finnish administrative and health registers have comprehensive national coverage for primary and secondary care (contacts and diagnoses in the inpatient and outpatient setting).

The data sources in Spain will include the QuintilesIMS Longitudinal Health Search Database (LPD) database and the Spanish Minimum Basic Data Set (MBDS). The LPD is a national database, covering primary care data for approximately 4% of the Spanish population (~2 million individuals). The MBDS is a national inpatient hospital discharge database with close to complete coverage (~95%) of hospital discharges in Spain (18–21).

All analyses will be conducted separately in each of the three databases (Finland, LPD, and MBDS). The Spanish study databases represent separate data sources that cannot be linked or combined.

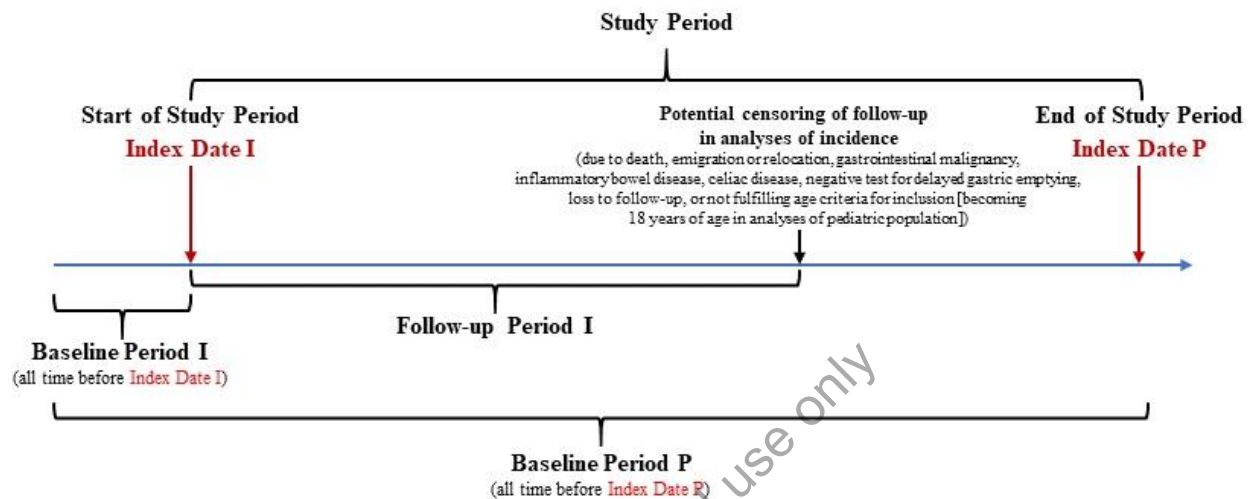
7.2.2 Study time frames

The **Study Period** will be defined according to the availability of data in each study database. The start of the study period will occur one year after the date of availability of complete data in

the specific database. The end date will be defined based on the last date of available data. In Finland the study period will be January 1, 2012-December 31, 2020 (or the date of most recent data available). In LPD and MBDS, the study period will be defined according to the date of the earliest and last record in each database.

An overview of the analytic study time frames is shown in **Figure 1**. It should be noted that separate time frames will be applied for the analyses of incidence and prevalence, respectively.

Figure 1. Overview of study time frames



Analyses of incidence

For the analyses of incidence, **Index Date I** will be defined as the date of the start of the Study Period or fulfilling the age criteria for inclusion, whichever occurs last. For the analyses in LPD, Index Date I may additionally occur at the earliest one year after enrollment in the database (not applicable to children less than one year of age at the date of enrollment), to ensure a minimum of baseline data before start of follow-up for each participant. **Baseline Period I** will include all time before Index Date I. **Follow-up Period I** will include all time between Index Date I and the date of the first occurrence of the following: fulfilling case definition criteria (**Section 7.3.1**), censoring (**Section 7.2.4.3**), or end of study period.

Analyses of prevalence

For the analyses of prevalence, **Index Date P** will be defined as the time point for prevalence assessment and will equal the end date of the study period in each specific study database. **Baseline Period P**, the time period during which case criteria are evaluated, will include all time before Index Date P.

Descriptive analyses of cases of gastroparesis

The descriptive analyses will include all incident cases of gastroparesis identified during Follow-up Period I; the time point for ascertainment will be the date when the case occurred, based on information ascertained during Baseline Period I and Follow-up Period I. The different characteristics included in the assessment are described in **Section 7.7.3** and

Annex 3.

7.2.3 Source population

The overall source populations for analyses in the different databases will be defined as below.

- Finland: all individuals residing in the HUS or PSSHP district (representing approximately 50% [~2.7 million inhabitants] of the country's population) at any time during the study period. The source population will be identified and ascertained using individual-level data from the Finnish national administrative registers.
- LPD: all individuals enrolled at any time during the study period, identified and ascertained using individual-level data from the database.
- MBDS: the entire population of Spain (~46.5 million). Because individual-level information on the entire Spanish population will not be included in the available data, the size of the source population (used to calculate the population denominator and the number of person-years of follow-up for analyses of prevalence and incidence) will be estimated based on publicly available Spanish census data.

7.2.4 Analysis population

The analysis populations for each database and patient population will be formed based on the source populations and a set of inclusion and exclusion criteria, as detailed below. Detailed definitions of the inclusion, exclusion and censoring criteria are provided in

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Annex 3. An illustration of the selection of the analysis population is shown in **Annex 4.**

7.2.4.1 Inclusion criteria for analysis population

Different criteria for inclusion and exclusion will be applied in the analyses of incidence and prevalence.

For the analyses of incidence:

- Part of the source population at any time during the Study Period
- Available information on sex and date of birth
- For analyses of adult population: age ≥ 18 years at any time during the Study Period
- For analyses of pediatric population: age < 18 years at any time during the Study Period

For the analyses of prevalence:

- Part of the source population on Index Date P
- Available information on sex and date of birth
- Applicable to LPD only: availability of data for at least one year before Index Date P (not applicable to children less than one year of age at the time of Index Date P). This criterion will be included to take into account that participants may enroll in the LPD during the course of Baseline Period P, which could result in left truncation of data. Specifically, participants will be required to have enrolled (first record of contact) at least one year (≥ 365 days) before Index Date P. This requirement will ensure that there is a minimum time period during which prevalent cases at Index Date P can be identified.
- Applicable to LPD only: at least one record of contact in the previous two years (≤ 730 days) before Index Date P. This criterion will be included to take into account that participants may unenroll from the LPD during the course of Baseline Period P, which could result in right truncation of data. The requirement of at least one record of contact within two years will increase the likelihood that participants are truly enrolled in the LPD at the time of Index Date P.
- For analyses of adult population: age ≥ 18 years on Index Date P
- For analyses of pediatric population: age < 18 years on Index Date P

7.2.4.2 Exclusion criteria for analysis population

For the analyses of incidence:

- Fulfilling the case definition criteria at any time during Baseline Period I
- Gastrointestinal malignancy, inflammatory bowel disease (IBD), or celiac disease at any time before Index Date I. These criteria will be intended to remove patients with known or identifiable causes of gastroparesis symptoms or delayed gastric emptying.
- Negative test for delayed gastric emptying (normal or accelerated gastric emptying)

For the analyses of prevalence:

- Gastrointestinal malignancy, IBD, or celiac disease at any time before Index Date P. These criteria will be intended to remove patients with known or identifiable causes of gastroparesis symptoms or delayed gastric emptying. (normal or accelerated gastric emptying)

7.2.4.3 *Censoring and loss to follow-up*

Censoring criteria will be applied according to availability of data in each database. In Finland, information on date of death, relocation to hospital region other than HUS or PSSHP, and emigration will be available and included as censoring criteria. For the databases in Spain, comprehensive and detailed records of emigration or death will not be available. Withdrawal from the Finnish national registers and the nationwide MBDS database is not possible. For LPD, however, unenrollment (e.g. due to change in health care provider) is a possibility. Because information on date of unenrollment is not available, participants with no record of contact in two years will be assumed to have unenrolled and censored in the analyses.

For the analyses of incidence, the following censoring criteria will apply:

1. Applicable to Finland only: death
2. Applicable to Finland only: emigration or relocation to region other than HUS or PSSHP
3. Gastrointestinal malignancy, IBD, or celiac disease
4. Negative test for delayed gastric emptying (normal or accelerated gastric emptying).
5. Applicable to LPD only: loss to follow-up (no record of contact in two years)
6. Applicable to analyses of pediatric population only: no longer fulfilling the age inclusion criteria (i.e., becoming 18 years of age during Follow-up Period I)

For the analyses of prevalence, participants fulfilling any of the censoring criteria during Baseline Period P will not be included in the analysis population at Index Date P.

7.3 **Variables**

7.3.1 **Case definitions**

The ICD-10 classification, used in Finland and the MBDS (from 2016), does not provide a specific code for gastroparesis. In the ICD-9-CM classification, currently used in the LPD and previously used in the MBDS, gastroparesis is coded as 536.3. For this study, the classification of potential cases will rely on information on diagnoses and other clinical records, records of tests and test results, procedures, and recorded pharmacological and non-pharmacological treatment. The case definition will be based on a set of case criteria, each defined as a composite of different components; the definition of each criterion and the specific data sources used for ascertainment is provided in

Annex 3. An overview of the case definition criteria and the different components included in each criterion is provided in **Table 1**. Based on the different case criteria, each potential case will be classified as *definite*, *likely*, or *possible* gastroparesis.

The following three case definitions will be applied:

- Definite gastroparesis:
 - Main gastroparesis symptoms and delayed gastric emptying
- Likely gastroparesis:
 - Main gastroparesis symptoms and diagnosis of or treatment procedure for gastroparesis, but delayed gastric emptying unknown (i.e., absence of a record for a conducted test or absence of test result)
 - Delayed gastric emptying, but no record of main gastroparesis symptoms
- Possible gastroparesis:
 - Main gastroparesis symptoms, but delayed gastric emptying unknown and no diagnosis of or treatment procedure for gastroparesis, or
 - Diagnosis of or treatment procedure for gastroparesis, but no record of main gastroparesis symptoms and delayed gastric emptying unknown

In the analyses of prevalence, a test result showing no delayed gastric emptying (i.e., gastric emptying normal or accelerated) will classify the patient as not having gastroparesis, regardless of other criteria fulfilled. However, if a negative test is followed by a subsequent positive test, the patient will be classified in accordance with the latter (positive) test and the other criteria fulfilled. In the analyses of incidence, a test result showing no delayed gastric emptying (test negative) will be included as a censoring criterion (**Section 7.2.4.3**).

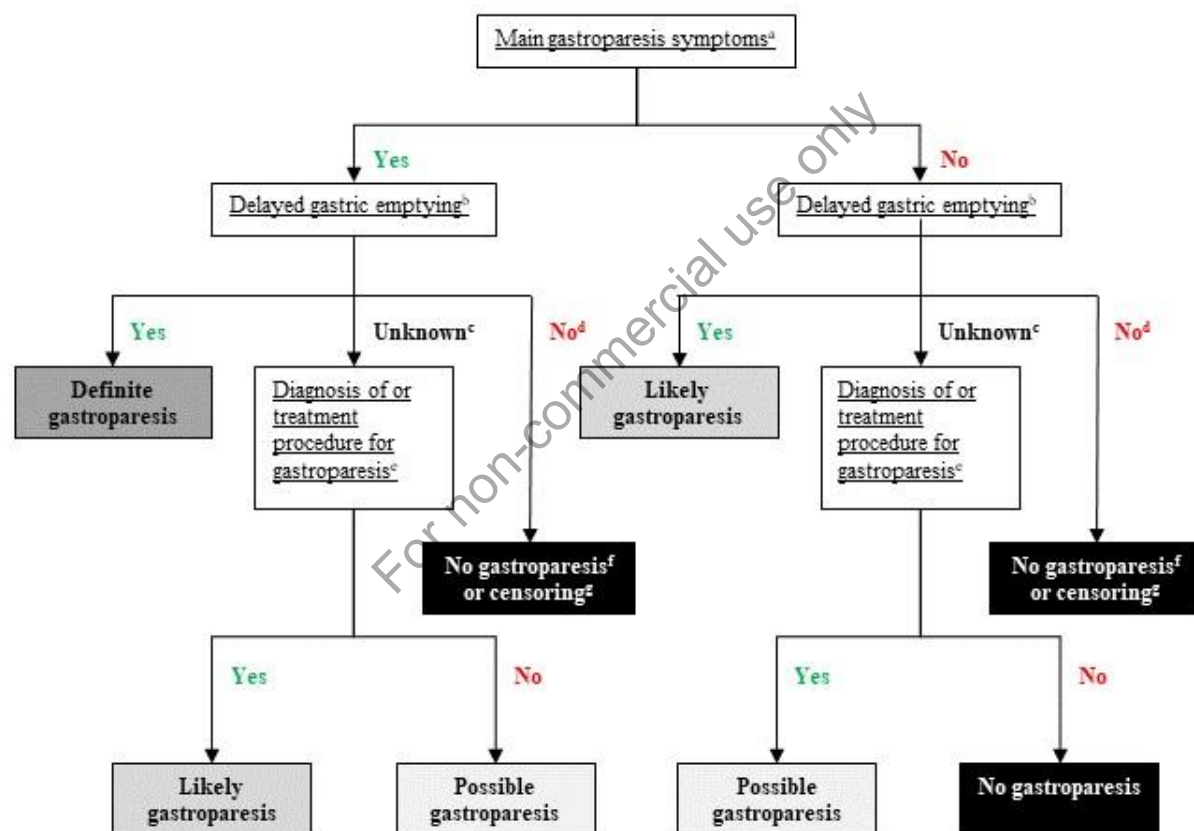
A flowchart with additional description of the case classification is provided in **Figure 2**.

Separate analyses according to each of the three case definitions will be conducted (**Section 7.7**). For the analyses of incidence, **Case Date I** (the date of case occurrence) will be defined as the date when all the respective case definition criteria are fulfilled during Follow-up Period I. For the analyses of prevalence, the occurrence of cases is retrospectively assessed on the date of Index Date P; a case is defined to have occurred if all the respective case definition criteria were fulfilled at any time during Baseline Period P (no specific case date will be defined).

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Figure 2. Illustration of classification according to case definition criteria

Patients fulfilling the criteria main gastroparesis symptoms and delayed gastric emptying will be classified as having **definite gastroparesis**. Among those fulfilling the criterion main gastroparesis symptoms, but with delayed gastric emptying unknown, the criterion diagnosis of or treatment procedure for gastroparesis will be evaluated; if this is fulfilled, patients will be classified as having **likely gastroparesis**. If it is not fulfilled, patients will be classified as having **possible gastroparesis**. Patients with recorded main gastroparesis symptoms, but a test result showing no delayed gastric emptying (i.e., gastric emptying normal or accelerated) will be classified as **not having gastroparesis** in the analyses of prevalence; in the analyses of incidence, a negative test result will lead to **censoring**. Among those not fulfilling the criterion main gastroparesis symptoms, patients with delayed gastric emptying will be classified as having **likely gastroparesis**. Patients not fulfilling main gastroparesis symptoms and with delayed gastric emptying unknown will be evaluated on the criterion diagnosis of or treatment procedure for gastroparesis; if this criterion is fulfilled, patients will be classified as having **possible gastroparesis**. If it is not fulfilled, patients will be classified as **not having gastroparesis**. Patients not fulfilling main gastroparesis symptoms and with a test result showing no delayed gastric emptying will be classified as **not having gastroparesis** in the analyses of prevalence; in the analyses of incidence, a negative test result will lead to **censoring**.



^a Including nausea or vomiting, abdominal pain, early satiety, postprandial fullness, bloating, and prescription for anti-emetic drug

^b Including test and test results for delayed gastric emptying using gastric emptying scintigraphy, gastric emptying breath test, or wireless motility capsule

^c Meaning an absence of a record for a conducted test (regardless of the result) or absence of test result

^d Meaning that the test result was available and negative for delayed gastric emptying

^e Including diagnosis of gastroparesis, gastric electrical neurostimulation, and pyloric injection

^f In the analyses of prevalence

^g In the analyses of incidence

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Table 1. Definitions of criteria included in the case definition

Case criteria	Components	General description and definition ^a
Main gastroparesis symptoms	Nausea or vomiting	Included to reflect main gastroparesis symptoms, based on diagnostic codes or other available information from EMR. ^b
	Abdominal pain	
	Early satiety	
	Postprandial fullness	
	Bloating	
	Prescription for anti-emetic drug	Included to reflect presence of nausea or vomiting, based on prescriptions for anti-emetic agents (including metoclopramide, domperidone, and other anti-emetics and anti-nauseants).
Delayed gastric emptying	Gastric emptying scintigraphy	Record of diagnostic test with positive result, to reflect objective evidence of delayed gastric emptying. Ascertainment will be based on procedure codes, laboratory results and other available information from EMR. ^b
	Gastric emptying breath test	
	Wireless motility capsule	
Diagnosis of or treatment procedure for gastroparesis	Diagnosis of gastroparesis	Record of diagnosis for gastroparesis, based on diagnostic codes ^c or other available information from EMR. ^b
	Gastric electrical neurostimulation	Records of procedures used in gastroparesis. Ascertainment will be based on procedure codes and other available information from EMR. ^b
	Pyloric injection	

Abbreviations: EMR, electronic medical records

^a Specific definitions of case criteria are provided in

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Annex 3

^b The exact search method of the EMR data will be defined as part of the data application process

^c Diagnosis code for gastroparesis (536.3) is included in the ICD-9-CM classification, used in the LPD (during the entire study period) and the MBDS (1987-2015), but not in the ICD-10 classification (used in Finland)

7.3.2 Demographic and clinical characteristics

Cases of gastroparesis will be described in terms of demographic and socio-demographic characteristics, etiologic factors (including medical history and other conditions associated with gastroparesis), clinical characteristics (including lifestyle health factors, medical history, laboratory test results, and health care utilization), diagnostic practices (including diagnostic procedures and examinations), and treatment practices (including pharmacological and non-pharmacological treatment). Variables included in the assessment are shown in

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Annex 3. Different variables may be included in the form of binary, categorical, or continuous covariates, depending on the available data in each database.

7.4 Data sources

The study will be based entirely on secondary data from structured databases and EMR. An overview of the data sources included is presented in **Table 2**; a description of the overall contents and structure of the respective databases is provided in **Annex 5**.

The data sources in Finland will include structured secondary care EMR data and information from national administrative and health registers, linked on the unique national personal identification number available for all residents and citizens of Finland. The data sources in Spain will include routinely captured data from, respectively, primary and secondary care, organized in two separate databases. No linkage of other data sources will be conducted in Spain.

Unenrollment from the national administrative and health registers in Finland or the MBDS is not possible and loss to follow-up may occur only due to emigration or death. For the LPD, loss to follow-up may additionally occur due to unenrollment from the database, e.g. due to change in health care provider. Methodological considerations to take into account the potential for unenrollment in the analyses of LPD are described in **Section 7.2.3** and **Section 7.2.4.3**.

Table 2. Overview of data sources and data contents

Data source (data holder)	Years of available data	Description of data contents
Database: Finland		
HUS - Hospital District of Helsinki and Uusimaa including Helsinki University Hospital	2007 ^a -2020	Structured hospital EMR data extracted from the HUS hospital district (~1.9 million inhabitants). The information will include laboratory test results, diagnostic tests and test results, and other clinical information recorded in the inpatient or outpatient hospital setting.
PSSHP and KUH - Hospital District of North Savo including Kuopio University Hospital	2008 ^b -2020	Structured hospital EMR data extracted from the PSSHP hospital district (~0.8 million inhabitants). The information will include laboratory test results, diagnostic tests and test results, and other clinical information recorded in the inpatient or outpatient hospital setting.
Prescription registry (Social Insurance Institute)	1994-2020	Register on all prescriptions dispensed at community pharmacies in Finland. The information for each prescription includes date of dispense and ATC code.
Care register for Health Care Visits, HILMO (THL)	1996 ^c -2020	Register on secondary health care inpatient and outpatient contacts in Finland, including information on date of admission and discharge, diagnoses (primary and secondary, classified according to ICD-10), and surgical and non-surgical procedures (classified according to the national classification for health procedures, based on the NCSP).

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Register of Primary Health Care Visits, AvoHILMO (THL)	2011-2020	Register on primary health care visits in Finland, including date of contact, diagnoses (ICPC-2 and ICD-10), and procedures.
Statistics Finland	1994-2020	Socio-demographic data, including individual-level information on income and education for the entire population of Finland.
Digital and Population Data Services Agency/ Population Register Centre	1969-2020	Demographic and administrative population data, including sex, date of birth, date of death, immigration and emigration, and place of residency for the entire population of Finland.
Database: LPD (Spain)		
QuintilesIMS LPD Health Search Database Longitudinal (QuintilesIMS/IQVIA)	2008-2020	Structured EMR database on primary care contacts, covering approximately 4% of the Spanish population. The information includes date of contact, diagnoses (classified according to ICD-9-CM with bridging [translation] to ICD-10), prescribed medications (ATC codes), laboratory tests and test results, specialist referrals, demographic characteristics (e.g. year of birth, sex, employment), and lifestyle factors (including BMI, blood pressure, and blood glucose values). Medical procedures (classified according to ICD-9-PCS) are partially covered. Information on date of death and unenrollment from the database is not included.
Database: MBDS (Spain)		
Hospital Discharge Minimum Basic Dataset (MBDS) (Spanish Ministry of Health)	1987 ^d -2020	Hospital discharge database including structured information on date of admission and discharge, diagnoses (primary and secondary, classified according to ICD-10 and ICD-9-CM), and surgical and non-surgical procedures. The database is considered to have practically complete coverage of hospital discharges in Spain (18–21). Unstructured clinical EMR data (free text) may also be used (e.g. through data mining techniques) for additional clinical characterization, according to availability.

Abbreviations: ATC, Anatomical Therapeutic Chemical; AvoHILMO, Register of Primary Health Care Visits (Finland); EMR, Electronic Medical Records; HILMO, Care Register for Health Care (Finland); HUS, Hospital District of Helsinki and Uusimaa; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICD-9-PCS, International Classification of Diseases, 9th Revision, Procedure Coding System; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; ICPC-2. International Classification of Primary Care, 2nd edition; KUH, Kuopio University Hospital; LPD, QuintilesIMS LPD Health Search Database Longitudinal; MBDS, Spanish Minimum Basic Data Set; NCSP, Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures; PSSHP, Hospital District of North Savo; THL, National Institute for Health and Welfare

^a EMR are available from 2007; contents and availability of specific data may vary across the period

^b Hospital district was started in 2008; contents and availability of specific data may vary across the period

^c Since the availability of ICD-10 codes

^d Year of establishment; the study period for the MBDS will be defined based on availability of data.

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For the optional exploratory objectives on validation, additional data sources will be needed. If the optional explorative objectives will be addressed, an amendment to the current protocol will be made, including detailed information on methods for validation and the data required.

7.5 Study size

The sample size required to estimate the prevalence of gastroparesis with different levels of precision is shown in **Table 3**. Estimates assuming a prevalence between 0.01% and 1.00% were calculated, based on the reported prevalence in previous observational data (8,13,15,16,22). As an example, assuming that the observed prevalence was 0.10%, 383,776 participants would be required to obtain a precision of 0.01% for prevalence estimates using a 95% CI. Based on the size of the different study source populations (~2.7 million in Finland [population of the hospital regions included in the study]; ~2.0 million in the LPD [number of individuals enrolled in the database]; ~46.5 million in the MBDS [the national population of Spain]), estimates indicate that prevalence may be estimated with adequate or high precision.

Table 3. Estimated sample sizes for analyses of prevalence with various precision and prevalence estimates, using 95% confidence intervals

Estimated prevalence	Precision	Sample size with 95% confidence intervals					
		0.50%	0.25%	0.1%	0.05%	0.01%	0.005%
1.00%		1522	6086	38,032	152,128	3,803,184	15,212,736
0.50%			3058	19,112	76,448	1,911,196	7,644,784
0.25%				9,580	38,320	957,999	3,831,996
0.10%					15,352	383,776	1,535,104
0.01%							153,649

The required number of person-years of follow-up to estimate the incidence rate for gastroparesis with different precision is shown in **Table 4**. Estimates of number of person-years required were calculated for incidence rates ranging from 0.5 to 10.0 per 100,000 person-years (8,22). As an example, assuming that the observed incidence rate was 2.0 per 100,000 person-years, 12,293,120 person-years would be required for a precision of 0.25. Based on the size of the source populations and the study period duration (ranging from a minimum of nine years in Finland [2012-2020] and with likely longer duration in the Spanish databases), estimates indicate that incidence rates may be estimated with adequate or high precision.

Table 4. Estimated sample sizes for analyses of incidence various precision and incidence estimates, using 95% confidence intervals

Estimated incidence rate per	Precision	Number of person-years needed with 95% confidence intervals					
		5.0	2.5	1.0	0.5	0.25	0.1

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100,000 person-years							
10.0		153,664	614,656	3,841,600	15,366,400	61,465,600	384,160,000
5.0			307,328	1,920,800	7,683,200	30,732,800	192,080,000
2.0				768,320	3,073,280	12,293,120	76,832,000
1.0					1,536,640	6,146,560	38,416,000
0.5						3,073,280	19,208,000

7.6 Data management

The processes for database management will differ by country. Generally, the data is stored at the database level and analyzed locally. SAS (version 9.4, or above), R software (version 3.5.0, or above), or an equivalent statistical analysis software will be used for access to raw data, to manage data, and to conduct data analysis.

The study will be conducted by IQVIA, and the datasets and analytic programs will be stored according to IQVIA's procedures, data holder requirements, and local legislation. For data from LPD, an authorized statistician of the IQVIA project team will be granted access to analyze data locally, by remote connection. The Sponsor will not have access to health records at the level of the individual patient form any of the databases, but only to tables with aggregated data.

This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Conference on Harmonisation (ICH) guidelines for data management.

7.7 Data analysis

For all analyses, separate investigations according to the three different case definitions will be conducted. Cases included in the three sets of analyses will be:

- 1) Cases classified as definite
- 2) Cases classified as definite or likely, and
- 3) Cases classified as definite, likely, or possible

For the analyses of incidence, the first date of fulfilling any of the case definitions included in the analysis (definite, likely, or possible) will be defined as Case Date I. For example, if in the analyses including *cases classified as definite, likely, or possible*, the participant first fulfilled the case definition criteria for *possible gastroparesis*, and, after that, the criteria for *likely gastroparesis*, the date of *possible gastroparesis* will count as Case Date I. Additionally, for the analyses of incidence, the exact criteria for exclusion due to having fulfilled the case definition criteria during the baseline period (**Section 7.2.4.2**) will vary in accordance with the specific case definition (**Section 7.3.1** and **Table 1**) under analysis. For example, participants only fulfilling the case definition criteria for possible gastroparesis during Baseline Period I will be excluded

CONFIDENTIAL

from the analyses including *cases classified as definite, likely, or possible*, but not from analyses including *cases classified as definite* or *cases classified as definite or likely*.

The analyses will be conducted separately in each patient population (adult, pediatric, and overall) and by study database. The pediatric patient population will be defined to include children under 18 years of age at the time of Index Date I (for analyses of incidence) and Index Date P (for analyses of prevalence), respectively. Correspondingly, the adult patient population will include individuals aged 18 years or older at the time of Index Date I and Index Date P.

Meta-analysis methods may be considered to combine the results of the analyses of incidence and prevalence across study databases. Details of the meta-analysis will be provided in the SAP.

The data analyses will be described and further detailed in the Statistical Analysis Plan (SAP). The described analyses might be revised, and adjustments might occur as needed.

7.7.1 Incidence

For the analyses of incidence in Finland and the LPD, person-years of follow-up will be calculated as the time between Index Date I and the date of the first occurrence of the following events: fulfilling case definition criteria ([Section 7.3.1](#)), censoring ([Section 7.2.4.3](#)), or end of study period ([Section 7.2.2](#)). In the MBDS, the amount of person-years of follow-up will be estimated based on Spanish census data. The number of observed cases will be divided by the sum of person-years of follow-up, to calculate incidence rates with 95% confidence intervals (CIs) separately for each patient population (adult, pediatric, overall) and study database (Finland, LPD, and MBDS). Incidence rates will be reported overall and stratified by age group, sex, and calendar year. Age- and sex standardized incidence (with 95% CIs), based on the Eurostat European standard population (23), will also be calculated.

7.7.2 Prevalence

Prevalence will be calculated as the proportion of patients fulfilling the case definition under analysis (i.e., respectively *definite*; *definite or likely*; and *definite, likely, or possible*) among the analysis population, at the time of Index Date P. The population denominator for prevalence estimation will include all individuals included in the analysis population (and part of the specific patient population under analysis) at the time of Index Date P. In the MBDS, the population denominator will be estimated using Spanish census data. Prevalence with 95% CIs will be calculated overall, by sex, and by age group. Age- and sex standardized prevalence (with 95% CIs), based on the Eurostat European standard population (23), will also be calculated.

7.7.3 Descriptive analysis of cases of gastroparesis

The descriptive analyses will include all incident cases of gastroparesis identified during Follow-up Period I; the analyses will be conducted separately for each of the three case definitions. The list of characteristics included in the analyses is shown in

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Annex 3. For continuous variables, numbers for the following measures will be reported: participants with and without missing data, mean, standard deviation, median, and distribution quartiles. For categorical variables, the number of non-missing observations, number of participants with missing data, and the proportion and frequency of patients in each category will be reported.

7.7.4 Validation of cases of gastroparesis

As an optional explorative objective, the validity of ascertainment of gastroparesis may be assessed in EMR chart review of cases identified in the analyses of the primary objectives. Specifically, the validation would be conducted in Finland and the MBDS, based on case review by local clinical experts, after the completion of the analyses of the primary objectives. The decision on whether the validation will be conducted and the optional explorative objectives addressed will rely on the observed case count. Uncertainty regarding the prevalence and incidence of gastroparesis based on case ascertainment using the case definition prevents strong assumptions regarding the expected number of observed cases. The assessment of whether the exploratory objectives may be reliably addressed will therefore rely on information obtained from the analyses of the primary objectives. If the number of observed cases suggests that validation can be conducted with adequate accuracy and precision, the optional explorative objectives will be pursued and the protocol will be amended accordingly. Access to additional data required for the case validation will be subject to a protocol amendment and additional review and approval by the data holders and Ethical/Research Review Boards in each country. A detailed description of data, methods, and study conduct to address the optional explorative objectives will be provided in the protocol amendment. An overview of the planned methods and parameters for validation is provided below.

In Finland, cases of gastroparesis will be assessed in terms of positive predictive value (PPV; *probability that a patient classified as having gastroparesis truly has gastroparesis*), sensitivity (*probability that a patient with gastroparesis is classified as having gastroparesis*), specificity (*probability that a patient without gastroparesis is classified as not having gastroparesis*), and negative predictive value (NPV; *probability that a patient classified as not having gastroparesis truly does not have gastroparesis*), along with 95% CIs. The validation will be conducted in the HUS-region, in which information on EMR medical charts will be available. The assessment of PPV will be based on cases identified in the analyses of the primary objectives; EMR medical charts will be independently reviewed by local clinical experts, to classify cases in terms of true gastroparesis. For the assessment of sensitivity, specificity, and NPV, an unselected population-based sample will be drawn from the population residing in the HUS-region, based on information from Statistics Finland. Among those included in the sample, all contacts with gastroenterology, endocrinology, and pediatric hospital departments (the departments where patients with gastroparesis would most likely be treated) will be identified and their medical charts reviewed. This approach will allow the identification of true cases of gastroparesis not identified using the case definition (for assessment of sensitivity) and participants who truly did not have gastroparesis (for assessment of specificity and NPV).

For the MBDS, cases will be validated in terms of PPV, based on EMR medical chart review by clinical experts. Given that complete individual-level information on the underlying source

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population in Spain will not be available (i.e., information will not be available for individuals not recorded in the MBDS), estimation of sensitivity, specificity, and NPV will not be possible.

As part of the validation, the characteristics of cases classified as having gastroparesis in the EMR chart review will be described, using the same set of characteristics and analytic approach as in the descriptive analysis of cases identified using the case definition. In addition, estimates of occurrence of gastroparesis (incidence and prevalence), adjusted for the PPV and sensitivity observed in the EMR chart review, will be estimated. For the adjustment, the results of the EMR chart review (PPV and sensitivity) will be used to estimate an adjusted number of cases in each study database. The adjusted prevalence and incidence will represent estimates of the occurrence of gastroparesis, would there have been perfect PPV and sensitivity of case ascertainment (24). Additional details of the calculations for adjusted occurrence will be provided in the study SAP.

7.7.5 Sensitivity analyses

Several sensitivity analyses will be conducted to assess the robustness and validity of the results. An overview of pre-planned sensitivity analyses is shown in **Table 5**.

Table 5. Overview of planned sensitivity analyses

No.	Main analysis method	Sensitivity analysis (rationale and method)
Sensitivity analyses to be conducted in all databases		
1	The baseline period for analyses of incidence and prevalence will include all time before Index Date I and Index Date P, respectively.	Given different study periods, the availability of baseline data will vary between databases and individuals, which could influence estimates of occurrence (incidence and prevalence). <u>In this sensitivity analysis, the impact of applying a baseline period of maximum three years before the index date in all analyses (incidence, prevalence, descriptive) will be investigated.</u>
2	The overall quality and completeness of data for some variables (e.g. diagnostic tests and test results) is uncertain. The sensitivity and specificity of diagnoses and other clinical records may similarly vary. This may influence the performance and validity of the case definition.	<u>If any specific information in the case definition is found to be inadequate, incomplete, or not fulfill the requirements, modifications to the case definition may be considered in sensitivity analysis.</u> The sensitivity analysis may be conducted locally (if concerns of completeness are limited to a specific database) or for all study databases.
Sensitivity analyses to be conducted in selected databases		
3	For the analyses of incidence, Index Date I will occur at the last occurring of the following events: start of the study period, fulfilling the age criteria for inclusion, and, for the analyses in the LPD, one year after enrollment in study database (not applicable to children less than one year of age at the date of enrollment).	<u>In this local sensitivity analysis of incidence in the LPD, Index Date I will occur at the latest occurring event of start of the study period, fulfilling the age criteria for inclusion, and three years after enrollment in study database.</u> Increasing the time period after enrollment at which time individuals are eligible for follow-up will improve the sensitivity of detecting true prevalent cases at Index Date I.

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4	For the analyses of LPD, a minimum of one year of available data before Index Date P is required for inclusion in the analyses of prevalence.	In this local sensitivity analysis of prevalence in the LPD, a minimum of three years of available data before Index Date P will be required for inclusion (i.e., <u>enrollment at least three years before Index Date P</u>). Increasing the required available baseline data may improve the sensitivity of case ascertainment at Index Date P.
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Abbreviations: LPD, QuintilesIMS LPD Health Search Database Longitudinal

7.8 Quality control

For the IQVIA EU data sources, quality control is conducted at several levels depending on the database. At the database level, the quality unit of the production department of IQVIA verifies continuously the quality of its sources in terms of representativeness and consistency of collected data. The study will use existing databases which have been widely used for research. All study programs, log files, and output files will be stored on a secure server.

For analyses performed by IQVIA, the study will be conducted according to IQVIA SOPs.

Remote access to the LPD database will be provided to an authorized trained IQVIA investigator through a secure remote set-up. Additional details of data access will be described in the country-specific sections of the SAP.

At the study level, all aspects of the study from protocol development to the reporting of the results will be conducted within the framework of the IQVIA Quality Management System and in accordance with the relevant policies and procedures.

A Quality Control plan for the study will be developed and executed, which will include quality control on the study methodology, SAP, programming, data management and analysis, study results, conclusions, and interim and final study report.

Furthermore:

- The study QC plan will establish ownership for the execution of the individual QC steps.
- The Principal in Charge of the study will ensure that individuals responsible for the execution of specific QC steps will have the knowledge, capability, and experience necessary to perform the assigned tasks.
- The result of the execution of the individual steps of the QC plan will be documented and will include the required corrective actions, if any. The execution of any required corrective action will be documented (if necessary).
- The QC plan will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study.
- Datasets and analytic programs will be stored according to IQVIA and data holder procedures, with access restricted to authorized study personnel at the respective entities.

The study will be executed in line with all applicable regulations and guidelines – such as best-practice guidelines applicable to non-interventional studies, including, but not limited to, the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist

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for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP).

7.9 Limitations of the research methods

Several potential limitations of the study should be noted.

- Cases of gastroparesis will be identified based on information on diagnoses and clinical records, records of tests, medical procedures, and pharmacological and non-pharmacological treatment. While the case definition will include a broad range of clinical information relevant to the identification of gastroparesis, the overall validity of case ascertainment is uncertain. Any significant limitations in terms of sensitivity or PPV would result in under- or overestimation of the occurrence of gastroparesis. If the number of observed cases are sufficient for case validation and the explorative objectives are addressed, this will provide firm evidence on the validity of the primary analyses of occurrence and patient characteristics associated with gastroparesis. In case the results significantly differ from previous investigations of occurrence and other previous clinical evidence, alterations to the case definition will be considered. This will include an expanded case definition criteria, based on other evidence associated with gastroparesis. The selection of variables that may be used for an expanded case definition are listed in [Annex 3](#) (Section IV).
- The available data will vary between the study databases, both with regard to coverage and content. In Finland, data will comprehensively cover contacts and diagnoses in primary and secondary care, filled prescriptions, medical procedures, and EMR data. The LPD and MBDS will include information on contacts and diagnoses, procedures, tests and test results, but from, respectively, primary- and secondary care alone. Furthermore, the availability of information on hospital outpatient diagnoses in the MBDS is uncertain (the contents and availability of EMR data, including outpatient contacts, in the MBDS will be explored as part of the data application process). Differences in the available data may be associated with different sensitivity of case ascertainment and ascertainment of case characteristics between databases. For instance, lack of information or poor coverage of gastric emptying test results in individual databases would mean that few patients could be classified as having definite gastroparesis, leading to limited sensitivity for this case definition in the specific database. The study results will be evaluated and compared across databases to assess consistency and potential differences. If the number of observed cases are sufficient and the explorative objectives are addressed, the validation of cases of gastroparesis in Finland (HUS region) and the MBDS will provide additional information on validity of case ascertainment by database.
- Although the Finnish administrative and health registers have practically complete coverage of health contacts in the public sector, contacts in the private health care sector are not comprehensively covered. Because inpatient and highly specialized outpatient care is uncommon in the private sector in Finland, the absence of private sector data will mainly affect the completeness of information from primary care. Underascertainment of diagnoses and procedures in private primary care would impact the sensitivity of ascertainment of primarily early manifestations and symptoms of gastroparesis, which

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may typically be first recorded in the primary setting. In addition, if diagnoses or procedures that were first recorded in private care were not captured by the study data sources but ascertained at a later date in another data source, this could lead to misclassification of the timing of variables, including the case date.

- While analyses in Finland and the MBDS will rely on databases with practically comprehensive and complete national coverage, the source population for analyses in the LPD will consist of patients enrolled in the database after contact with primary care. Although primary care patients are likely broadly representative of the general population, potential influence from this difference in source population on the results (e.g. in terms of estimated prevalence and incidence) cannot be excluded.
- While the Spanish databases have a partial overlap in source population, the different data sources (LPD and MBDS) cannot be linked or combined. Case ascertainment or characterization for the same patient using data from both databases will, accordingly, not be possible.
- Given the usually lengthy process of reaching diagnosis for gastroparesis, the baseline period for all analyses will include all time before the index date, to maximize the sensitivity and validity of case ascertainment. However, the length of the study period and the baseline period will differ between databases, which could cause estimates of occurrence (incidence and prevalence) and observed characteristics to vary according to availability of historic data. In sensitivity analysis, the impact of applying a fixed baseline period of three years before the index date in all analyses will be assessed.
- For the analyses of incidence in the LPD, Index Date I will occur at the earliest one year after enrollment in the database; this criterion will be intended to allow the identification of prevalent cases at the start of Follow-up Period I. If the definition of required baseline data was not sufficiently long (i.e., that previous fulfillment of case criteria was not adequately captured among those with limited duration of baseline data, using a one-year required baseline period), this could incorrectly classify prevalent cases as incident, leading to an overestimation of incidence. The impact of allowing Index Date I to occur at the earliest three years after enrollment in the database will be investigated in sensitivity analyses of incidence of gastroparesis in the LPD.
- Correspondingly, for the analyses of prevalence in the LPD, participants will be required to have at least one year of available data before Index Date P, to allow reliable identification of cases. If this one-year period was too short for adequate ascertainment of cases, the true prevalence would be underestimated. The impact of using a required minimum of three years of available data before Index Date P will be investigated in sensitivity analyses of prevalence of gastroparesis in the LPD.
- The overall quality and completeness of some information, e.g. diagnostic tests, laboratory results, and medical procedures, in the different databases is uncertain. Similarly, the sensitivity and specificity of diagnoses and other clinical records associated with gastroparesis may potentially vary. As with any study using secondary data, information will be available only to the extent that it is recorded in clinical practice. The validity and completeness of information (sensitivity and specificity) will influence the ability to identify cases of gastroparesis, as defined by the case definition. If any specific information included in the case definition is found to be inadequate (e.g. in large parts

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missing or in other ways not fulfilling the necessary requirements), post-hoc sensitivity analyses using alterations to the case definition will be considered.

- Patients with gastrointestinal malignancy, IBD, or celiac disease will be excluded, to remove patients with known or identifiable causes of gastroparesis symptoms or delayed gastric emptying. If not excluded, it is possible that patients with e.g. celiac disease would constitute a substantial proportion of patients classified as possible gastroparesis, due to symptoms overlapping with gastroparesis (e.g. bloating or abdominal pain). While this exclusion will increase the likelihood of identifying true cases of gastroparesis, certain patient subgroups (e.g. those with gastroparesis and well-treated IBD or celiac disease) will not be included.
- The LPD is known to have an underrepresentation of children aged 15 years or younger; consequently, the results for analyses in the pediatric population in this database will be interpreted accordingly.
- While the etiology of gastroparesis in the adult population is well-investigated, the underlying mechanisms of pediatric gastroparesis are less well understood (25). If variables included in descriptive analysis of cases of gastroparesis are observed to not adequately capture characteristics and etiologic factors in the pediatric population, modifications to the selection and definition of variables will be considered.
- Furthermore, although the criterion standard for diagnosing gastroparesis is similar for the adult and the pediatric populations, lack of normative data and standardization may limit the utility and reliability of diagnostic tests (including gastric emptying scintigraphy) in children (25). This could impact the reliability of classification of cases (e.g. according to gastroparesis diagnostic test results) for the analyses of the pediatric patient population. If the case definition is found to be inadequate, modifications of the case criteria for improved validity in the pediatric population will be considered.
- Finally, cases will be identified among patients that were cared for in primary or secondary care; participants with gastroparesis who were not in contact with health services (likely those with less severe manifestations of gastroparesis) will not be accounted for, neither with regard to occurrence or assessment of clinical characteristics.

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8.0 PROTECTION OF HUMAN SUBJECTS

This study only involves the use of pseudonymized electronic healthcare records. The researchers will not have any access to named or identifiable patient information.

To ensure the full data protection of patients, all the research data in each country is pseudonymized. The implications of the General Data Protection Regulation (EU) 2016/679 on the national legislations, during the course of the study, will be considered.

Before commencement of the study, an application including the study protocol and other necessary study documentation will be submitted to relevant independent Ethical/Research Review Boards in each country. Permit processes by other agencies, data holders, or regulatory entities may also be required. Country-specific details of the requirements of the local Ethical Research Review Boards, any outcome of an ethical review procedure, and data protection requirements will be described and addressed in country specific sections of the SAP.

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9.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

Pursuant to the requirements for reporting of adverse events for secondary data, according to GVP module VI, VI.C.1.2.1.2, adverse event reporting will not be conducted as part of this study given the study objectives will be met through the use of secondary data. Thus, the Sections 9.1-9.2 will not be applicable for this study.

9.1 Definitions

Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for a serious adverse event (SAE)
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Health care provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

Adverse Drug Reactions

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An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product
- Accidental/Occupational exposure
- Use outside the terms of the marketing authorization, also known as “off-label”
- Use of falsified medicinal product
- Use of counterfeit medicinal product
- Drug-drug interactions and drug-food interactions
- Inadvertent or accidental exposure with or without an AE
- Unintended benefit

A SSR should be reported even if there is no associated AE.

9.2 Collection and notifying of Adverse Events, Special Situation Reports and Product Quality Issues to Takeda Pharmacovigilance

SAEs, AEs, ADRs, SSRs and PQIs in the healthcare record or other applicable source data that are part of the study objectives or endpoints

Events/issues which are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

SAEs, AEs, SSRs and PQIs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints

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Events/Issues which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.

SAEs, AEs, ADRs, SSRs and PQIs spontaneously reported to the investigator(s) or research team

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQI where the event/issue pertains to a Takeda product (or unbranded generic), such information should be forwarded to the relevant Takeda Pharmacovigilance department at the Local Operating Company (LOC) within 1 working day for fatal or life-threatening SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events. This includes events spontaneously notified to the investigator(s) or research team which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

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10.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

One final full-scale study report is planned. The full-scale study report will accurately and completely present the study objectives, methods, results, limitations, and interpretation of the findings.

Based on the study report, the principal and co-investigators (together referred to as “investigators”), listed under the responsible parties (**Section 2.0**), and all IQVIA and Takeda Project Study Team members who made substantial contributions to the study concept, design, and interpretation of results for this project, will prepare the report findings for publication and will be eligible to qualify for authorship. The investigators will decide the publication forums.

A scientific summary of the Master Protocol will be registered in the ENCePP E-register of Studies (<http://www.encepp.eu/encepp/studiesDatabase.jsp>). Furthermore, within three months following the study report, a scientific summary of the study findings will be made available to the public through the European Union electronic Register of Post-Authorization Studies register. According to the ENCePP Code of Conduct, the principal investigator is responsible for the publication of results. The main results of the study will be published, whether positive or negative, including results from a possibly prematurely terminated study. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests.

Any additional dissemination of study results (e.g. presentations at scientific conferences) will be discussed by the IQVIA and Takeda Project Study Team. The principal investigator or other investigators representing IQVIA will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (scientific summaries in journals or newspapers, oral presentations, etc.), either in whole or in part, by investigators representing IQVIA will require pre-submission review and approval by the Sponsor. The Sponsor is entitled to review the final results and interpretations thereof prior to submission for publication and to comment in advance of submission as agreed in the research contract and without unjustifiably delaying the publication.

The principal investigator and the Sponsor are committed to ensuring that the authorship of all publications complies with the criteria defined by the International Committee of Medical Journal Editors. It is stated that each author should have participated sufficiently in the work to take public responsibility for the content. These conditions apply equally to external investigators and to the employees of the Sponsor. Study reports will be prepared using a template following the Guideline on Good Pharmacovigilance Practices (GVP), Module VIII, Section B.6.3.

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11.0 REFERENCES

1. Camilleri M, Bharucha AE, Farrugia G. Epidemiology, Mechanisms and Management of Diabetic Gastroparesis. *Clin Gastroenterol Hepatol*. 2011 Jan;9(1):5-e7.
2. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L, American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol*. 2013 Jan;108(1):18–37; quiz 38.
3. Parkman HP. Idiopathic gastroparesis. *Gastroenterol Clin North Am*. 2015 Mar;44(1):59–68.
4. Parrish CR. Nutritional considerations in the patient with gastroparesis. *Gastroenterol Clin North Am*. 2015 Mar;44(1):83–95.
5. Soykan I, Sivri B, Sarosiek I, Kiernan B, McCallum RW. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. *Dig Dis Sci*. 1998 Nov;43(11):2398–404.
6. Camilleri M, Chedid V, Ford AC, Haruma K, Horowitz M, Jones KL, et al. Gastroparesis. *Nat Rev Dis Primers*. 2018 01;4(1):41.
7. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L, American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol*. 2013 Jan;108(1):18–37; quiz 38.
8. Jung H-K, Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Szarka LA, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology*. 2009 Apr;136(4):1225–33.
9. Fosso CL, Quigley EMM. A Critical Review of the Current Clinical Landscape of Gastroparesis. *Gastroenterol Hepatol (N Y)*. 2018 Mar;14(3):140–5.
10. Liu N, Abell T. Gastroparesis Updates on Pathogenesis and Management. *Gut Liver*. 2017 Sep 15;11(5):579–89.
11. Camilleri M, Shin A. Novel and validated approaches for gastric emptying scintigraphy in patients with suspected gastroparesis. *Dig Dis Sci*. 2013 Jul;58(7):1813–5.
12. Bharucha AE. EPIDEMIOLOGY AND NATURAL HISTORY OF GASTROPARESIS. *Gastroenterol Clin North Am*. 2015 Mar;44(1):9–19.
13. Syed AR, Wolfe MM, Calles-Escandon J. Epidemiology and Diagnosis of Gastroparesis in the United States: A Population-based Study. *J Clin Gastroenterol*. 2020 Jan;54(1):50–4.

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14. Ye Y, Bennett D. The First National Prevalence Estimation of Gastroparesis in the United States Using a Large-scale Retrospective Database. *J Clin Gastroenterol*. 2020 Jan;54(1):106.
15. Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Melton LJ, Talley NJ. Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. *Am J Gastroenterol*. 2012 Jan;107(1):82–8.
16. Rey E, Choung RS, Schleck CD, Zinsmeister AR, Talley NJ, Locke GR. Prevalence of hidden gastroparesis in the community: the gastroparesis “iceberg.” *J Neurogastroenterol Motil*. 2012 Jan;18(1):34–42.
17. Ye Y, Jiang B, Manne S, Moses PL, Almansa C, Bennett D, et al. Epidemiology and outcomes of gastroparesis, as documented in general practice records, in the United Kingdom. *Gut*. 2020 Jun 3;
18. Alvaro-Meca A, Ryan P, Martínez-Larrull E, Micheloud D, Berenguer J, Resino S. Epidemiological trends of deep venous thrombosis in HIV-infected subjects (1997-2013): A nationwide population-based study in Spain. *Eur J Intern Med*. 2018;48:69–74.
19. López-de-Andrés A, Jiménez-García R, Carrasco-Garrido P, Alvaro-Meca A, Galarza PG, de Miguel AG. Hospitalizations associated with rotavirus gastroenteritis in Spain, 2001-2005. *BMC Public Health*. 2008 Apr 8;8:109.
20. Santos-Sancho J, Gil-Prieto R, Álvaro-Meca A, Gil-de Miguel A. Epidemiology of hospitalizations caused by measles in the general population in Spain (1997–2006). *Journal of Pediatric Infectious Diseases*. 2015 Jul 28;05(02):131–7.
21. Muñoz-Moreno MF, Ryan P, Alvaro-Meca A, Valencia J, Tamayo E, Resino S. National Temporal Trend Analysis of Infective Endocarditis among Patients Infected with HIV in Spain (1997–2014): A Retrospective Study. *Journal of Clinical Medicine*. 2019 Aug 4;8(8):1167.
22. Ye Y, Manne S, Moses PL, Almansa C, Bennett D, Dolin P. Mo1603 – Prevalence and Incidence of Gastroparesis in the United Kingdom: Real World Evidence from the Clinical Practice Research Datalink. *Gastroenterology*. 2019 May;156(6):S-797.
23. Eurostat. Revision of the European Standard Population: report of Eurostat’s task force : 2013 edition. [Internet]. Publications Office; 2013 [cited 2020 Jun 5]. Available from: <http://dx.publications.europa.eu/10.2785/11470>
24. Ho C, Jiang J, Eastwood CA, Wong H, Weaver B, Quan H. Validation of two case definitions to identify pressure ulcers using hospital administrative data. *BMJ Open*. 2017 Aug 28;7(8):e016438.

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25. Kovacic K, Elfar W, Rosen JM, Yacob D, Raynor J, Mostamand S, et al. Update on pediatric gastroparesis: A review of the published literature and recommendations for future research. *Neurogastroenterol Motil.* 2020;32(3):e13780.
26. Cuesta-Peredo D, Arteaga-Moreno F, Belenguer-Varea Á, Llopis-Calatayud JE, Sivera-Gimeno S, Santaeugenia SJ, et al. Influence of hospital adverse events and previous diagnoses on hospital care cost of patients with hip fracture. *Arch Osteoporos.* 2019 11;14(1):88.
27. Care Register for Health Care - THL [Internet]. Finnish Institute for Health and Welfare (THL), Finland. [cited 2020 Jun 4]. Available from: <https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/care-register-for-health-care>
28. Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. *Scand J Public Health.* 2012 Aug;40(6):505–15.
29. Register of primary health care visits - THL [Internet]. Finnish Institute for Health and Welfare (THL), Finland. [cited 2020 Jun 4]. Available from: <https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/register-of-primary-health-care-visits>

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Appendices

Annex 1 List of stand-alone documents

None.

Annex 2 ENCePP checklist

Doc.Ref. EMA/540136/2009

ENCEPP Checklist for Study Protocols (Revision 3)

Study title:

Real-World Evidence on Diagnosed Gastroparesis in Europe: Multi-database observational epidemiological study

Study reference number:

TAK-906-5003

<u>Section 1: Milestones</u>	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection ¹	☒	☐	☐	4.0
1.1.2 End of data collection ²	☒	☐	☐	4.0
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	4.0, 10.0
1.1.6 Final report of study results.	☒	☐	☐	4.0

Comments:

1.1.3 and 1.1.4: Study progress report and Interim progress report are not included

<u>Section 2: Research question</u>	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	5.0, 6.0, 7.2
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)	☒	☐	☐	5.0

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.

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<u>Section 2: Research question</u>	Yes	No	N/A	Section Number
2.1.2 The objective(s) of the study?	☒	☐	☐	6.0
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	☐	☐	☒	

Comments:

2.1.4 and 2.1.5: No predefined hypotheses are to be tested in this study.

<u>Section 3: Study design</u>	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.1, 7.2.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	7.7.1, 7.7.2
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
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)	☒	☐	☐	9.2

Comments:

3.4: No analyses of association are in the scope of this study.

<u>Section 4: Source and study populations</u>	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	7.2.3
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	7.2.2
4.2.2 Age and sex?	☒	☐	☐	7.2.3, 7.2.4
4.2.3 Country of origin?	☒	☐	☐	7.2.1, 7.2.3
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Duration of follow-up?	☒	☐	☐	7.2.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2.3, 7.2.4

Comments:

4.2.4: No specific disease/indication is required for inclusion

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Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
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 classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4	Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

5.1-5.4: No exposure is defined or in the scope of this study

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?	☒	☐	☐	7.1, 7.3.1
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.1
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	7.9
6.4	Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYs, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

6.3: The validity of case definition is unknown; limitations and considerations described in 7.9.

6.4: Endpoints relevant for Health Technology Assessment are not in scope of the study.

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
	7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2	Does the protocol address:	☒	☐	☐	
	7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
	7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	7.7.5, 7.9
7.3	Does the protocol address the validity of the study covariates?	☐	☐	☒	

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Comments:

7.1., 7.1.1, 7.2.1: No exposure associations will be investigated in this study; hence, confounding and selection bias is not applicable.

7.3: No exposure associations will be investigated in this study; hence, no covariates are included.

<u>Section 8: Effect modification</u>	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:

8.1: No exposure is included in this study; hence, no effect modifiers will be investigated.

<u>Section 9: Data sources</u>	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.4, Annex 5
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.4, Annex 5
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	7.4, Annex 5
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	7.4

Comments:

9.1.1, 9.2.1, 9.3.1: No exposure variables are included.

9.1.3, 9.2.3, 9.3.3: No covariate variables are included.

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<u>Section 10: Analysis plan</u>	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	☒	☐	☐	7.7.1-7.7.3
10.2 Are descriptive analyses included?	☒	☐	☐	7.7.3
10.3 Are stratified analyses included?	☒	☐	☐	7.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	7.7.2, 7.7.3
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	7.5

Comments:

10.4: No analyses of association are included in this study.

<u>Section 11: Data management and quality control</u>	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)	☒	☐	☐	7.8
11.2 Are methods of quality assurance described?	☒	☐	☐	7.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

11.3: No independent review is planned within the scope of the project.

<u>Section 12: Limitations</u>	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	7.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	7.5

Comments:

12.1.1 and 12.1.3: No exposure associations will be investigated in this study; hence, confounding and selection bias is not applicable.

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<u>Section 13: Ethical issues</u>	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8.0
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	8.0

Comments:

13.2: No outcomes of ethical review procedures have yet occurred.

<u>Section 14: Amendments and deviations</u>	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3.0

Comments:

<u>Section 15: Plans for communication of study results</u>	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	10.0
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10.0

Comments:

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Annex 3. Definitions of inclusion- and exclusion criteria, variables for case definition, and variables for descriptive analyses of cases of gastroparesis

NOTE: Additional codes and other information from EMR for variable definitions will be explored as part of the data application process. Specific variables may be re-defined, split into additional variables, or merged, as part of the SAP development and data extraction process. Additional codes used specifically for the Spanish data sources (including surgical- and non-surgical procedure codes and diagnoses classified according to ICD-9-CM) will be defined in the SAP or in the data application process. The selection of codes will be made in accordance with the variable definitions used for the Finnish database (i.e., ICD-10 codes will be translated to ICD-9-CM; procedure codes in Spain corresponding to those identified in THL – Toimenpideluokitus and SPAT will be included).

I) Definitions of inclusion-, exclusion-, and censoring criteria

Variable ^a	Code(s) ^b	Variable definition	Data source(s) by study population		
			FINLAND	LPD ^c	MBDS ^c
INCLUSION CRITERIA					
Age (<18 years in analysis of pediatric population; ≥18 years in analyses of adult population)	NA	<u>For analyses of incidence</u> : Age in years at Index Date I <u>For analyses of prevalence</u> : Age in years at Index Date P	Statistics Finland, Digital and Population Data Services Agency		
EXCLUSION CRITERIA					
Gastrointestinal malignancy	<u>ICD-10</u> : C15.x-C26.x (<i>Malignant neoplasms of digestive organs</i>) <u>ICPC-2 (Finland)</u> : D74 (<i>Malignant neoplasm stomach</i>) D75 (<i>Malignant neoplasm colon/rectum</i>) D76 (<i>Malignant neoplasm pancreas</i>) D77 (<i>Malignant neoplasm digest other/NOS</i>)	<u>For analyses of incidence</u> : Any record at any time before and including Index Date I <u>For analyses of prevalence</u> : Any record at any time before and including Index Date P	AvoHILMO, HILMO		
Inflammatory bowel disease	<u>ICD-10</u> : K50.x (<i>Crohn disease [regional enteritis]</i>) K51.x (<i>Ulcerative colitis</i>) <u>ICPC-2 (Finland)</u> : D94 (<i>Chronic enteritis/ulcerative colitis</i>)				

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Celiac disease	<u>ICD-10:</u> K90.0 (<i>Celiac disease</i>)			
Negative test for delayed gastric emptying	NA	<u>For analyses of incidence:</u> Any record of negative test result (normal or accelerated gastric emptying) for GES, GEBT, or WMC at any time before and including Index Date I <u>For analyses of prevalence:</u> NA	EMR	
CENSORING CRITERIA				
Death	NA	<u>For analyses of incidence in Finland:</u> Death (date of death) during Follow-up Period I	Statistics Finland, Digital and Population Data Services Agency	
Emigration	NA	<u>For analyses of incidence in Finland:</u> Emigration (date of emigration) during Follow-up Period I		
Relocation	NA	<u>For analyses of incidence in Finland:</u> Relocation (date of relocation) to region other than HUS or PSSHP during Follow-up Period I		
Gastrointestinal malignancy	<u>ICD-10:</u> C15.x-C26.x (<i>Malignant neoplasms of digestive organs</i>) <u>ICPC-2 (Finland):</u> D74 (<i>Malignant neoplasm stomach</i>) D75 (<i>Malignant neoplasm colon/rectum</i>) D76 (<i>Malignant neoplasm pancreas</i>) D77 (<i>Malignant neoplasm digest other/NOS</i>)	<u>For analyses of incidence:</u> Any record at any time during Follow-up Period I	AvoHILMO, HILMO	
Inflammatory bowel disease	<u>ICD-10:</u> K50.x (<i>Crohn disease [regional enteritis]</i>) K51.x (<i>Ulcerative colitis</i>) <u>ICPC-2 (Finland):</u> D94 (<i>Chronic enteritis/ulcerative colitis</i>)			
Celiac disease	<u>ICD-10:</u> K90.0 (<i>Celiac disease</i>)			
Negative test for delayed gastric emptying	NA	<u>For analyses of incidence:</u> Any record of negative test result (normal or accelerated gastric emptying) for GES, GEBT, or WMC at any time during Follow-up Period I	EMR	

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		Cutoffs for definition of negative test results will be defined according to local practice and guidelines in each study database			
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Abbreviations: AvoHILMO, Register of Primary Health Care Visits (Finland); GEBT, gastric emptying breath test; GES, gastric emptying scintigraphy; HILMO, Care Register for Health Care (Finland); ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; ICPC-2, International Classification of Primary Care, 2nd edition; LPD, QuintilesIMS Longitudinal Health Search Database; MBDS, Spanish Minimum Basic Data Set; NA, not applicable; NOS, not otherwise specified; WMC, wireless motility capsule

^a Definitions in Section I include only those variables that need to be defined for evaluation

^b Additional codes and other information from EMR for variable definitions will be explored as part of the data application process. Specific variables may be re-defined, split into additional variables, or merged, as part of the SAP development and data extraction process. Additional codes used specifically for the Spanish data sources will be defined in the SAP or in the data application process. The selection of codes will be made in accordance with the variable definitions used for the Finnish database.

^c Name of specific data set within database from which variables will be ascertained will be defined as part of the SAP development or the data application and extraction process

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II) Definitions of case criteria

Case criteria	Components	Code(s) ^{a,b}	Variable definition	Data source(s) by study database		
				FINLAND	LPD ^c	MBDS ^c
Main gastroparesis symptoms	Abdominal pain	ICD-10: R10.x (<i>Abdominal pain</i>) ICPC-2 (Finland): D01 (<i>Abdominal pain/cramps general</i>) D02 (<i>Abdominal pain epigastric</i>)	<u>For analyses of incidence:</u> Records of ≥ 2 different components at any time during Baseline Period I or Follow-up Period I. Additionally, records of components have to have occurred on ≥ 2 different dates ≥ 30 days apart during Baseline Period I or Follow-up Period I. <u>For analyses of prevalence:</u> Records of ≥ 2 different components at any time during Baseline Period P. Additionally, records of components have to have occurred on ≥ 2 different dates ≥ 30 days apart during Baseline Period P.	AvoHILMO, HILMO, Prescription registry		
	Nausea and vomiting	ICD-10: R11.x (<i>Nausea and vomiting</i>) ICPC-2 (Finland): D09 (<i>Nausea</i>) D10 (<i>Vomiting</i>)				
	Early satiety	d				
	Postprandial fullness	d				
	Bloating	ICD-10: R14.x (<i>Flatulence and related conditions, incl. bloating</i>) ICPC-2 (Finland): D08 (<i>Flatulence/gas/belching</i>)				
	Prescription for anti-emetic drug	ATC (Finland and LPD): A03FA01 (<i>Metoclopramide</i>) A03FA03 (<i>Domperidone</i>) A04A (<i>Antiemetics and antinauseants</i>)				e
Delayed gastric emptying	GES (including test result)	NA	<u>For analyses of incidence:</u> Any record of positive test result for GES, GEPT, or WMC at any time during Baseline Period I or Follow-up Period I <u>For analyses of prevalence:</u> Any record of positive test result for GES, GEPT, or WMC, at any time during Baseline Period P Cutoffs for definition of positive and negative test results will be	EMR		
	GEPT (including test result)					
	WMC (including test result)					

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			defined according to local practice and guidelines in each study database		
Diagnosis of or treatment procedure for gastroparesis	Diagnosis of gastroparesis	^d	<u>For analyses of incidence:</u> Any record at any time during Baseline Period I or Follow-up Period I <u>For analyses of prevalence:</u> Any record at any time during Baseline Period P	HILMO, EMR	
	Gastric electrical neurostimulation	^f			
	Pyloric injection	<u>THL – Toimenpideluokitus (Finland):</u> JDA32 (<i>Endoscopic injection in stomach or pylorus</i>)			

Abbreviations: ATC, Anatomical Therapeutic Chemical; AvoHILMO, Register of Primary Health Care Visits (Finland); EMR, electronic medical records; GEBT, gastric emptying breath test; GES, gastric emptying scintigraphy; HILMO, Care Register for Health Care (Finland); ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; ICPC-2, International Classification of Primary Care, 2nd edition; LPD, QuintilesIMS Longitudinal Health Search Database; MBDS, Spanish Minimum Basic Data Set; THL, National Institute for Health and Welfare (Finland); WMC, wireless motility capsule

^a For procedures codes and ATC codes shown in truncated form, all (untruncated) sub codes will be included in the variable definition

^b Additional codes and other information from EMR for variable definitions will be explored as part of the data application process. Specific variables may be re-defined, split into additional variables, or merged, as part of the SAP development and data extraction process. Additional codes used specifically for the Spanish data sources will be defined in the SAP or in the data application process. The selection of codes will be made in accordance with the variable definitions used for the Finnish database.

^c Name of specific data set within database from which variables will be ascertained will be defined as part of the SAP development or the data application and extraction process

^d No code in the ICD-10 classification; the availability of additional information (including EMR data) for variable definition will be explored as part of the data application process

^e If administered and recorded during in-patient hospital care; records of medication will depend on availability of unstructured EMR data (free-text) from the MBDS, which will be explored as part of the data application process

^f No code in the Finnish national procedure classification (THL – Toimenpideluokitus); the availability of additional information (including EMR data) for variable definition will be explored as part of the data application process

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III) Variables for descriptive analyses of cases of gastroparesis

Variable	Code(s) ^{a,b}	Variable definition ^b	Data source(s) by study database		
			FINLAND	LPD ^c	MBDS ^c
DEMOGRAPHIC AND SOCIODEMOGRAPHIC CHARACTERISTICS					
Age (continuous)	NA	Age in years at Case Date I	Statistics Finland, Digital and Population Data Services Agency		
Sex	NA	Sex at Case Date I			
Geographical area	NA	Area of residence at Case Date I			
Highest level of education	NA	Educational level at latest time point with available data before and including Case Date I (using categories high/intermediate/low)	Statistics Finland		
Income	NA	Personal income at the latest time point with available data before and including Case Date I (in Euros [continuous] and categories according to national income distribution quartiles)			
LIFESTYLE HEALTH FACTORS					
Body mass index (BMI)	NA	Result of the latest available measurement before and including Case Date I, reported as a continuous and categorized variable (using categories: underweight [<18.5], normal [$18.5-24.9$], overweight [$25-29.9$], and obese [>30])	AvoHILMO, HILMO, EMR		
Overweight and obesity	ICD-10: E66.x (<i>Obesity</i>) ICPC-2 (Finland): T82 (<i>Obesity</i>) T83 (<i>Overweight</i>)	Any record of diagnosis for overweight/obesity or record of BMI $\geq 25 \leq 12$ months before and including Case Date I			
Smoking	ICD-10: F17.2 (<i>Dependence smoking</i>) ICPC-2 (Finland): P17 (<i>Tobacco abuse</i>) ATC (Finland and LPD): N07BA (<i>Drugs used in nicotine dependence</i>)	Any record ≤ 12 months before and including Case Date I	AvoHILMO, HILMO, Prescription registry, EMR		

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Alcohol misuse	<u>ICD-10:</u> F10.x (<i>Mental and behavioral disorders due to use of alcohol</i>) <u>ICPC-2 (Finland):</u> P15 (<i>Chronic alcohol abuse</i>) P16 (<i>Acute alcohol abuse</i>) <u>ATC (Finland and LPD):</u> N07BB (<i>Drugs used in alcohol dependence</i>)	Any record of diagnosis or prescription ≤12 months before and including Case Date I			
LABORATORY TEST RESULTS					
Glucose control in HbA1c (% of total hemoglobin)	NA	Result of the latest test before and including Case Date I, reported as a continuous and categorized variable (using categories: normal [$<5.7\%$], prediabetes [$5.7-6.4\%$], diabetes [$6.5>\%$])	EMR		
Systolic blood pressure (mmHg)	NA	Result of the latest test before and including Case Date I, reported as a continuous and categorized variable (using categories: normal [<120], elevated [$120-129$], stage 1 hypertension [$130-139$], stage 2 hypertension [$140>$])			
Diastolic blood pressure (mmHg)	NA	Result of the latest test before and including Case Date I, reported as a continuous and categorized variable (using categories: normal [<80], stage 1 hypertension [$80-89$], stage 2 hypertension [$90>$])			
Elevated blood pressure or hypertension	<u>ICD-10:</u> I10.x (<i>Hypertension</i>) <u>ICPC-2:</u> K85 (<i>Elevated blood pressure</i>)	Any record of diagnosis for elevated blood pressure/hypertension or test result with systolic blood pressure ≥ 120 mmHg/diastolic blood pressure ≥ 80 mmHg ≤ 12 months before and including Case Date I	AvoHILMO, HILMO, EMR		
Blood glucose level (mg/dL)	NA	Result of the latest test before and including Case Date I, reported as a continuous variable	EMR		
Elevated blood glucose level	<u>ICD-10:</u> R73.x (<i>Elevated blood glucose level</i>)	Any record of diagnosis for elevated blood glucose or test result with blood glucose level (mg/dL) ≥ 140 ≤ 12 months before and including Case Date I	HILMO, EMR		

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HEALTH CARE UTILIZATION					
Number of days hospitalized	NA	Number of days hospitalized ≤12 months before and including Case Date I (continuous variable)	HILMO		
Number of primary care visits	NA	Number of primary care visits ≤12 months before and including Case Date I (continuous variable)	AvoHILMO		
Number of specialist outpatient visits	NA	Number of specialist outpatient visits ≤12 months before and including Case Date I (continuous variable)	HILMO		
Number of gastroenterologist specialist visits	NA	Number of gastroenterology department visits ≤12 months before and including Case Date I (continuous variable)			
Number of pediatrician visits	NA	Number of pediatric department visits ≤12 months before and including Case Date I (continuous variable)			
Number of endocrinologist visits	NA	Number of endocrinologist department visits ≤12 months before and including Case Date I (continuous variable)			
Number of unique medications	NA	Number of prescription drugs (ATC codes) used ≤12 months before and including Case Date I (continuous variable)	Prescription registry		d
MEDICAL HISTORY					
Conditions included in the Charlson Comorbidity Index (not elsewhere included)					
Myocardial infarction	ICD-10: I21.x (<i>Acute myocardial infarction</i>) I22.x (<i>Subsequent myocardial infarction</i>) I23.x (<i>Certain current complications following acute myocardial infarction</i>)	Any record at any time before and including Case Date I	HILMO		
Congestive heart failure	ICD-10: I50.x (<i>Heart failure</i>) I11.0 (<i>Hypertensive heart disease with (congestive) heart failure</i>) I13.0 (<i>Hypertensive heart and renal disease with (congestive) heart failure</i>)				

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	I13.2 (<i>Hypertensive heart and renal disease with both (congestive) heart failure and renal failure</i>)
Peripheral vascular disease	<u>ICD-10:</u> I70.x (<i>Atherosclerosis</i>) I71.x (<i>Aortic aneurysm and dissection</i>) I72.x (<i>Other aneurysm and dissection</i>) I73.x (<i>Other peripheral vascular diseases</i>) I74.x (<i>Arterial embolism and thrombosis</i>) I77.x (<i>Other disorders of arteries and arterioles</i>)
Cerebrovascular disease	<u>ICD-10:</u> I60.x-I69.x (<i>Cerebrovascular diseases</i>), G45.x (<i>Transient cerebral ischemic attacks and related syndromes</i>) G46.x (<i>Vascular syndromes of brain in cerebrovascular diseases</i>)
Dementia	<u>ICD-10:</u> F00.x (<i>Dementia in Alzheimer disease</i>) F01.x (<i>Vascular dementia</i>) F02.x (<i>Dementia in other diseases classified elsewhere</i>) F03.x (<i>Unspecified dementia</i>) F05.1 (<i>Delirium superimposed on dementia</i>) G30.x (<i>Alzheimer disease</i>)
Chronic pulmonary disease	<u>ICD-10:</u> J40.x-J47.x (<i>Chronic lower respiratory diseases</i>) J60.x (<i>Coalworker pneumoconiosis</i>) J61.x (<i>Pneumoconiosis due to asbestos and other mineral fibres</i>) J62.x (<i>Pneumoconiosis due to dust containing silica</i>) J63.x (<i>Pneumoconiosis due to other inorganic dusts</i>) J64.x (<i>Unspecified pneumoconiosis</i>) J65.x (<i>Pneumoconiosis associated with tuberculosis</i>) J66.x (<i>Airway disease due to specific organic dust</i>) J67.x (<i>Hypersensitivity pneumonitis due to organic dust</i>) J68.4 (<i>Chronic respiratory conditions due to chemicals, gases, fumes and vapours</i>) J70.1 (<i>Chronic and other pulmonary manifestations due to radiation</i>) J70.3 (<i>Chronic drug-induced interstitial lung disorders</i>) J84.1 (<i>Other interstitial pulmonary diseases with fibrosis</i>)

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	J92.0 (<i>Pleural plaque with presence of asbestos</i>) J96.1 (<i>Chronic respiratory failure</i>) J98.2 (<i>Interstitial emphysema</i>) J98.3 (<i>Compensatory emphysema</i>)			
Hemiplegia	<u>ICD-10:</u> G81.x (<i>Hemiplegia</i>) G82.x (<i>Paraplegia and tetraplegia</i>)			
Moderate/severe renal disease	<u>ICD-10:</u> I12.x (<i>Hypertensive renal disease</i>) I13.x (<i>Hypertensive heart and renal disease</i>) N00.x (<i>Acute nephritic syndrome</i>) N01.x (<i>Rapidly progressive nephritic syndrome</i>) N02.x (<i>Recurrent and persistent haematuria</i>) N03.x (<i>Chronic nephritic syndrome</i>) N04.x (<i>Nephrotic syndrome</i>) N05.x (<i>Unspecified nephritic syndrome</i>) N07.x (<i>Hereditary nephropathy, not elsewhere classified</i>) N11.x (<i>Chronic tubulo-interstitial nephritis</i>) N14.x (<i>Drug- and heavy-metal-induced tubulo-interstitial and tubular conditions</i>) N17.x-N19.x (<i>Renal failure</i>) Q61.x (<i>Cystic kidney disease</i>)			
Cancer	<u>ICD-10:</u> C00.x-C97.x (not C44.x) (<i>Malignant neoplasms</i>)			
Metastatic solid tumor	<u>ICD-10:</u> C76.x-C80.x (<i>Malignant neoplasms of ill-defined, secondary and unspecified sites</i>)			
HIV/AIDS	<u>ICD-10:</u> B20.x-B24.x (<i>Human immunodeficiency virus [HIV] disease</i>)			
Endocrine disorders				
Type 1 diabetes	<u>ATC (Finland and LPD):</u> A10A (<i>Insulins and analogues</i>) <u>ICD-10:</u> E10.x (<i>Type 1 diabetes mellitus</i>) <u>ICPC-2 (Finland):</u> T89 (<i>Diabetes insulin dependent</i>)	Any record of diagnosis for Type 1 diabetes at any time before and including Case Date I <u>OR</u> Both of the below criteria fulfilled: 1) At least one record of issued (LPD) or dispensed (Finland) prescription with ATC code A10A and no issued or dispensed prescription	AvoHILMO, HILMO, Prescription registry	

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		with ATC code A10B ≤12 months before and including Case Date I 2) Age <30 years at the time of the record for prescription with ATC code A10A In Finland, additional information on reimbursement codes for dispensed prescriptions may be used to identify and distinguish between patients with type 1 diabetes, type 2 diabetes, and other indications for diabetes drugs, respectively.			
Type 2 diabetes	<u>ATC (Finland and LPD):</u> A10B (<i>Blood glucose lowering drugs excl. insulins</i>) <u>ICD-10:</u> E11.x (<i>Type 2 diabetes mellitus</i>) <u>ICPC-2 (Finland):</u> T90 (<i>Diabetes non-insulin dependent</i>)	Either of the below criteria fulfilled: 1) Any record of diagnosis for Type 2 diabetes at any time before and including Case Date I 2) At least one record of issued (LPD) or dispensed (Finland) prescription with ATC code A10B ≤12 months before and including Case Date I In Finland, additional information on reimbursement codes for dispensed prescriptions may be used to identify and distinguish between patients with type 1 diabetes, type 2 diabetes, and other indications for diabetes drugs, respectively.			
Hypothyroidism	<u>ICD-10:</u> E02.x (<i>Subclinical iodine-deficiency hypothyroidism</i>) E03.x (<i>Other hypothyroidism</i>) E06.3 (<i>Autoimmune thyroiditis</i>) <u>ICPC-2 (Finland):</u> T86 (<i>Hypothyroidism/myxedema</i>)	Any record at any time before and including Case Date I	AvoHILMO, HILMO		
Hyperthyroidism	<u>ICD-10:</u> E05.x (<i>Thyrotoxicosis [hyperthyroidism]</i>) E06.2 (<i>Chronic thyroiditis with transient thyrotoxicosis</i>) <u>ICPC-2 (Finland):</u> T85 (<i>Hyperthyroidism/thyrotoxicosis</i>)				
Hyperparathyroidism	<u>ICD-10:</u> E21.0 (<i>Primary hyperparathyroidism</i>) E21.2 (<i>Other hyperparathyroidism</i>)				

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	E21.3 (<i>Hyperparathyroidism, unspecified</i>)			
Hypopituitarism	ICD-10: E23.0 (<i>Hypopituitarism</i>)			
Addison disease	ICD-10: E27.1 (<i>Primary adrenocortical insufficiency</i>) E27.2 (<i>Addisonian crisis</i>)			
Psychiatric conditions				
Mood disorders	ICD-10: F30.x-F39.x (<i>Mood disorders</i>) ICPC-2 (Finland): P74 (<i>Anxiety disorder/anxiety state</i>) P76 (<i>Depressive disorder</i>) ATC (Finland and LPD): N06A (<i>Antidepressants</i>) N06CA (<i>Antidepressants in combination with psycholeptics</i>)	Either of the below criteria fulfilled: 1) Any record of diagnosis for mood disorder at any time before and including Case Date I 2) At least one record of issued (LPD) or dispensed (Finland) prescription ≤12 months before and including Case Date I	AvoHILMO, HILMO, Prescription registry	
Somatoform autonomic dysfunction	ICD-10: F45.3 (<i>Somatoform autonomic dysfunction</i>) ICPC-2 (Finland): P75 (<i>Somatization disorder</i>)	Any record at any time before and including Case Date I	AvoHILMO, HILMO	
Eating disorders	ICD-10: F50.x (<i>Eating disorders</i>) ICPC-2 (Finland): P86 (<i>Anorexia nervosa/bulimia</i>)			
Autistic-spectrum disorders	ICD-10: F84.x (<i>Pervasive developmental disorders</i>)			
Attention-deficit/hyperactivity disorder	ICD-10: F90.x (<i>Hyperkinetic disorders</i>) ICPC-2 (Finland): P81 (<i>Hyperkinetic disorder</i>) ATC (Finland and LPD): C02AC02 (<i>Guanfacin</i>) N06BA01 (<i>Amphetamine</i>) N06BA02 (<i>Dexamphetamine</i>) N06BA04 (<i>Methylphenidate</i>) N06BA09 (<i>Atomoxetine</i>) N06BA12 (<i>Lisdexamfetamin</i>)	Either of the below criteria fulfilled: 1) Any record of diagnosis for mood disorder at any time before and including Case Date I 2) At least one record of issued (LPD) or dispensed (Finland) prescription with ATC code C02AC02, N06BA01, N06BA02, N06BA04, N06BA09, or N06BA12 ≤12 months before and including Case Date I	AvoHILMO, HILMO, Prescription registry	

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Psychiatric disorder	<u>ICD-10:</u> F01.x-F99.x (<i>Mental and behavioral disorders</i>) <u>ICPC-2 (Finland):</u> P01-P13, P15-P20, P22-P25, P27-P29, P70-P82, P85, P86, P98, P99 (<i>Psychological</i>)	Any record at any time before and including Case Date I	AvoHILMO, HILMO		
Neurologic conditions					
Parkinson disease	<u>ICD-10:</u> G20.x (<i>Parkinson disease</i>) <u>ICPC-2:</u> N87 (<i>Parkinsonism</i>)	Any record at any time before and including Case Date I	AvoHILMO, HILMO		
Dysautonomia	<u>ICD-10:</u> G90.x (<i>Disorders of autonomic nervous system</i>)				
Muscular dystrophies					
Muscular dystrophy	<u>ICD-10:</u> G71.0 (<i>Muscular dystrophy</i>)	Any record at any time before and including Case Date I	HILMO		
Mitochondrial disorders	<u>ICD-10:</u> G71.3 (<i>Mitochondrial myopathy, not elsewhere classified</i>)				
Gastrointestinal conditions					
Diseases of esophagus, stomach, and duodenum	<u>ICD-10:</u> K20.x-K31.x (<i>Diseases of esophagus, stomach and duodenum</i>) <u>ICPC-2 (Finland):</u> D84 (<i>Esophagus disease</i>) D85 (<i>Duodenal ulcer</i>) D86 (<i>Peptic ulcer other</i>)	Any record at any time before and including Case Date I	AvoHILMO, HILMO, EMR		
Gastro-oesophageal reflux disease	<u>ICD-10:</u> K21.x (<i>Gastro-oesophageal reflux disease</i>) <u>ICPC-2 (Finland):</u> D84 (<i>Esophagus disease</i>)				
Ulcer disease	<u>ICD-10:</u> K22.1 (<i>Ulcer of oesophagus</i>) K25.x (<i>Gastric ulcer</i>) K26.x (<i>Duodenal ulcer</i>) K27.x (<i>Peptic ulcer, site unspecified</i>) K28.x (<i>Gastrojejunal ulcer</i>)				

CONFIDENTIAL

	<u>ICPC-2 (Finland):</u> D85 (<i>Duodenal ulcer</i>) D86 (<i>Peptic ulcer other</i>)
Functional dyspepsia	<u>ICD-10:</u> K30.x (<i>Functional dyspepsia</i>) <u>ICPC-2 (Finland):</u> D07 (<i>Dyspepsia/indigestion</i>)
Other specified diseases of stomach and duodenum	<u>ICD-10:</u> K31.8 (<i>Other specified diseases of stomach and duodenum incl. achlorhydria, gastropstosis, and hourglass contraction of stomach</i>)
Disease of stomach and duodenum, unspecified	<u>ICD-10:</u> K31.9 (<i>Disease of stomach and duodenum, unspecified</i>)
Diseases of appendix	<u>ICD-10:</u> K35.x-K38.x (<i>Diseases of appendix</i>) <u>ICPC-2 (Finland):</u> D88 (<i>Appendicitis</i>)
Hernia	<u>ICD-10:</u> K40.x-K46.x (<i>Hernia</i>) <u>ICPC-2 (Finland):</u> D89 (<i>Inguinal hernia</i>) D90 (<i>Hiatus hernia</i>) D91 (<i>Abdominal hernia other</i>)
Noninfective enteritis and colitis (excluding Crohn disease and Ulcerative colitis)	<u>ICD-10:</u> K52.x (<i>Other noninfective gastroenteritis and colitis</i>)
Other diseases of intestines	<u>ICD-10:</u> K55.x-K64.x (<i>Other diseases of intestines</i>)
Paralytic ileus and intestinal obstruction without hernia	<u>ICD-10:</u> K56.x (<i>Paralytic ileus and intestinal obstruction without hernia</i>)
Irritable bowel syndrome	<u>ICD-10:</u> K58.x (<i>Irritable bowel syndrome</i>) <u>ICPC-2 (Finland):</u> D93 (<i>Irritable bowel syndrome</i>)

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Diseases of peritoneum	<u>ICD-10:</u> K65.x-K67.x (<i>Diseases of peritoneum</i>)			
Diseases of liver	<u>ICD-10:</u> K70.x-K77.x (<i>Diseases of liver</i>) <u>ICPC-2 (Finland):</u> D97 (<i>Liver disease</i>)			
Portal hypertension	<u>ICD-10:</u> K76.6 (<i>Portal hypertension</i>)			
Disorders of gallbladder, biliary tract and pancreas	<u>ICD-10:</u> K80.x-K87.x (<i>Disorders of gallbladder, biliary tract and pancreas</i>)			
Other diseases of the digestive system	<u>ICD-10:</u> K90.x-K93.x (<i>Other diseases of the digestive system</i>)			
Chronic intestinal pseudo-obstruction	^e			
Pediatric intestinal pseudo-obstruction	^e			
Postprocedural disorders of digestive system	<u>ICD-10:</u> K91.x (<i>Postprocedural disorders of digestive system</i>)			
Connective tissue disorders				
Rheumatoid arthritis	<u>ICD-10:</u> M05.x (<i>Seropositive rheumatoid arthritis</i>) M06.x (<i>Other rheumatoid arthritis</i>) M08.0 (<i>Juvenile rheumatoid arthritis</i>) <u>ICPC-2 (Finland):</u> L88 (<i>Rheumatoid/seropositive arthritis</i>)	Any record at any time before and including Case Date I	AvoHILMO, HILMO	
Dermatopolymyositis	<u>ICD-10:</u> M33.x (<i>Dermatopolymyositis</i>)			
Systemic sclerosis	<u>ICD-10:</u> M34.x (<i>Systemic sclerosis</i>)			
Systemic lupus erythematosus	<u>ICD-10:</u> M32.x (<i>Systemic lupus erythematosus</i>)			
Sjögren syndrome	<u>ICD-10:</u> M35.0 (<i>Sicca syndrome [Sjögren]</i>)			

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Mixed connective tissue disease	<u>ICD-10:</u> M35.1 (<i>Mixed connective tissue disease</i>)				
Ehlers-Danlos syndrome hypermobile type	<u>ICD-10:</u> Q79.6 (<i>Ehlers-Danlos Syndrome hypermobile type</i>)				
Viral infection					
Rotavirus	<u>ICD-10:</u> A08.0 (<i>Rotaviral enteritis</i>)	Any record ≤6 months before and including Case Date I	AvoHILMO, HILMO		
Norovirus	<u>ICD-10:</u> A08.1 (<i>Acute gastroenteropathy due to Norovirus</i>)				
Other viral intestinal infection	<u>ICD-10:</u> A08.2 (<i>Adenoviral enteritis</i>) A08.3 (<i>Other viral enteritis</i>) A08.4 (<i>Viral intestinal infection, unspecified</i>)				
Herpesviral infections	<u>ICD-10:</u> B00.x (<i>Herpesviral [herpes simplex] infections</i>) B02.x (<i>Zoster [herpes zoster]</i>) <u>ICPC-2 (Finland):</u> S70 (<i>Herpes zoster</i>) S71 (<i>Herpes simplex</i>)				
Varicella	<u>ICD-10:</u> B01.x (<i>Varicella</i>) <u>ICPC-2 (Finland):</u> A72 (<i>Chickenpox</i>)				
Cytomegalovirus	<u>ICD-10:</u> B25.x (<i>Cytomegaloviral disease</i>)				
Epstein-Barr virus	<u>ICD-10:</u> B27.x (<i>Infectious mononucleosis</i>) <u>ICPC-2 (Finland):</u> A75 (<i>Infectious mononucleosis</i>)				
Influenza	<u>ICD-10:</u> J09.x (<i>Influenza due to identified zoonotic or pandemic influenza virus</i>) J10.x (<i>Influenza due to identified seasonal influenza virus</i>) J11.x (<i>Influenza, virus not identified</i>) <u>ICPC-2 (Finland):</u> R80 (<i>Influenza</i>)				

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Other autoimmune, congenital, or genetic conditions					
Cystic fibrosis	ICD-10: E84.x (<i>Cystic fibrosis</i>)	Any record at any time before and including Case Date I	AvoHILMO, HILMO		
Amyloidosis	ICD-10: E85.x (<i>Amyloidosis</i>)				
Scoliosis	ICD-10: M41.x (<i>Scoliosis</i>) Q67.5 (<i>Congenital deformity of spine</i>) Q76.3 (<i>Congenital scoliosis due to congenital bony malformation</i>)				
Congenital anomaly of digestive system	ICD-10: Q39.x (<i>Congenital malformations of esophagus</i>) Q43.x (<i>Other congenital malformations of intestine</i>) Q79.0 (<i>Congenital diaphragmatic hernia</i>) ICPC-2 (Finland): D81 (<i>Congenital anomaly digestive system</i>)				
Turner Syndrome	ICD-10: Q96.x (<i>Turner syndrome</i>)				
Symptoms and other conditions associated with gastroparesis					
Abdominal pain	ICD-10: R10.x (<i>Abdominal pain</i>) ICPC-2 (Finland): D01 (<i>Abdominal pain/cramps general</i>) D02 (<i>Abdominal pain epigastric</i>)	Any record ≤12 months before and including Case Date I	AvoHILMO, HILMO		
Nausea and vomiting	ICD-10: R11.x (<i>Nausea and vomiting</i>) ICPC-2 (Finland): D09 (<i>Nausea</i>) D10 (<i>Vomiting</i>)				
Early satiety	e				
Postprandial fullness	e				
Bloating	ICD-10: R14.x (<i>Flatulence and related conditions, incl. bloating</i>) ICPC-2 (Finland):				

CONFIDENTIAL

	D08 (<i>Flatulence/gas/belching</i>)			
Heartburn	ICD-10: R12.x (<i>Heartburn</i>) ICPC-2 (Finland): D03 (<i>Heartburn</i>) D07 (<i>Dyspepsia/indigestion</i>)			
Malnutrition	ICD-10: E43.x (<i>Unspecified severe protein-energy malnutrition</i>) E44.x (<i>Protein-energy malnutrition of moderate and mild degree</i>) E46.x (<i>Unspecified protein-energy malnutrition</i>) ICPC-2 (Finland): T91 (<i>Vitamin/nutritional deficiency</i>)			
Dehydration	ICD-10: E86.0 (<i>Volume depletion incl. dehydration</i>) ICPC-2 (Finland): T11 (<i>Dehydration</i>)			
Constipation	ICD-10: K59.0 (<i>Constipation</i>) ICPC-2 (Finland): D12 (<i>Constipation</i>)			
Weight loss	ICD-10: R63.4 (<i>Abnormal weight loss</i>) ICPC-2 (Finland): T08 (<i>Weight loss</i>)			
Intestinal surgical procedures^f				
Surgical procedure on the digestive system and spleen	THL – Toimenpideluokitus (Finland): J (<i>Surgical procedure on the digestive system and spleen</i>)	For analyses of characteristics at the time of fulfilling the case definition criteria: Any record ≤12 months before and including Case Date I For analyses of characteristics in the time period after fulfilling the case definition criteria: Any record ≤12 months after Case Date I	HILMO, EMR	
Surgical procedure on the abdominal wall, mesentry, peritoneum, and greater omentum	THL – Toimenpideluokitus (Finland): JA (<i>Abdominal wall, mesentry, peritoneum and greater omentum</i>)			
Surgical procedure on the diaphragm and gastro-oesophageal reflux	THL – Toimenpideluokitus (Finland): JB (<i>Diaphragm and gastro-oesophageal reflux</i>)			

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Surgical procedure on the esophagus	<u>THL – Toimenpideluokitus (Finland):</u> JC (<i>Esophagus</i>)			
Surgical procedure on stomach and duodenal bulb	<u>THL – Toimenpideluokitus (Finland):</u> JD (<i>Stomach and duodenal bulb</i>)			
Surgical procedure on the appendix	<u>THL – Toimenpideluokitus (Finland):</u> JE (<i>Appendix</i>)			
Surgical procedure on the intestine	<u>THL – Toimenpideluokitus (Finland):</u> JF (<i>Intestine</i>)			
Surgical procedure on rectum	<u>THL – Toimenpideluokitus (Finland):</u> JG (<i>Rectum</i>)			
Surgical procedure on the anus and perianal tissue	<u>THL – Toimenpideluokitus (Finland):</u> JH (<i>Anus and perianal tissue</i>)			
Surgical procedure on the liver	<u>THL – Toimenpideluokitus (Finland):</u> JJ (<i>Liver</i>)			
Surgical procedure on the biliary tract	<u>THL – Toimenpideluokitus (Finland):</u> JK (<i>Biliary tract</i>)			
Surgical procedure on the pancreas	<u>THL – Toimenpideluokitus (Finland):</u> JL (<i>Pancreas</i>)			
Surgical procedure on the spleen	<u>THL – Toimenpideluokitus (Finland):</u> JM (<i>Spleen</i>)			
Reoperations in gastroenterological surgery	<u>THL – Toimenpideluokitus (Finland):</u> JW (<i>Reoperations in gastroenterological surgery</i>)			
Abdominal operations with other or overlapping anatomical location	<u>THL – Toimenpideluokitus (Finland):</u> JX (<i>Abdominal operations with other or overlapping anatomical location</i>)			
Postprocedural disorder of the digestive system	<u>ICD-10:</u> K91.x (<i>Postprocedural disorders of digestive system, not elsewhere classified</i>)			
Gastrojejunostomy	<u>THL – Toimenpideluokitus (Finland):</u> JDE00 (<i>Gastrojejunostomy</i>)			
Jejunostomy placement	<u>THL – Toimenpideluokitus (Finland):</u> TJF00 (<i>Insertion of jejunal tube</i>) TJF10 (<i>Insertion of jejunal tube through gastrostomy</i>)			
Diagnostic tests for gastroparesis				

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Gastric emptying scintigraphy	<u>THL – Toimenpideluokitus (Finland):</u> JD1FN (<i>Gamma imaging of gastric function</i>)	Any record ≤12 months before and including Case Date I. <u>All variables will be reported as:</u> 1) Result of the latest test before and including Case Date I, reported using the observed mean (standard deviation) and median (interquartile range) values 2) The frequency and proportion of patients with a test conducted and a positive test result. Cutoffs for definition of positive test result will be defined according to local practice and guidelines in each study database	HILMO, EMR		
Gastric emptying breath test	g		EMR		
Wireless motility capsule (WMC) test	g				
Other gastrointestinal diagnostic procedures and examinations					
Gastrointestinal transit with radio-opaque markers	<u>THL – Toimenpideluokitus (Finland):</u> JX1JB (<i>Gastrointestinal passage X-ray examination</i>)	Any record ≤12 months before and including Case Date I . <u>All variables will be reported as:</u> 1) Result of the latest test or examination before and including Case Date I, reported using the observed mean (standard deviation) and median (interquartile range) values (where applicable) 2) The frequency and proportion of patients with a test conducted and (where applicable) a positive test result. Cutoffs for definition of positive test result will be defined according to local practice and guidelines in each study database	HILMO, EMR		
Intestinal passage with contrast enema	<u>THL – Toimenpideluokitus (Finland):</u> JF1AB (<i>Passage examination of small bowel with X-ray</i>)				
Abdominal tomography	<u>THL – Toimenpideluokitus (Finland):</u> JN3HA (<i>Tomography of abdominal or pelvic organs</i>)				
Electrogastrography (EGG)	g		EMR		
Antroduodenal manometry	g				
Colonic manometry	g				
Oesophageal manometry	<u>THL – Toimenpideluokitus (Finland):</u> XJC00 (<i>Oesophageal manometry</i>)		HILMO, EMR		
Abdominal ultrasonography	<u>THL – Toimenpideluokitus (Finland):</u> XJA00 (<i>Intraoperative abdominal ultrasonography</i>)				
Magnetic resonance imaging (MRI)	<u>THL – Toimenpideluokitus (Finland):</u> JN1AF (<i>Simple MRI examination of upper part of abdomen with median intensity magnet</i>) JN1AG (<i>Simple MRI examination of upper part of abdomen with high intensity magnet</i>) JN1AM (<i>Upper part of abdomen simple MRI examination with 3 Tesla magnet</i>)				

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	JN1BF (MRI examination of upper part of abdomen with median intensity magnet) JN1BG (MRI examination of upper part of abdomen with high intensity magnet) JN1BM (Upper part of abdomen MRI examination with 3 Tesla magnet) JN1CF (Extensive MRI examination of upper part of abdomen with median intensity magnet) JN1CG (Extensive MRI examination of upper part of abdomen with high intensity magnet) JN1CM (Upper part of abdomen extensive MRI examination with 3 Tesla magnet) JN1DF (Very extensive MRI examination of upper part of abdomen with median intensity magnet) JN1DG (Very extensive MRI examination of upper part of abdomen with high intensity magnet) JN1DM (Upper part of abdomen very extensive MRI examination with 3 Tesla magnet)			
Single-photon emission computed tomography (SPECT)	<u>THL – Toimenpideluokitus (Finland):</u> JF1AQ (Ectopic gastric epithelium SPECT with low dose)	HILMO, EMR		
Satiety testing	g	EMR		
Ultrasound examination of upper abdomen	<u>THL – Toimenpideluokitus (Finland):</u> JN1AE (Ultrasound examination of upper part of abdomen) <u>SPAT (Finland):</u> 1120 (Ultrasound examination of upper abdomen)	AvoHILMO, HILMO, EMR		
Oesophagoscopy	<u>THL – Toimenpideluokitus (Finland):</u> UJC02 (Rigid oesophagoscopy) UJC12 (Flexible oesophagoscopy)	HILMO, EMR		
Gastroscopy	<u>THL – Toimenpideluokitus (Finland):</u> UJD02 (Gastroscopy)			
Esophagoscopy, gastroscopy, and duodenoscopy	<u>THL – Toimenpideluokitus (Finland):</u> UJD10 (Esophagoscopy, gastroscopy and duodenoscopy) <u>SPAT (Finland):</u> 1130 (Esophago-, gastro- and duodenoscopy)	AvoHILMO, HILMO, EMR		
Capsular endoscopy	<u>THL – Toimenpideluokitus (Finland):</u> UJF92 (Capsular endoscopy)	HILMO, EMR		

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PHARMACOLOGICAL AND NON-PHARMOCOLOGICAL TREATMENT					
Pharmacological treatment used in gastroparesis					
Antiemetics	ATC (Finland and LPD): A04A (<i>Antiemetics and antinauseants</i>)	For analyses of characteristics at the time of fulfilling the case definition criteria: Any record of issued (LPD) or dispensed (Finland) prescription ≤12 months before and including Case Date I	Prescription registry		d
Metoclopramide	ATC (Finland and LPD): A03FA01 (<i>Metoclopramide</i>)				
Cisapride	ATC (Finland and LPD): A03FA02 (<i>Cisapride</i>)	For analyses of characteristics in the time period after fulfilling the case definition criteria: Any record of issued (LPD) or dispensed (Finland) prescription ≤12 months after Case Date I			
Domperidone	ATC (Finland and LPD): A03FA03 (<i>Domperidone</i>)				
Other propulsives	ATC (Finland and LPD): A03FA04 (<i>Bromopride</i>) A03FA05 (<i>Alizapride</i>) A03FA06 (<i>Clebopride</i>) A03FA07 (<i>Itropride</i>) A03FA08 (<i>Cinitapride</i>) A03FA09 (<i>Mosapride</i>)				
Macrolides with motilin agonist properties: erythromycin and azithromycin	ATC (Finland and LPD): J01FA01 (<i>Erythromycin</i>) J01FA10 (<i>Azithromycin</i>)				
Tricyclic antidepressants: amitriptyline and nortriptyline	ATC (Finland and LPD): N06AA09 (<i>Amitriptyline</i>) N06AA10 (<i>Nortriptyline</i>)				
Prucalopride	ATC (Finland and LPD): A06AX05 (<i>Prucalopride</i>)				
Other drugs for constipation	ATC (Finland and LPD): A06A (<i>Drugs for constipation</i>) (<u>not</u> A06AX05 <i>prucalopride</i>)				
Non-pharmacological treatment used in gastroparesis					
Gastric electrical neurostimulation	g	For analyses of characteristics at the time of fulfilling the case definition criteria: Any record ≤12 months before and including Case Date I	EMR		
Pyloric injection	THL – Toimenpideluokitus (Finland): JDA32 (<i>Endoscopic injection in stomach or pylorus</i>)		HILMO, EMR		

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Other pyloric intervention	<u>THL – Toimenpideluokitus (Finland):</u> JDH63 (<i>Pyloroplasty</i>) JDH60 (<i>Pyloromyotomy</i>)	<u>For analyses of characteristics in the time period after fulfilling the case definition criteria:</u> Any record ≤12 months after Case Date I			
Dietary counselling	<u>ICD-10:</u> Z71.3 (<i>Dietary counselling and surveillance</i>)				
Medications associated with delayed gastric emptying					
Cannabinoids	<u>ATC (Finland and LPD):</u> A04AD10 (<i>Dronabinol</i>) A04AD11 (<i>Nabilone</i>) N02BG10 (<i>Cannabinoids</i>) N03AX24 (<i>Cannabidiol</i>)	Any record of issued (LPD) or dispensed (Finland) prescription ≤12 months before and including Case Date I	Prescription registry		d
Glucagon-like peptide-1 (GLP-1) analogues	<u>ATC (Finland and LPD):</u> A10BJ (<i>Glucagon-like peptide-1 [GLP-1] analogues</i>)				
Calcium-channel blockers	<u>ATC (Finland and LPD):</u> C08C (<i>Selective calcium channel blockers with mainly vascular effects</i>) C08D (<i>Selective calcium channel blockers with direct cardiac effects</i>)				
Somatostatin and analogues	<u>ATC (Finland and LPD):</u> H01CB (<i>Somatostatin and analogues</i>)				
Opioids	<u>ATC (Finland and LPD):</u> N02A (<i>Opioids</i>)				
Anticholinergic agents for Parkinson disease	<u>ATC (Finland and LPD):</u> N04A (<i>Anticholinergic agents</i>)				
Other drugs with anticholinergic properties	<u>ATC (Finland and LPD):</u> A03AA (<i>Synthetic anticholinergics, esters with tertiary amino group</i>) A03AB (<i>Synthetic anticholinergics, quaternary ammonium compounds</i>) A03AX03 (<i>Chlorbenzoxamine</i>) A03B (<i>Belladonna and derivatives, plain</i>) A03CA (<i>Synthetic anticholinergic agents in combination with psycholeptics</i>) A03CB31 (<i>Hyoscyamine and psycholeptics</i>) A03DA (<i>Synthetic anticholinergic agents in combination with analgesics</i>) A03FA01 (<i>Metoclopramide</i>)				

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	A04AD01 (<i>Scopolamine</i>) A04AD12 (<i>Aprepitant</i>) C01BA01 (<i>Quinidine</i>) C01BA03 (<i>Disopyramide</i>) C01BA51 (<i>Quinidine, combinations excluding psycholeptics</i>) C01BA71 (<i>Quinidine, combinations with psycholeptics</i>) G04BD (<i>Drugs for urinary frequency and incontinence</i>) M03B (<i>Muscle relaxants, centrally acting agents</i>) N05AA01 (<i>Chlorpromazine</i>) N05AA02 (<i>Levomepromazine</i>) N05AB01 (<i>Dixyrazine</i>) N05AB02 (<i>Fluphenazine</i>) N05AB03 (<i>Perphenazine</i>) N05AB04 (<i>Prochlorperazine</i>) N05AC01 (<i>Periciazine</i>) N05AC02 (<i>Thioridazine</i>) N05AF01 (<i>Flupentixol</i>) N05AF03 (<i>Chlorprothixene</i>) N05AF05 (<i>Zuclopenthixol</i>) N05BB01 (<i>Hydroxyzine</i>) N06AA04 (<i>Clomipramine</i>) N06AA06 (<i>Trimipramine</i>) N06AA09 (<i>Amitriptyline</i>) N06AA12 (<i>Doxepin</i>) R01BA01 (<i>Phenylpropanolamine</i>) R01BA51 (<i>Phenylpropanolamine, combinations</i>) R03BB (<i>Anticholinergics</i>) R06AB01 (<i>Brompheniramine</i>) R06AE03 (<i>Cyclizine</i>) R06AE53 (<i>Cyclizine, combinations</i>) S01FA (<i>Anticholinergics</i>)
Dopa and dopa derivatives	<u>ATC (Finland and LPD):</u> N04BA (<i>Dopa and dopa derivatives</i>)
Dopamine agonists	<u>ATC (Finland and LPD):</u> N04BC (<i>Dopamine agonists</i>)
Antidepressants	<u>ATC (Finland and LPD):</u> N06A (<i>Antidepressants</i>) N06CA (<i>Antidepressants in combination with psycholeptics</i>)

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Sympathomimetics	ATC (Finland and LPD): N06BA (Centrally acting sympathomimetics)			
Parasympathomimetics	ATC (Finland and LPD): N07A (Parasympathomimetics)			

Abbreviations: ATC, Anatomical Therapeutic Chemical; AvoHILMO, Register of Primary Health Care Visits (Finland); EMR, electronic medical records; HILMO, Care Register for Health Care (Finland); ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; ICPC-2, International Classification of Primary Care, 2nd edition; LPD, QuintilesIMS Longitudinal Health Search Database; MBDS, Spanish Minimum Basic Data Set; NA, not applicable; SPAT, Finnish classification of functions in outpatient primary health care; THL, National Institute for Health and Welfare (Finland);

^a For procedures codes and ATC codes shown in truncated form, all (untruncated) sub codes will be included in the variable definition

^b Additional codes and other information from EMR for variable definitions will be explored as part of the data application process. Specific variables may be re-defined, split into additional variables, or merged, as part of the SAP development and data extraction process. Additional codes used specifically for the Spanish data sources will be defined in the SAP or in the data application process. The selection of codes will be made in accordance with the variable definitions used for the Finnish database.

^c Name of specific data set within database from which variables will be ascertained will be defined as part of the SAP development or the data application and extraction process

^d If administered and recorded during in-patient hospital care; records of medication will depend on availability of unstructured EMR data (free-text) from the MBDS, which will be explored as part of the data application process

^e No specific code identified in the ICD-10 classification; the availability of additional information (including EMR data) for variable definition will be explored as part of the data application process

^f The final definition of variables will include only surgical procedures; the exact codes used for the definition of each variable will be defined as part of the SAP development and data application process

^g No code in the Finnish national procedure classification (THL – Toimenpideluokitus); the availability of additional information (including EMR data) for variable definition will be explored as part of the data application process

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IV) Variables for expanded case definition criteria

Variable	Code(s) ^{a,b}	Variable definition ^b	Data source(s) by study database		
			FINLAND	LPD ^c	MBDS ^c
OTHER EVIDENCE ASSOCIATED WITH GASTROPARESIS					
Endoscopy or upper gastrointestinal study	<u>THL – Toimenpideluokitus (Finland):</u> UJD02 (<i>Gastroscopy</i>) UJD10 (<i>Esophagoscopy, gastroscopy and duodenoscopy</i>) <u>SPAT (Finland):</u> 1130 (<i>Esophago-, gastro- and duodenoscopy</i>)	For analyses of incidence: Any record at any time during Baseline Period I or Follow-up Period I <u>For analyses of prevalence:</u> Any record at any time during Baseline Period P	AvoHILMO, HILMO, EMR		
Dietary counselling	<u>ICD-10:</u> Z71.3 (<i>Dietary counselling</i>)				
Functional dyspepsia	<u>ICD-10:</u> K30.x (<i>Functional dyspepsia</i>) <u>ICPC-2 (Finland):</u> D07 (<i>Dyspepsia/indigestion</i>)				
Somatoform autonomic dysfunction	<u>ICD-10:</u> F45.3 (<i>Somatoform autonomic dysfunction</i>)				
Diabetic neuropathy	<u>ICD-10:</u> E10.4 (<i>Type 1 diabetes with neurological complications</i>) E11.4 (<i>Type 2 diabetes with neurological complications</i>)				
Diabetes	<u>ICD-10:</u> E10.x (<i>Type 1 diabetes mellitus</i>) E11.x (<i>Type 2 diabetes mellitus</i>) <u>ICPC-2 (Finland):</u> T89 (<i>Diabetes insulin dependent</i>) <u>ATC (Finland and LPD):</u> A10A (<i>Insulins and analogues</i>) A10B (<i>Blood glucose lowering drugs excl. insulins</i>)		AvoHILMO, HILMO, EMR, Prescription registry		

Abbreviations: AvoHILMO, Register of Primary Health Care Visits (Finland); EMR, electronic medical records; HILMO, Care Register for Health Care (Finland); ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; ICPC-2, International Classification of Primary Care, 2nd edition; LPD, QuintilesIMS Longitudinal Health Search Database; MBDS, Spanish Minimum Basic Data Set; NA, not applicable; THL, National Institute for Health and Welfare (Finland)

^a For procedures codes and ATC codes shown in truncated form, all (untruncated) sub codes will be included in the variable definition

^b Additional codes and other information from EMR for variable definitions will be explored as part of the data application process. Specific variables may be re-defined, split into additional variables, or merged, as part of the SAP development and data extraction process. Additional codes used specifically for the Spanish data sources will be defined in the SAP or in the data

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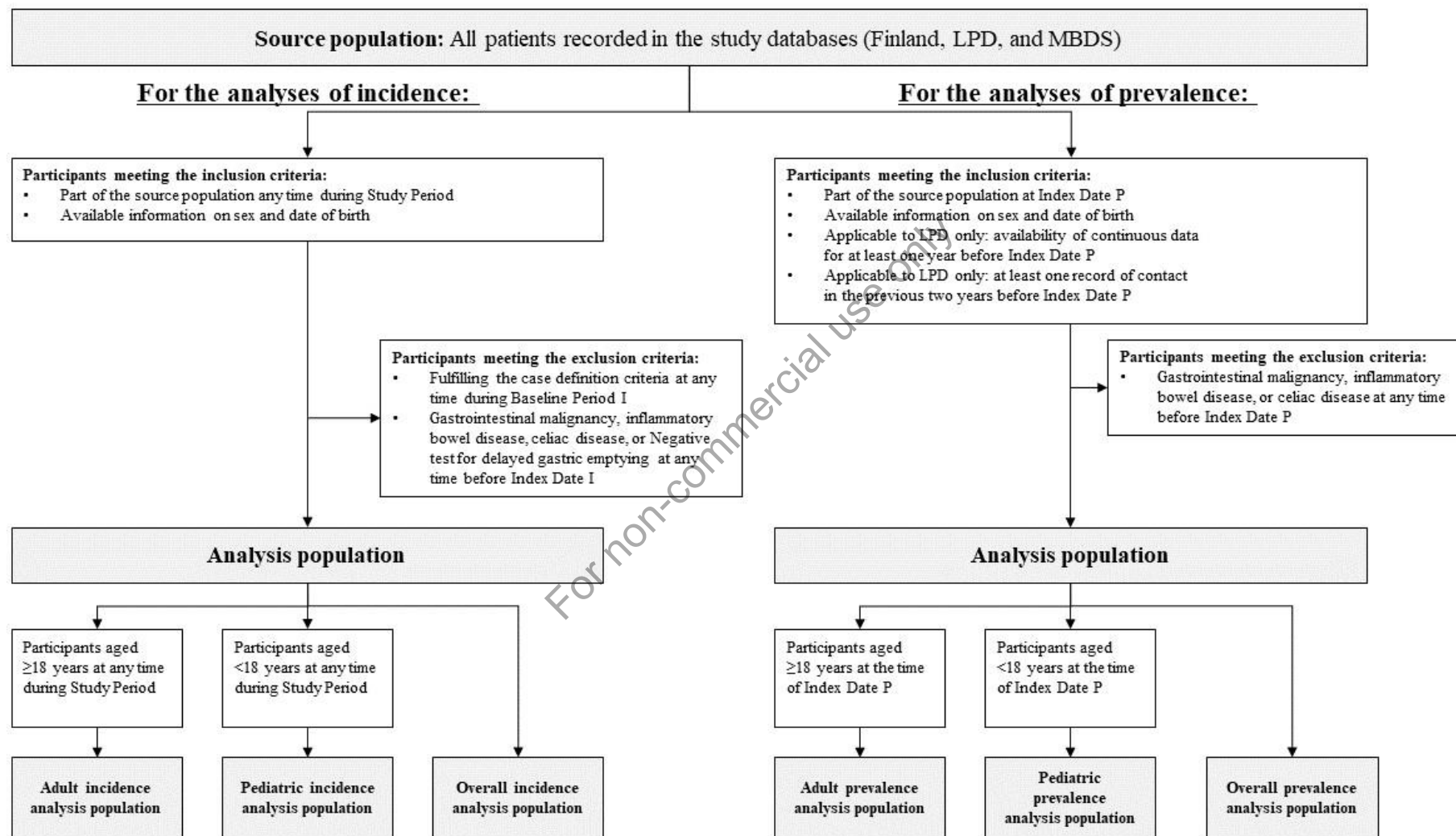
application process. The selection of codes will be made in accordance with the variable definitions used for the Finnish database.

^c Name of specific data set within database from which variables will be ascertained will be defined as part of the SAP development or the data application and extraction process

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Annex 4. Illustration of the selection of the analysis population



Abbreviations: LPD, QuintilesIMS Longitudinal Health Search Database; MBDS, Spanish Minimum Basic Data Set

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Annex 5. Data source descriptions

Spain

Hospital discharge minimum basic dataset (MBDS)

Data on hospital contacts in Spain will be obtained from the MBDS, a nationwide hospital discharge database covering an estimated ~95% of hospital discharges in the country (18–21). The MBDS was established in 1987 and has practically complete national coverage since 1996 (20). The information captured by the database includes date of admission and discharge, diagnoses, and surgical and non-surgical procedures. Diagnoses are coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) system since January 2016; before that, the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) was used (26). The information is considered to be detailed, complete, and of high quality. The available information may additionally include unstructured clinical EMR data (free-text), which can be used (e.g. through data mining techniques) for additional clinical characterization. The availability and contents of EMR data will be explored as part of the data application process. Data from the MBDS is available for research purposes with an approximate lag time of 2-3 years (21).

QuintilesIMS LPD Health Search Database Longitudinal (EMR, mixed data)

The LPD is an EMR database, based on records collected from a constant panel of primary and specialist care physicians in Spain. The database is estimated to hold information on more than 2 million individuals, covering approximately 4% of the Spanish population. The information in the database includes basic demographic characteristics (sex, year of birth), date of registration, physician visits, diagnoses, laboratory tests and test results, specialist referrals, and medications prescribed in primary care. Diagnoses are coded according to ICD-9-CM, with bridging to ICD-10 established within the database. Information on medical procedures (classified according to the International Classification of Diseases, 9th Revision, Procedure Coding System [ICD-9-PCS]) is included with partial coverage. Patient information is routinely collected from the affiliated physicians using the Cegedim EMR software. Individuals enter the dataset by visiting a physician connected to the Cegedim reporting system. Information on death, emigration, or disenrollment from the database (e.g. due to change of health care provider) is not included. The LPD is generally nationally representative for the Spanish adult population in terms of sex and age, whereas children under the age of 15 years are underrepresented.

Finland

The Finnish registries used in this study have nationwide comprehensive coverage, including all individuals residing in the country. Withdrawal from the Finnish national registers is not possible and loss to follow-up can occur only due to emigration or death.

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Prescription registers

In Finland, there are two different registers covering drug prescriptions in the community setting: the traditional Prescription Register and the new e-prescription Register. The traditional Prescription register was established in 1994 and is managed by the Social Insurance Institute. The e-prescription register is held by the Social Insurance Institute and managed by the National Institute for Health and Welfare (THL). The use of e-prescriptions has been compulsory in public health care since April 2013 and in private health care since January 2015. The Prescription Register covers all reimbursed purchased medications in Finland, whereas the e-Prescription Register covers all prescriptions, regardless of reimbursement status. The data contents are similar in both registers, including information on date of purchase, ATC code, and other characteristics of the drug product (e.g. package size and drug strength). Both registers are updated on a monthly basis and data is available for research purposes without lag time.

Care Register for Health Care (HILMO)

The Care Register for Health Care (HILMO) is managed by the National Institute for Health and Welfare (THL) and holds information on secondary care (inpatient and outpatient) contacts in Finland data since 1994 (27). The information in the register includes date of admission and discharge, setting of care, diagnoses (classified according to ICD-10), and surgical and non-surgical procedures. Procedures are classified according to the Finnish national classification for health procedures (THL – Toimenpideluokitus), which is based on the Nordic Medico-Statistical Committee (NOMESCO) classification for surgical procedures (NCSP). The quality of data and registration is generally considered to be very high, although certain variation (e.g. with regard to reporting rate and accuracy of secondary diagnoses) exists (28). Access to data for research is applied for the through the Health and Social Data Permit Authority, Findata.

Register of Primary Health Care Visits (AvoHILMO)

The Register of Primary Health Care Visits (AvoHILMO) is managed by the THL and holds information on contacts with primary health care services in Finland since 2011 (29). The information in the register includes date of contact, diagnoses (classified according to the International Classification of Primary Care, 2nd edition [ICPC-2] and ICD-10 codes), and procedures (Finnish classification of functions in outpatient primary health care [SPAT] codes). Access to data for research purposes is applied for through the Health and Social Data Permit Authority, Findata. The register is updated on a yearly basis.

EMR data from HUS and PSSHP

Regional laboratory databases contain laboratory measurements collected in all domains of public healthcare in Finland. Guidelines for accessing the data from these numerous regional data sources vary across the country. Data for research purposes is applied for through the Health and Social Data Permit Authority, Findata. For this study, EMR data from the HUS (including Helsinki University Hospital) and PSSHP (including Kuopio University Hospital [KUH]) districts will be included. The HUS area covers approximately 1.6 million inhabitants (2019) whereas PSSHP provide specialized medical care for the 247,000 inhabitants of the district and specialty medical care for nearly one million Eastern and Central Finnish individuals at the KUH. The contents and availability of specific data in the EMR extract may vary across the

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study period, but will include laboratory results, diagnostic tests and test results, and other clinical information (such as diagnoses, symptoms, procedures, pharmaceutical and non-pharmaceutical treatment) recorded in the inpatient or outpatient hospital setting.

Statistics Finland

Statistics Finland is the public authority for official statistics in Finland. The data available for research include a large number of socio-demographic and socio-economic variables, including individual-level information on education and income for the entire Finnish population. Data is available in electronic format since 1971.

Digital and Population Data Services Agency

The Digital and Population Data Services Agency holds administrative demographic information on the entire Finnish population, including date of birth, migration, place of residency, and sex. Data is available in electronic format since 1969.

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