AbbVie Deutschland GmbH & Co. KG

CONFIDENTIAL
When used outside AbbVie

STUDY PROTOCOL

Study Title:

Linaclotide Safety Study for the Assessment of Diarrhoea—Complications and Associated Risk Factors in Selected European Populations with IBS-C

Study Protocol Code: EVM-18888

Medicinal Product: Linaclotide, Guanylate cyclase-C agonist

Phase of development: Post-authorisation

Protocol version identifier: 13.3

Date of last version of protocol: 15 October 2024

PROTOCOL SIGNATURES

Protocol Code: EVM-18888

Protocol Title: Linaclotide Safety Study for the Assessment of Diarrhoea—Complications and Associated Risk Factors in Selected European Populations with IBS-C

Protocol Final Version date: 15 October 2024 for Version 13.3

The individuals signing this study protocol EVM-18888 are responsible for the trial and agree to conduct it in adherence to the present document, any amendments, to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and to local regulatory requirements wherever to be performed.

Evidera

[redacted] *Signature* *Date*
[redacted] Real-World Evidence

AbbVie

[redacted] *Signature* *Date*
Pharmacovigilance and Patient Safety

[redacted] *Signature* *Date*
Pharmacovigilance & Patient Safety

[redacted] *Signature* *Date*
Pharmacovigilance & Patient Safety

Database Investigators

	Signature	*Date*
	Signature	*Date*
	Signature	*Date*

Note: Additional research teams may participate based on the actual use of linaclotide in countries with databases.

PASS information

Title	Linaclotide Safety Study for the Assessment of Diarrhoea Complications and Associated Risk Factors in Selected European Populations with IBS-C
Protocol version identifier	13.3
Date of last version of protocol	15 October 2024
EU PAS register number	EUPAS15353
Active substance	Linaclotide ATC code: A06AX04
Medicinal product	Constella 290 µg hard capsules
Product reference	EMEA/H/C/002490
Procedure number	MA number: EU/1/12/801/001-002-00-005
Marketing authorisation holder(s)	AbbVie Deutschland GmbH & Co. KG.
Joint PASS	No
Research question and objectives	What is the estimated risk of SCD among IBS-C patients prescribed linaclotide? What are the risk factors associated to SCD in patients with IBS-C? Specifically, linaclotide prescription.
Country(-ies) of study	United Kingdom, Sweden, Spain
Author	[redacted]

Marketing authorisation holder(s) (MAH)

Marketing authorisation holder(s)	AbbVie Deutschland GmbH & Co. KG Knollstraße 50, 67061 Ludwigshafen Germany
MAH contact person	[redacted] Pharmacovigilance & Patient Safety [redacted] Tel: [redacted]

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

5-HT4	5-Hydroxytryptamine 4
AE	Adverse event
AEMPS	Agencia Española del Medicamento y Productos Sanitarios
AIC	Akaike's Information Criterion
AP-DRG	All patients – diagnostic-related groups
ATC	Anatomical therapeutic chemicals
BIFAP	Base de datos para la investigación Farmacoepidemiológica en Atención Primaria
CD-ROM	Compact disk read-only memory
CI	Confidence interval
CKD	Chronic kidney disease
CPRD	Clinical Practice Research Datalink
DUS	Drug utilisation study
DVD	Digital versatile disk
EMA	European Medicines Agency
EMIS	Egton Medical Information System
EMR	Electronic medical records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General practitioner
GPP	Good Pharmacoepidemiology Practices
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
IACS	Instituto Aragonés de Ciencias de la Salud
IBS	Irritable bowel syndrome
IBS-C	IBS predominately with constipation
IBS-D	IBS predominately with diarrhoea
IBS-M	IBS predominately with mixed bowel habits
ICD-10	International Classification of Diseases and Related Health Problems (10th revision)

ICD-9	International Classification of Diseases and Related Health Problems (Ninth Revision)
ICD-9-CM	International Classification of Diseases and Related Health Problems (Ninth Revision) Clinical Modification
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MAH	Marketing authorisation holder
MAOI	Monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Health Care Products Regulatory Agency
NEC	Necrotizing enterocolitis
NHS	National Health Service
NNH	Number needed to harm
NOS	Not otherwise specified (or unspecified)
NSAIDS	Non-steroidal anti-inflammatory drugs
O/E	On examination
OPCS	Operating procedure code supplement
OR	Odds ratio
PASS	Post-authorisation safety study
PCP	Primary care physician
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
PSUR	Periodic Safety Update Report
QPPV	Qualified person for Pharmacovigilance
R&D	Research & Development
RMP	Risk management plan
SCD	Severe complications of diarrhoea
SIDIAP	Information System for the Development of Research in Primary Care
SNOMED	Systematized Nomenclature of Medicine Clinical Terms

SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitors
STROBE	Strengthening the reporting of observational studies in epidemiology
TBD	To be determined
TCA	Tricyclic antidepressants
THIN	The Health Information Network
UK	United Kingdom
US	United States
UTS	Up to standard
WHO	World Health Organization

3 RESPONSIBLE PARTIES

AbbVie Deutschland GmbH & Co. KG Knollstraße 50, 67061 Ludwigshafen Germany
[redacted] Medical Safety Physician, Chief Medical Office
[redacted] Head of Epidemiology; Pharmacovigilance & Patient Safety (PPS)
[redacted] EU QPPV; Pharmacovigilance Excellence, Pharmacovigilance & Patient Safety (PPS)

Evidera The Ark, 2nd Floor, 201 Talgarth Road, London, W6 8BJ
[redacted] Real-World Evidence
[redacted], Real-World Evidence

4 ABSTRACT

4.1 TITLE

Linaclotide Safety Study for the Assessment of Diarrhoea-Complications and Associated Risk Factors in Selected European Populations with IBS-C.

4.2 RATIONALE AND BACKGROUND

Irritable bowel syndrome (IBS) is a chronic, relapsing gastrointestinal condition characterised by abdominal pain, bloating, and changes in bowel habits. Prevalence estimations vary with the diagnostic criteria used, and in the United Kingdom (UK) were estimated between 9.5% and 22%. IBS can be classified according to Rome III criteria on the basis of the stool's characteristics: IBS predominantly with diarrhoea (IBS-D); IBS predominantly with constipation (IBS-C); and IBS with mixed bowel habits (IBS-M). Approximately one-third of IBS patients have each type of the disease.

The commercialisation of linaclotide (Constella®), a guanylate cyclase-C receptor agonist with visceral analgesic and secretory activities, was approved as the first medicine authorised for the symptomatic treatment of moderate-to-severe IBS-C in adults in the European Union (EU).

Therefore, this study is planned to assess the safety of linaclotide in terms of the risk of severe complications of diarrhoea (SCD) during treatment and other risk factors among patients with IBS-C.

4.3 RESEARCH QUESTION AND OBJECTIVES

The specific research questions and objectives for this study are to:

- Estimate the risk (case-control odds ratio [OR]) of SCD (case) among patients with IBS-C (source population) who received linaclotide prescriptions vs those who did not, controlling for other potential SCD risk factors (socio-demographics, comorbidities [up to 15], co-medications [up to 15] and other potential variables of interest [up to 10])
- Investigate potential risk factors associated to SCD in patients with IBS-C
- Describe the crude incidence of diarrhoea among patients with IBS-C

If allowed by the results of the cases and controls validation as discussed below, two additional objectives will be addressed:

- Describe the crude incidence of SCD among patients with IBS-C (source population) prescribed linaclotide (first-time users)

- Describe the crude incidence of SCD among patients with IBS-C (source population) prescribed linaclotide (first-time users) who are at increased risk of SCD:
    - Patients ≥ 65 years
    - Patients with hypertension, diabetes, or cardiovascular disease diagnostic codes

4.4 STUDY DESIGN

4.5 RETROSPECTIVE CASE-CONTROL NESTED IN A COHORT OF PATIENTS WITH IBS-C (CASES WILL BE PATIENTS SUFFERING FROM SCD) POPULATION

This study will use observational data from three different countries: the UK, Sweden, and Spain. The study population will be a cohort of IBS-C patients. Patients with less than 12 months of computerised records prior to IBS-C cohort entry date or no follow-up time will not be included.

4.6 VARIABLES

The outcomes of interest are severe complications of diarrhoea including dehydration that requires intravenous rehydration, dehydration that requires oral rehydration with solutions of electrolytes, electrolyte imbalance (potassium and sodium), oliguria, anuria, new onset-thromboembolism, new-onset orthostatic hypotension, new-onset syncope, new-onset dizziness, new-onset vertigo, acute renal failure, hypovolemic shock, hospitalisation due to diarrhoea, stupor, coma, or death.

All variables will be identified using diagnostic and procedure codes from general practitioner (GP) electronic medical records. IBS type and safety outcomes will be validated through a questionnaire to physicians treating the cases and controls included in the study.

4.7 DATA SOURCES

The feasibility of conducting the utilisation and safety study has been assessed in the countries of interest, and the most suitable databases identified are as follows:

- In the UK, the Clinical Practice Research Datalink (CPRD) contains information recorded by GPs as part of their routine clinical practice. Currently, CPRD offers two databases – CPRD GOLD and CPRD Aurum. CPRD Aurum contains data contributed by practices using Egton Medical Information System (EMIS), while CPRD GOLD holds data from In Practice Systems Limited Vision. As of March 2024, CPRD Aurum covered more than 24% of the UK population and CPRD GOLD covered approximately 4.4% of the UK population. Core data in both databases include information on socio-demographic characteristics, diagnoses, symptoms, referrals, tests ordered, some test results, prescriptions issued, and additional clinical information. Prescriptions as prescribed by the primary care physician (PCP) or GP have fields for strength and dose. Medical data in CPRD Aurum are coded using a mixture of Read, Systematized Nomenclature of Medicine Clinical Terms (SNOMED), and local EMIS codes; medical data in CPRD GOLD are coded using the Read coding system only. When linked to secondary care data from the Hospital Episode Statistics (HES), hospitalisation reasons for admission are coded by the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10); hospital tests and hospital procedures are coded by operating procedure code supplement (OPCS) codes.

  There is a potential for overlap between the two CPRD databases, since several GP practices that previously contributed data to CPRD GOLD when using In Practice Systems Limited Vision software are now supported by EMIS software, and have agreed to contribute data to CPRD Aurum. Where this is the case, duplicates will be removed, and only data from CPRD Aurum will be retained.

GPs can be contacted by researchers to request details beyond what can be found in the computerised records or to confirm details of patient conditions and treatments. The latest version of the datasets as of the data application date will be used.

- For Spain, the Information System for the Development of Research in Primary Care (SIDIAP) is a primary care database that collects longitudinal data from electronic medical records (EMRs) from 274 primary care centres in Catalonia since 2006, representing approximately 12% of the Spanish population. Data from primary care, specialised care, hospitals, and pharmacies are available, as well as patient characteristics like gender and date of birth, GP-diagnosed conditions, GP prescriptions, prescription dosing and size, date of prescription and dispensation, laboratory test results, other procedures, specialist referrals and diagnosis, hospital referrals, hospital procedures and discharge diagnosis, death date, and pregnancy information. GP diagnoses are coded following the ICD-10 codes, and hospital admissions are classified following the International Statistical Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9). Since 2018, SIDIAP no longer allows the possibility to contact physicians for extracting extended additional information on the patient through long questionnaires. However, there is the possibility of a text review of the primary care records. This text review can be used to validate cases of interest and it would be conducted by IDIAP's clinical researchers. For this study, it is recommended by the data custodians that a review of free-text in the patient's medical records is conducted to improve the validity of the actual study, in place of the previously planned validation strategy using questionnaires to GPs. This free-text review will be made after an anonymisation process of the clinical records and a natural language processing of the text.
- For Sweden, the National Patient Registry (NPR) and Prescribed Drug Register (PDR):
  Information on diagnoses will be obtained from the Swedish NPR, which covers all public inpatient care since 1987 and all outpatient visits since 2001. The medical data include main and up to 21 secondary diagnoses and up to 30 surgical procedures from public and private service providers (National Board of Health and Welfare (Sweden), 2012). Diagnoses are coded using ICD-10 codes and surgical procedures with the Nordic Classification of Surgical Procedures. Primary care is not yet covered in the NPR. At present, the NPR is updated once a year.
  Information about treatment use will be obtained from the Swedish PDR. Its coverage is close to 100% of all prescribed medicines from both primary health care centres and outpatient specialists dispensed to the Swedish population, and information is available since July 2005 (Wettermark et al., 2007). The register contains data on the substance, brand name, formulation, and package, dispensed amount, dosage, expenditure, and reimbursement as well as date of dispensing. Dispensation of over-the-counter (OTC) medications is not included.

4.8 STUDY SIZE

The sample size expected by 2016 in the three countries (available for analysis two to six months later) was at least 200,000 patients with IBS-C (cohort). Based on projected post-authorisation usage data provided by Almirall [MAH of linaclotide at the time of development of this protocol] in the linaclotide risk management plan (RMP), it was expected that roughly 9,665 patients using linaclotide could be captured by the proposed databases in the UK, Spain, and Sweden over the first four years of commercialisation, assuming Almirall [MAH of linaclotide at the time of development of this protocol] sales forecasts were correct, or approximately 5% of all patients with IBS-C would have been exposed to linaclotide.

In the progress report for 2016, users of linaclotide included in each of the study database were reported to be below the targeted numbers. Following the recommendation of the PRAC rapporteur, the end of the data collection was then extended by one year until December 2017. In October 2022, the PRAC recommended to further extend the study period in the UK until at least March 2021or later if possible (the most recent CPRD and HES data at the time of data extraction), and include the CPRD Aurum dataset (in addition to the CPRD GOLD dataset originally proposed) to increase the sample size in the

UK.

Using the latest available information, the sample size across the three countries is approximately 329,000 patients with IBS-C or potential IBS-C, with an exposure to linaclotide rate ranging from 1% to 4%. If the results of the validation of cases are satisfactory with positive predictive value of SCD algorithms in the UK and Spain ≥ 95%, information from the whole cohort will be used to estimate risk of developing SCD across the groups of patients with or without linaclotide exposure, under a cohort study design. If the positive predictive values are < 95%, a case-control analysis will be performed. Assuming the percentage of patients exposed to linaclotide among controls is around 1%, a minimum of 401 case-control pairs would be required to detect an OR ≥ 4 and 745 possible case-control pairs to detect an OR≥ 3 with 80% power, under a matched case-control study design. Within the total IBS-C cohort, it is expected to accrue approximately 11,800 algorithm-identified, potential SCD cases. The final number of case-control pairs to be included in the analyses will depend on the performance of SCD algorithms and case validation results and is expected to be sufficient to detect an OR≥ 3 at 80% power, given the number of potential SCD cases identified by the algorithms.

4.9 DATA ANALYSES

Country-specific analyses will be conducted, and the heterogeneity of the results will be tested. If heterogeneity is not confirmed, then a pooled analysis aggregating data for all three countries will be conducted and country effect will not be assessed.

Patient characteristics at cohort entry date will be described for the full cohort of patients with IBS-C, as well as incidence rate of diarrhoea.

If the results of the validation of cases are satisfactory positive predictive value of EMRs in the UK and Spain ≥ 95% and negative predictive value ≥ 99%, then information from the whole cohort will be used to estimate incidence and incidence density rates for those groups of patients with IBS-C prescribed linaclotide and those who are potentially at increased risk of SCD and prescribed linaclotide. The crude incidence of diarrhoea and of severe complications of diarrhoea will be described by calculating the proportion of patients with IBS-C experiencing diarrhoea and SCD, respectively, and their associated 95% confidence intervals (CIs). Crude incidence density rates of SCD will be also calculated.

Additionally, the hazard ratios of SCD and the exposures of interest (mainly prescription of linaclotide) will be estimated using Cox proportional hazard models. ORs of SCD and the same exposures of interest will be estimated using data from cases and matched controls by applying conditional logistic regression analysis.

If the results of the validation of cases in the UK and Spain are not satisfactory (positive predictive value of our outcome algorithm in the UK and Spain < 95% or negative predictive value < 99%), only the nested case-control study will be performed and ORs of SCD and the same exposures of interest will be estimated using data from cases and matched controls by applying conditional logistic regression analysis.

The goal is to assess SCD among patients who were treated with linaclotide, were ≥ 65 years old, and had history of hypertension, diabetes or cardiovascular disease diagnostic codes (i.e., SCD occurrence is the outcome variable [yes/no]. and the independent variables of main interest are whether the patient has a prescription for linaclotide, a prescription for laxatives, the patient is ≥ 65 years old, and the patient has hypertension, diabetes, or cardiovascular disease diagnostic codes, all of them at index date, or not, controlling for potential confounders).

Statistical analyses will be conducted using SAS® statistical software.

4.10 MILESTONES

The start of data collection was in February 2013 in Sweden, May 2013 in the UK, and September 2014 in Spain. The end of data collection was to be based on the linaclotide uptake and has been extended to

December 2018 in Sweden and Spain, and the most recent HES and CPRD data available by the time of data extraction in 2024 in the UK.

Due to delays on data processing from the Swedish data custodians, data became available for the planned analyses in December 2019. The validation questionnaires to GPs in the UK were eventually available electronically in February 2020. Very low response rate of GPs to questionnaires to validate SCD diagnosis, because of COVID-19 shut down in the UK, motivated a proposal that the validation questionnaires to the GPs in the UK would be sent out again in Q1 2021, aiming to improve the response rate. Continued COVID-19 related shut down in the UK necessitated further postponement of sending the validation questionnaires to GPs in the UK to Q4 2021. When approached on this matter in Q4 2021, the planning manager at CPRD explained that CPRD paused GP questionnaire studies until further notice due to the shortage of primary care clinical staff in the UK to continue focusing their resources on supporting COVID-19 activities. In Q2 2022, CPRD confirmed that they have reopened GP questionnaire services and suggested the study team to resume the validation questionnaires in Q4 2022 given CPRD's resources and current pipeline of work. In the protocol version 12.0, the MAH proposed to reopen the UK validation study in October 2022 until January 2023 with planned study report date in Q3 2023. In response to the MAH's proposal, in the preliminary assessment report for the PASS protocol amendment submission (3rd Oct 2022), PRAC requested the MAH to extend the UK observational period up to the most recent possible date in order to include all available data and to revise the data collection period in the milestones accordingly, without further postponement of the final report (Q3 2023). The MAH contacted CPRD to confirm next steps for data extraction and validation study rerun. CPRD required that the MAH submit a new protocol to the CPRD review committee before requesting the new datasets and re-running the validation study. This is due to the change of dataset from CRRD GOLD to CPRD GOLD and CPRD Aurum, and the change of the observational period. Of note, most practices have moved from CPRD GOLD to CPRD Aurum in the last few years, which makes the CPRD GOLD dataset much smaller. In parallel the MAH informed the EMA / PRAC Rapporteur on 31st March 2023, of the challenges faced due to the protocol update and the consequential impact to the final PASS CSR deliverable. The process from the submission of the protocol amendment until receiving datasets from CRPD is approximately 3-4 months. The MAH submitted a new protocol to CPRD in April 2023 and expected to receive approval and the new datasets in Q3 2023. The MAH proposed to identify the new SCD cases and controls from the new datasets first and reopen the UK validation study in Q4 2023 - Q1 2024 to validate the new cases and controls. However, due to delays in data access, the MAH received the latest CPRD GOLD and CPRD Aurum data cut in March 2024. The validation will be conducted in Q2-Q3 2024.

Study reports will be issued when Periodic Safety Update Reports (PSURs) are due (every six months for the first two years and yearly thereafter). No additional interim report is planned for this study, and the final report of study results will be submitted to PRAC in Q1 2025.

5 AMENDMENTS AND UPDATES

Version	Date	Section of study protocol	Amendment or update	Reason
5.0	17 Jul 2015	N/A	Protocol version approved by PRAC.	N/A
6.0	07 Jun 2016	Marketing Authorisation Holder Annex 3: Physician's Questionnaire	Change from Almirall to Allergan. Change to the proposed questionnaire.	Change in MAH responsible for linaclotide. Improve questionnaire comprehension.

6.1	26 Jan 2017	Several sections in protocol abstract and main text	Timeline extended by one year and agreed with Rapporteur	2016 progress report counts of linaclotide users lower than planned
6.2	08 Jan 2018	Annex 3: Physician's Questionnaire	Language added to introduction paragraph	To ensure physicians only provide information about requested patient
7.0	18 Feb 2019	Several sections in protocol abstract and main text	Timeline extended by six months; change in Spain, from case validation through questionnaires to GP to free-text review of medical records; text added for clarity	The overall timelines are extended due to ongoing delays in data receipt from the Swedish authorities. The Spanish data custodian no longer offers the possibility to conduct validation using questionnaires to GP.
8.0	05 November 2020	Milestone Table	Timeline extended by one year	Very low response rate from UK GP to the questionnaire to validate SCD diagnosis, in February 2020, possibly because of the shutdown in the UK due to COVID 19 infections. Questionnaire will be resent in Q1 2021
9.0	01 March 2021	Milestone Table	Timeline extended by one year	Continued COVID-19 related shut down in the UK necessitated further postponement of sending the validation questionnaires to GPs in the UK to Q4 2021
10.0	07 March 2022	Responsible Parties; Milestone Table; Nested Case Control Analyses	Updated MAH contact details; updated milestone timelines; added proposed sensitivity analyses	CPRD paused GP questionnaire studies until further notice, due to the need for primary care clinical staff in the UK to continue focusing their resources on supporting clinical services; sensitivity

				analyses are proposed to deal with algorithm-classified cases and controls that are unable to be validated.
11.0*	04 August 2022	Milestone Table Marketing Authorisation Holder	Updated milestones Change of MAH from Allergan to AbbVie	MAH proposes to reopen UK validation study in October 2022 until January 2023 with planned study report date in Q3 2023 Update to the MAH from "Allergan Pharmaceuticals International Ltd" to "AbbVie Deutschland GmbH & Co. KG"
12.0	09 November 2022	Data sources Milestones Time periods and dates	Update data sources in the UK to CPRD GOLD and Aurum. Update the last data collection to March 2021 or the most recent HES data available. Update milestones to consider the time to obtain protocol amendment approval from CPRD, data extraction, analyses of new data, re-run of validation study.	Requested by the Health Authority
13.0	01 August 2023	Data sources Milestones Time periods and dates	Update data sources in the UK to CPRD GOLD and Aurum. Update the last data collection to the date of the most recent HES and CPRD data available in 2023 at the time of data access. Update milestones to consider the time to obtain protocol application approval	Update to obtain the most recent data was requested by the PRAC Due to the extension of the data collection and challenges faced by Evidera/MAH with CPRD, this resulted in a request to extend the final PASS CSR date by the MAH.

			from CPRD, data extraction, analyses of new data, re-run of validation study.	
13.1	12 October 2023	Rationale & Background Data Sources Research Method Limitations	Include background information on presentation of severe complications of diarrhoea. Update to representativeness of CPRD GOLD and CPRD Aurum databases. Update control selection criteria for CPRD GOLD and Aurum. Add different coverage period for HES linkage	Requested by CPRD Requested by the PRAC Requested CPRD Requested by CPRD
13.2	15 July 2024	Milestones Updates across sections	Update to reflect the progress of CPRD data access and the UK validation study Updates across multiple sections based on latest available data and information	Updated milestone information provided for extension request via type II variation process
13.3	15 October 2024	Study size Cohort size	Update to include additional text on cohort sample sizes to detect certain ORs. Update to remove some other text	Requested by PRAC Text previously included, now deemed unnecessary.

* Changes requested, pending acknowledgement by PRAC. In this version 13.2, the timelines for the study milestones have been updated to reflect the plan of re open UK validation study in Q2 2024. The updated timelines are provided in Table 1 in the Milestones section below.

6 MILESTONES

Table 1. Milestones

Milestone	Date
Start of data collection	February 2013 (Sweden) May 2013 (UK) September 2014 (Spain)

End of data collection	Electronic datasets: - Spain and Sweden: Data collected up to December 2018. Effective date when data up to December 2018 can be accessed (incorporating time for data access applications to be processed) - UK: the most recent HES and CPRD data available at the time of data access in 2024, i.e., 20 October 2023 for CPRD Aurum, 17 November 2023 for CPRD GOLD 31 March 2021 for HES APC 31 October 2020

Milestone	Date
	for HES OP, 31 March 2020 for HES AE and 29 March 2021 for ONS death data. Validation: - UK: Q2-Q3 2024 - Spain: Q2 2020 Analytical dataset completely available: Q4 2024
Registration in the EU PAS register	September 2016
Study progress reports	With each PSUR
Interim reports	No
Final report of study results	Q4 2024
EMA submission	Q1 2025

Abbreviations: CPRD Clinical Practice Research Datalink; EU European Union; GP general practitioner; HES Hospital Episode Statistics; PAS post authorisation study; PSUR periodic safety update report; UK United Kingdom; NPR National Patient Register; PDR Prescription Drug Register

7 RATIONALE AND BACKGROUND

IBS is a chronic, relapsing gastrointestinal condition characterised by abdominal pain, bloating, and changes in bowel habits. The first presentation of patients with IBS symptoms to a physician is usually in the 30- to 50-year age group, and there is a decrease in reporting frequency among older subjects (Drossman et al., 2002; IBS Global, 2009). Typically, women are diagnosed with IBS two or three times as often as men in most studies, and all population-based studies have reported a female predominance (Keeling & Fielding, 1975; Thompson, 1984; 1997; Saito et al., 2002). Moreover, women make up 80% of the population with severe IBS (Longstreth & Wolde-Tsadik, 1993). Prevalence estimations vary with the diagnostic criteria used, and in the UK were estimated between 9.5% and 22% (Spiller et al., 2007).

IBS can be classified according to Rome III criteria, on the basis of the stool's characteristics: IBS-D; IBS-C; and IBS-M. Patients can transition among these subgroups (IBS Global, 2009). Approximately one-third of IBS corresponds to IBS-D, one-third to IBS-C, and one-third to IBS-M (Tillisch et al., 2005). When there is insufficient abnormality of stool consistency to meet the criteria for any of the above subgroups, IBS is said to be unsubtyped (Longstreth et al., 2006).

Prior IBS treatments were limited to lifestyle modifications, psychological interventions, and symptomatic treatments (e.g., laxatives, anti-diarrhoeals, and anti-spasmodic agents), or drugs unauthorised for this indication in some of the countries. In a review, current IBS-C treatment options showed limited efficacy, and the risk-benefit profile of early 5-Hydroxytryptamine 4 (5-HT4) agonists restricted clinical use (Fortea et al., 2013).

Linaclotide (Constella®), a guanylate cyclase-C receptor agonist with visceral analgesic and secretory activities, has received approval for its commercialisation. It is the first medicine authorised for the symptomatic treatment of IBS in the EU. The target indication of linaclotide is the treatment of moderate-to-severe IBS-C in adults. Results from clinical trials and real-world research show that most common side effect of linaclotide is diarrhea (Bassotti et al, 2018; Nee et al, 2019). In clinical studies, severe diarrhea associated with dehydration have been reported among 2% of IBS-C patients who were prescribed linaclotide (Rey et al , 2017; Linaclotide Information Sheet, 2023). During post-marketing surveillance, the dehydration might present with tachycardia, hypotension, dizziness, syncope, and electrolyte abnormalities (hypokalemia, hyponatremia), necessitating hospitalization and intravenous fluid therapy (Kalola et al, 2023, Linaclotide information sheet, 2023).

The proposed study will assess the risk of SCD during treatment with linaclotide therapy and other risk factors among patients with IBS-C from three selected European countries: the UK, Sweden and Spain. This study is descriptive and there is not an *a priori* hypothesis.

8 RESEARCH QUESTIONS AND OBJECTIVES

8.1 RESEARCH QUESTIONS

The study will address the following research questions:

- What are the risk factors associated with SCD in patients with IBS-C (specifically linaclotide prescription vs no linaclotide prescription)?
- What is the estimated risk of SCD among IBS-C patients prescribed linaclotide (if allowed by the results of the cases and controls validation as discussed below)?

Both research questions will be assessed in three different countries: the UK, Sweden and Spain

8.2 OPERATIONAL OBJECTIVES

- To estimate the risk (case-control OR) of SCD (case) among patients with IBS-C (source population) who received linaclotide prescription vs those who did not, controlling for other potential SCD risk factors (socio-demographics, comorbidities [up to 15], co-medications [up to 15] and other potential variables of interest [up to 10])
- To describe the crude incidence of diarrhoea among patients with IBS-C (source population)

If allowed by the results of the cases and controls validation as discussed below:

- To describe the crude incidence of SCD among patients with IBS-C (source population) prescribed linaclotide (first-time users)
- To describe the crude incidence of SCD among patients with IBS-C (source population) prescribed linaclotide (first-time users) who are at increased risk of SCD:
    - Patients ≥ 65 years
    - Patients with hypertension, diabetes, or cardiovascular disease diagnostic codes

9 RESEARCH METHODS

9.1 STUDY DESIGN

The study will use observational data from three different countries: the UK, Sweden and Spain. The linaclotide PASS will be a retrospective case-control study nested in a cohort of patients with IBS-C. Cases will be patients suffering from SCD. If the validation is satisfactory (please refer to Section 9.3.4 *Validation of the Diagnosis and Safety Endpoints* below), then both study design components, the case-control and the cohort, will be analysed (please refer to Section 9.7 *Data Analysis* below).

9.2 SETTING

9.2.1 STUDY POPULATION

The source population for the safety study will be:

- UK: patients registered with a GP practice which contributes data to CPRD GOLD or Aurum
- Sweden: patients registered in the NPR linked to the PDR
- Spain: patients registered with a PCP office participating in the SIDIAP

Specific codes for IBS-C and a combination of IBS and constipation codes will be used to identify patients with IBS-C; these are described in Annex 3.

9.2.1.1 INCLUSION/EXCLUSION CRITERIA IN THE IBS-C COHORT

Patients in the study will be required to meet the following inclusion criteria:

- Patient meets IBS-C criteria, as identified through the combination of IBS and constipation codes, (please refer to Section 9.3.4 *Validation of the Diagnosis and Safety Endpoints* below and Annex 3) anytime during the study period
- Patient has at least 12 months of computerised records prior to IBS-C cohort entry date
- Patient meets 'acceptable' criteria from CPRD (the patient is permanently registered at the practice or the PCP and has a valid year of birth and gender) at IBS-C cohort entry date (UK); no equivalent criteria for Spain or Sweden.
- Patient is active (i.e., alive and permanently registered at a practice (UK) or a PCP office (Spain) or the national register (Sweden)) at IBS-C cohort entry date

The following exclusion criteria will apply:

- Patient has no follow-up time (for example, transfers out or dies on the date IBS-C criteria are first fulfilled)
- The practice's up-to-standard (UTS) date in CPRD GOLD is later than the IBS-C cohort entry date (UK); no equivalent criteria for CPRD Aurum, Spain or Sweden*.

*Note: For CPRD GOLD, practices meeting pre-defined quality control standards for completeness, continuity, and plausibility are registered as UTS since the date those standards are met. 'Acceptable' and 'up to standard' are two quality flags that will be taken into account when selecting the study cohort in CPRD GOLD in the UK. In CPRD Aurum, there is no equivalent flag for UTS, therefore, only the 'acceptable' flag will be used for cohort selection. In Spain, no such flags exist but the SIDIAP confirmed that given the study will be performed using data from 2014 onwards, all the data included is of good quality for research purposes. In Sweden, the data received has already been through a quality control by the National Board of Health and Welfare. This control includes checking that compulsory variables like personal registration number, hospital, and main diagnosis are reported, and the validity of all variables values tested. Therefore, no additional changes in the inclusion and exclusion criteria will be needed for Spain and Sweden.

Patients meeting IBS-C inclusion criteria (and not meeting exclusion criteria) at the beginning of the study period (see below) will be prevalent IBS-C patients. Patients meeting IBS-C inclusion criteria thereafter will be incident IBS-C patients.

Inclusion/exclusion criteria for Spain and Sweden will be the same but adapted to the respective database specifics.

9.2.1.2 CASE DEFINITION

Among patients with IBS-C, SCD cases will be patients suffering from diarrhoea (as documented by diagnostic codes) and subsequently (between the diarrhoea diagnosis date and 45 days afterwards) any of the following outcomes:

- Dehydration that requires intravenous rehydration
- Dehydration that requires oral rehydration with solutions of electrolytes
- Electrolyte imbalance: potassium (serum potassium levels 3.0–3.5 mEq/L or < 3.0 mEq/L) and sodium (serum sodium levels > 150 mEq/L)
- Oliguria (urine output < 400 mL in 24 h)
- Anuria (urine output < 50 mL in 24 h)

- New-onset thromboembolism episodes
- New-onset orthostatic hypotension
- New-onset syncope
- New-onset dizziness
- New-onset vertigo
- Acute renal failure
- Hypovolemic shock
- Hospitalisation due to diarrhoea
- Stupor
- Coma
- Death (death certificates will be requested to confirm the cause of death)

The case index date is the date of the first diarrhoea episode that is followed by the first recording of any of the previous outcomes from the list above.

Results of laboratory tests will be available as recorded into only two of the proposed data sources: in CPRD they are manually recorded, especially when they are abnormal; they are automatically recorded in the SIDIAP but there is no lab data information from the Swedish NPR.

9.2.1.3 CONTROL SELECTION

Among patients with IBS-C, each case will be matched by age (initially ±3 years), the number of years of active history in the database (initially ±3 years) (CPRD, Swedish NPR or SIDIAP), IBS-C prevalent or incident status, and geographic region and linkage availability (for CPRD only) at index date. Cases will be matched to up to four controls, depending on the number of cases and the total number of cases and controls for validation (see Section 9.3.4 *Validation of the Diagnosis and Safety Endpoints*). Controls will be selected randomly among those patients with IBS-C in the risk set at the case's index date. Cases and controls in the UK will have some variables from their automated information that will be validated through a questionnaire to their attending GPs (see Section 9.3.4 *Validation of the Diagnosis and Safety Endpoints*). Likewise, in Spain case validation will use any additional information obtained through review of free text from medical records by IDIAP's clinical researchers.

Control index date will be set as the same index date of the matched case. An IBS-C patient could, in theory, be a matched control to more than one case. Additionally, a control could, in theory, become a case during its follow-up period.

9.2.1.4 TIME PERIODS AND DATES

The study period is determined by the launch date of linaclotide, subsequent uptake, and length of time required to accrue a non-trivial number of SCD cases (see case definition above, Section 9.3.*Variables* and Section 9.5 *Study Size* below). The study period starts on the date of linaclotide commercialisation in each of the countries: in Sweden on February 2013, in the UK on May 2013, and in Spain on September 2014.

The end of data collection has been extended to November 2023 in the UK, and December 2018 in Sweden and in Spain, so the study period will include 50 months in Spain, approximately 10 years in the UK and 68 months in Sweden for medical and prescription data accrual, each database's lag time (for collected data to be available in each database, estimated in up to eight months or until August 2019), and seven months for initial data management and additional data collection from GPs (Q3 2019 for Spain and Sweden, and currently planned until Q3 2024 for the UK). Due to delays experienced in accessing data from the Swedish authorities, version 7.0. of the protocol proposed to extend the final delivery of the final report until June 2020. This is because data from Sweden was not anticipated to become available until Q3-Q4 2019. Version 9.0 of the protocol proposed to extend the final delivery of the final report to June 2022. A very low response rate by the UK GPs to questionnaires

sent to them in Q1 2020 to validate SCD diagnosis was observed. This was possibly because of the shut down in the UK due to COVID-19 infections. A decision was made to resend the questionnaire in Q1 2021. The continued COVID-19 related shutdown in the UK necessitated further postponement of resending the questionnaire to GPs. MAH proposed to resend the questionnaires in Q4 2021. When approached on this matter in Q4 2021, the planning manager at CPRD explained that CPRD paused all GP questionnaire studies until further notice due to the shortage of primary care clinical staff in the UK to continue focusing their resources on supporting COVID-19 activities. Version 11.0 of the protocol proposed to re-open UK validation study in October 2022 until January 2023 with planned study report in Q3 2023.

In response to the MAH's proposal, in the preliminary assessment report for the PASS protocol amendment submission (3rd Oct 2022), PRAC requested the MAH to extend the UK observational period up to the most recent possible date in order to include all available data and to revise the data collection period in the milestones accordingly, without further postponement of the final report (Q3 2023). The MAH contacted CPRD to confirm next steps for data extraction and validation study rerun. CPRD required that the MAH submits a new protocol to the CPRD review committee before requesting the new datasets and re-running the validation study. This is due to the change of dataset from CPRD GOLD to CPRD GOLD and CPRD Aurum, and the change of the observational period. The MAH submitted a new protocol to CPRD in April 2023 and expected to receive approval and the new datasets in Q3 2023. However, the actual process from application submission to data access took almost 12 months and the final data cut was eventually delivered in March 2024. The identification of new potential SCD cases as well as the initiation of validation activities have been completed in Q2 2024.

The validation of the diagnosis and SCD cases ended in Q2 2020 in Spain and expected to end in Q3 2024 in the UK. There is no validation study in Sweden. This study period is expected to allow for sufficient follow-up (long-term safety assessment) for those enrolled during the first period after linaclotide launch and for any subpopulations of interest (those with increased risk of SCD) to have the opportunity to accrue a sizable number of subjects for descriptive purposes. Please refer to Section 9.5 *Study Size* and Section 9.7 *Data Analysis* below.

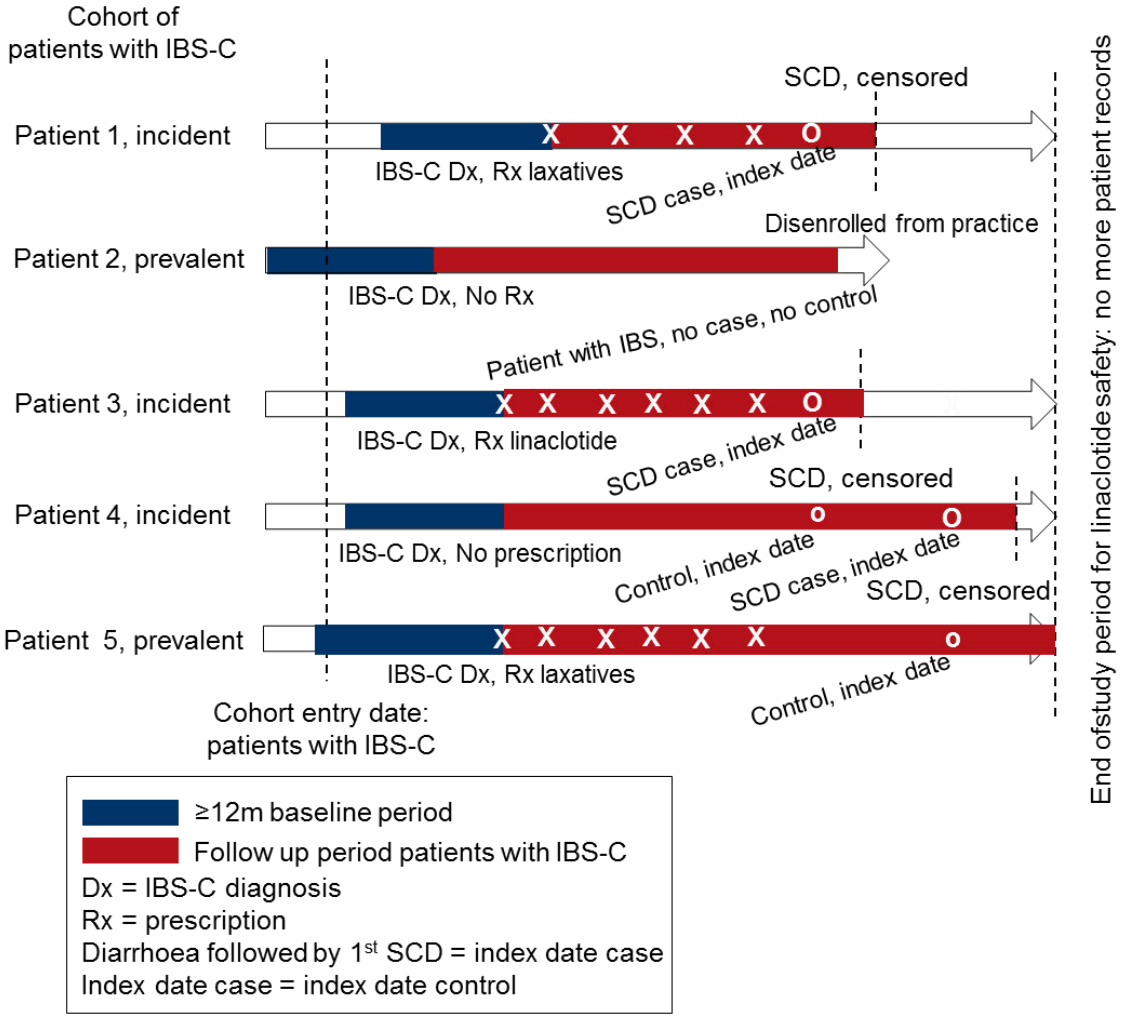
The IBS-C cohort entry date for each cohort member will be defined as the date IBS-C criteria are first fulfilled or 01 February 2013 in Sweden, 13 May 2013 in the UK, and 01 September 2014 in Spain (linaclotide launch dates), whichever is the latest.

The follow-up period for each study subject in the IBS-C cohort will be from the cohort entry date to the earliest of the following (end of follow-up date; one day is the minimum follow-up (Figure 1):

- End of the study period
- Disenrollment from the database (date of transfer out of the practice or the PCP or Sweden)
- Date of last data collection for the practice
- Death
- Index date

The baseline period is the ≥12-month period before IBS-C cohort entry date.

Figure 1. Study Periods in Linaclotide PASS



9.3 VARIABLES

Included patients will be described according to their characteristics and potential confounder information at cohort entry date (and at index date for cases and controls) using data from the baseline period, GP and hospital diagnoses, procedures, and prescription information from each data source:

9.3.1 PATIENT CHARACTERISTICS:

- Age (as continuous variable and categories < 18, 18–64, ≥ 65 years)
- Gender
- Height and weight
- Socioeconomic status[1]
- IBS-C prevalent or incident status
- Pregnancy and breast-feeding (when available)[2]

[1] When possible: CPRD includes Townsend data and the Index of Multiple Deprivation, SIDIAP includes MEDEA index

[2] Breast feeding cannot routinely be identified from database records.

9.3.2 POTENTIAL CONFOUNDER INFORMATION

- Age (as continuous variable and categories < 18, 18–64, ≥ 65 years) (potential confounder or effect modifier)
- Gender (potential confounder or effect modifier)
- IBS-C prevalent or incident status (proxy for unspecified confounders)
- Prior diarrhoea codes (potential confounder)
- Chronic constipation (potential confounder)
- Comorbidities:
- Potential confounders or effect modifiers (by time since first prescription without discontinuation or by age group or by gender):
- Cardiovascular disorders or risk factors—i.e., cerebrovascular disease, coronary artery disease, angina, myocardial infarction, heart failure, arrhythmias, use of antiarrhythmic drugs, hyperlipidaemia, or use of lipid-lowering drugs
- Hypertension or use of antihypertensive drugs
- Diabetes
- Other potential confounders:
- Hepatic impairment
- Chronic kidney disease (CKD) or chronic renal failure
- Inflammatory bowel conditions (i.e., Crohn's disease, ulcerative colitis, microscopic colitis)
- Mechanical gastrointestinal obstruction
- Any psychiatric disorder, as well as:
    - Depression diagnosis
    - Anxiety diagnosis
- Food intolerance (e.g., lactose)
- Celiac disease
- Cancer (e.g., colon)
- Bile salt malabsorption
- Immunodeficiency
- Obesity and eating disorders (anorexia nervosa, bulimia) that are suspected conditions related to potential for abuse or excessive use—e.g., use for weight loss or as laxative
- Medications: the two most commonly prescribed medication groups in addition to the following (Only around half of IBS-C patients are expected to be on prescribed medication, but the majority of patients are expected to be self-treated [Wilson et al., 2004].) potential confounders, defined as at least one prescription in the prior 45 days:
- Linaclotide
- Laxatives (i.e., bulk-forming laxatives, stimulant laxatives, faecal softeners, and osmotic laxatives) (Concomitant use of laxatives was described among one-third of the antispasmodic mebeverine users and it was associated with increased odds of hospitalisation [Goettsch WG, 2004].)
- Antispasmodics (i.e., anti-muscarinic agents and direct-action smooth muscle relaxants)
- Prokinetic drugs
- Antidepressants (i.e., tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], and monoamine oxidase inhibitors [MAOIs])
- Antibiotics

- Calcium and aluminium-containing antacids
- Magnesium-containing antacids
- H2 blockers
- Proton pump inhibitors
- Non-steroidal anti-inflammatory drugs (NSAIDS)
- Opioids
- Analgesics
- Other potential confounders:
- History of digestive surgery (especially history of cholecystectomy)
- Gastroenterology clinic referral
- Bacterial/viral/parasite lab information (positive versus negative or no information)

For prevalence of chronic comorbidities, prior diagnoses, or history of digestive surgery at index date, the patient's entire medical history will be explored.

Patients with IBS-C and SCD (or cases) will be defined as the occurrence during the follow-up period (between IBS-C cohort entry date and end of follow-up date) of any of the following safety outcomes of interest (primary endpoints) subsequent (see below) to diarrhoea, according to diagnostic codes and primary care laboratory test results:

- Dehydration that requires intravenous rehydration
- Dehydration that requires oral rehydration with solutions of electrolytes
- Electrolyte imbalance: potassium (serum potassium levels 3.0–3.5 mEq/L or < 3.0 mEq/L) and sodium (serum sodium levels > 150 mEq/L)
- Oliguria (urine output < 400 mL in 24 h)
- Anuria (urine output < 50 mL in 24 h)
- New onset thromboembolism episodes
- New-onset orthostatic hypotension
- New-onset syncope
- New-onset dizziness
- New-onset vertigo
- Acute renal failure
- Hypovolemic shock
- Hospitalisation due to diarrhoea
- Stupor
- Coma
- Death (death certificates will be requested to confirm the cause of death)

To identify these safety outcomes, diagnostic and procedure codes from electronic medical records will be used. We will employ combinations of diarrhoea and these safety outcomes codes to identify those that should be considered diarrhoea complications (diarrhoea-related suspected events). As the safety outcomes of interest mentioned above can occur in the absence of diarrhoea (for example, electrolyte imbalances are not only complications of diarrhoea), we will only consider those diarrhoea complications occurring between the diarrhoea diagnosis date and 45 days afterwards (beyond that time window, the occurrence of the proposed outcomes could be considered unrelated to the diarrhoea episode already resolved or, alternatively, associated to deficient patient management). A set of code lists is outlined in Annex 3.

For each medication of interest, a patient (cases and controls) will be classified at the index date according to the following user experience (time window of exposure to the medication):

- Current user, if there was a prescription or dispensation of the medication of interest with supply until the index date or supply that ended in the 90 days before the index date.
- Non-current user, if the last prescription or dispensation was issued longer than 90 days before index date
- Never user, if there is no prescription or dispensation history for that medication.

The main exposures or potential risk factors of interest are:

- Linaclotide user experience category as described above
- Laxatives user experience category as described above

Additionally, other variables listed above will be included in the analyses. Duration of medication use for each of the medications of interest will also be used (defined as time since the first documented prescription without discontinuation until the case or control index date).

9.3.3 IBS DIAGNOSIS AND SEVERITY DEFINITION

The target indication of linaclotide is the treatment of moderate-to-severe IBS-C in adults. There are several Read, SNOMED, ICD-9, or ICD-10 codes related to IBS.

GP testimonies gathered during our pilot study, suggests that patients with IBS are frequently assigned IBS codes after other diagnosis have been ruled out and not necessarily during initial consultations, consistent with published research (Harkness EF et al., 2013a and b). Instead, codes of abdominal pain and other abdominal symptoms, suggestive of IBS, and codes of abdominal examinations were mentioned as part of the codes used for these patients. Sometimes, confirmed diagnosis of IBS might not be coded as such and might only remain in the patient's record's notes.

In order to identify potential cases of IBS-C patients using codes, specific IBS-C codes and a combination of an IBS code with a code for constipation will be used. A combination of a code for abdominal pain and at least two abdominal unspecific codes, in addition to a code for constipation will also be used to identify potential cases of IBS-C. Table 4, Table 5 and Table 6 in Annex 3 include a broad list of Read codes, ICD-10, and ICD-9 codes for the identification of patients with IBS with different levels of specificity, as well as codes for constipation to be used in combination.

There are no Read, ICD-9, or ICD-10 codes to indicate the severity of IBS. The most studied and most commonly used tools for measuring IBS severity involve quality-of-life and patient-reported symptom metrics that are not routinely recorded in the computerised databases selected for this study.

9.3.4 VALIDATION OF THE DIAGNOSIS AND SAFETY ENDPOINTS

Information on IBS-C is not well-captured by standard diagnosis codes. SCD is also not coded as such in the databases. Therefore, IBS-C and SCD will be validated by the physicians treating the patients selected as cases or as controls. This will require additional primary data collection from GPs that is possible in the UK with the use of CPRD.

The process in the UK would consist of asking cases' attending GPs to confirm the type of IBS. All cases (patients with IBS-C experiencing SCD) will be characterised in further detail through contact with their PCPs. A questionnaire will be mailed to the GP with whom each identified subject is registered to validate both diagnoses (IBS and SCD [if applicable]; please refer to Annex 3).

The feasibility of using this questionnaire to collect validation information about cases was evaluated through a pilot study with a small number of physicians in the UK. This UK pilot study targeted a group of 25 PCPs to test the questionnaire and contribute to its development. The section, *Pilot Study Summary Report,* in Annex 3 reports on the pilot study conduct. This pilot study included additional questions to PCPs about preferred codes or code combinations used to record diagnoses of patients with IBS-C.

Although it was originally planned for the validation study to also be undertaken in Spain using GP questionnaires, since 2018, SIDIAP no longer allows the possibility to contact physicians for extracting extended additional information on the patient through long- questionnaires. However, there is the possibility of a text review of the primary care records. This text review can be used to validate cases of interest, conducted by IDIAP's clinical researchers. For this study, it is recommended by the data custodians that a review of free-text in the patient's medical records is conducted to improve the validity of the actual study, in place of the previously planned validation strategy using questionnaires to GPs. This free-text review is made after an anonymisation process of the clinical records and a natural language processing of the text.

We will validate our outcome identification algorithm by calculating the positive predictive value and the negative predictive value in both countries.

9.4 DATA SOURCES

In the UK, the proposed data source is the CPRD (both CPRD GOLD and CPRD Aurum). For Sweden and Spain, the proposed data sources are the Swedish NPR linked to the PDR and the SIDIAP, respectively.

A summary of potential data sources that were evaluated for use in the study can be found in the *Database Feasibility Assessment* section in Annex 3.

9.5 STUDY SIZE

If we assume a combined population in the UK, Sweden, and Spain of approximately 120 million people (Eurostat, 2014), a prevalence of IBS recorded in primary care of 3.5% (Harkness et al., 2013) and roughly one-third of those corresponding to IBS-C (Tillisch et al., 2005), then the three proposed databases could be expected to include around 216,000 active IBS-C patients. By December 2016, it was estimated that approximately 9,665 patients would have been exposed to linaclotide in the three target databases, for a combined exposure of more than 4,572 patient-years, with the UK contributing approximately 28% of patients, Spain 25%, and Sweden 47%. These estimated number of patients exposed to linalcotide is now expected to be reached by end of December 2017, so the data collection period has been extended accordingly.

Linaclotide clinical trial results (12 and 26 weeks in length) suggest that about 3% of IBS-C patients exposed to placebo and 19.6% of IBS-C patients exposed to linaclotide will experience diarrhoea over those periods, predominantly within the first weeks of initiating therapy. Among them, 4% in the placebo group and 10.1% in the linaclotide-exposed group will experience severe diarrhoea. Therefore, severe diarrhoea was experienced by 0.13% of all IBS-C patients exposed to placebo and by 1.99% of IBS-C patients exposed to linaclotide (Chey et al., 2012; Rao et al., 2012). Other treatments for patients with IBS-C are also associated with diarrhoea, usually of mild severity (Wood, 2012). Information sent to healthcare professionals by the manufacturer of a drug sometimes prescribed for IBS-C patients in the United States (US) warned of very serious diarrhoea complicated with hypovolaemia, hypotension, and syncope that required admission to the hospital and intravenous therapy in approximately one in 2,500 patients (or 0.04%) (Wooltorton, 2004).

9.5.1 COHORT SIZE

The linaclotide PASS is a case-control study nested in a cohort of patients with IBS-C. The information of main interest from the databases (refer to Section 9.3.4. *Validation of the Diagnosis and Safety Endpoints*) will be validated for cases and controls through primary data collection from GPs. If the validation results are satisfactory (positive predictive value of EMRs ≥ 95% and negative predictive value ≥ 99%), then information from the whole cohort would be used to estimate the incidence of diarrhoea and the incidence of SCD in the cohort of IBS-C patients and the relative risks of SCD and the exposures of interest (mainly prescriptions of linaclotide). Otherwise, only ORs of SCD and the same exposures of interest will be estimated using data from cases and controls.

Table 2 illustrates a range of sample sizes that are required to have 80% power to detect a certain OR for SCD, comparing patients with IBS-C and a certain risk factor to patients with IBS-C and no risk factor, assuming that patients with IBS-C and no risk factor experience SCD with a variety of incidences.

A cohort of patients with IBS-C, and assuming that 5% of subjects in that cohort will have the risk factor of interest, would require a total of approximately 200,000 patients (including 10,000 exposed to the risk factor of interest) with the necessary data for the analysis to have at least 80% power to detect the combination of increased OR (or larger ORs) for the incidence of SCD (or higher incidence); these are in bold in Table 2.

To detect an OR of ≥ 1.5 with 80% power at a 1.0% outcome incidence among unexposed patients, a minimum of 85,416 patients with IBS-C is required in the cohort. For an OR of ≥ 2, the required sample size is 25,022 patients. At a 0.5% outcome incidence among unexposed patients, the required sample size increases to 169,442 patients for detecting an OR of ≥ 1.5, and 49,501 patients for detecting an OR of ≥ 2, with 80% power.

Table 2. Sample Sizes of IBS-C Patients Exposed or Non-Exposed (Total Sample Size) to Risk Factors of Severe Complications of Diarrhoea (SCD) Required to Identify Increased ORs for SCD*

Outcome incidence in unexposed	OR = 1.5	OR = 2	OR = 3	OR = 4	OR = 6	OR = 8
0.01%	8,404,791	2,448,728	776,301	414,607	**197,410**	**124,546**
0.02%	4,203,079	1,224,630	388,274	207,387	**98,760**	**62,318**
0.05%	1,682,052	490,173	**155,457**	**83,055**	**39,572**	**24,981**
0.1%	841,711	245,354	**77,852**	**41,612**	**19,841**	**12,534**
0.2%	421,541	**122,944**	**39,049**	**20,890**	**9,977**	**6,312**
0.5%	**169,442**	**49,501**	**15,768**	**8,458**	**4,059**	**2,579**
1.0%	**85,416**	**25,022**	**8,009**	**4,315**	**2,087**	**1,335**

* Significance level is two sided α 0.05 and power is 1 β 80%, 20:1 number of unexposed to exposed patients with IBS C (equivalent to 5% exposure to risk factor), according to Fleiss (2003), Statistical Methods for Rates and Proportions, (with continuity correction).

Abbreviations: OR odds ratio

9.5.2 NESTED CASE CONTROL SIZE

Table 3 illustrates a range of sample sizes required to have 80% power to detect a certain OR for those patients exposed or unexposed to a certain risk factor for SCD from a matched case-control study, assuming a range of proportions for exposure of the controls to the risk factor of interest.

A case-control study (Table 3) of SCD cases nested in a cohort of patients with IBS-C (like the one previously mentioned with 200,000 subjects) would require, for example, a total of 94 case-control pairs (equivalent to an incidence of SCD = 0.05%) with the necessary data for the analysis to have at least 80% power to detect an OR = 4 (or larger), associating SCD with a risk factor present in 5% of controls (in bold and grey background in Table 3).

Table 3. Sample Sizes (Case-Control Pairs) of Patients with IBS-C and Severe Complications of Diarrhoea (SCD) to Identify Increased Case-Control OR (Rate Ratio Estimate) for Risk Factors of Interest*

Percentage exposed among controls	OR=1.5	OR=2	OR=3	OR=4	OR=6	OR=8
0.1%	77656	22791	7252	3868	**1831**	1147
0.5%	15625	4595	1468	786	375	237
1.0%	7872	2321	745	**401**	**193**	**123**
2.0%	3996	1184	384	209	103	67
3.0%	2705	806	264	145	72	48
4.0%	2060	616	204	113	57	38
5.0%	1674	503	**168**	**94**	**48**	**33**
6.0%	1417	428	144	81	42	29
7.0%	1233	374	127	72	38	27
8.0%	1096	334	114	65	35	25
9.0%	990	303	105	60	33	23

* Significance level is two sided α 0.05 and power is 1 β 80%, 1:1 number of cases (IBS C patients with severe complications of diarrhoea) to number of controls (IBS C patients without severe complications of diarrhoea) matched by number of years of active history in the CPRD (±1 years), IBS C prevalent or incident status, and region. A higher number of matched controls per case would increase statistical efficiency (Pang D, 1999).

Abbreviations: OR odds ratio

Initially, we proposed conducting the study with data collected up to December 2016, but based on the patients counts accrued by December 2016, the data collection period was extended. In the current version of the protocol, the data collection period has been extended to the date of the most recent data available in HES and CPRD at the time of data access for the UK only. As CPRD including Aurum data is about two times larger than the last data extraction, we expect more than 200,000 patients with IBS-C in CPRD. Among them, based on market uptake forecasts, we would also expect having around 2,000 patients exposed to linaclotide by that date (as potential risk factor of interest, or approximately 1% of patients with IBS-C).

If SCD occurs with a frequency of 0.05% among patients with IBS-C (cases) and we select one or more controls per case, then 94 case-controls sets would allow the detection of OR = 4 (or larger), with 80% power for a risk factor present in 5% of controls (approximately the expected proportion of patients with IBS-C exposed to linaclotide).

If we assume that SCD occurs with a frequency of 0.08%, then around 168 case-control sets would allow the detection of OR = 3 or larger, with 80% power for a risk factor present in 5% of controls (in bold in Table 3).

9.6 DATA MANAGEMENT

We will collect electronic patient records from the CPRD in the UK, Swedish NPR in Sweden, and SIDIAP in Spain. Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programmes. In Spain, SIDIAP will be in charge of the data management.

Each database custodian will maintain any patient-identifying information securely on site according to internal standard operating procedures. Evidera will maintain the data cuts according to internal procedures.

An Evidera data analyst will write and review programs to implement the analyses outlined in the *Data Analysis* section below. The project team will review all data outputs, including SAS® code as needed. Changes and corrections to programs stemming from the review will be made as appropriate. All programs will be saved, and the process documented. Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on compact disk read-only memory [CD-ROM] or digital versatile disk [DVD]) with periodic backup of files to tape. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.7 DATA ANALYSIS

Country-specific analyses will be conducted, and the heterogeneity of the results will be tested. If heterogeneity is not confirmed, then a pooled analysis will be conducted, and country effect will not be assessed.

9.7.1 PATIENT CHARACTERISTICS AND MEDICAL HISTORY

Patient characteristics at the IBS-C cohort entry date will be described for the full cohort of patients with IBS-C by reviewing data for a minimum of 12 months prior. Patient characteristics at the index date will be described for the cases and controls by reviewing data for a minimum of 12 months prior to index date.

The linaclotide PASS is a case-control study nested in a cohort of patients with IBS-C. The information of main interest from the databases (refer to Section 9.3.4 *Validation of the Diagnosis and Safety Endpoints*) will be validated for cases and controls through primary data collection from GPs in the UK and free-text review in Spain. If the validation results are satisfactory positive predictive value of EMRs in the UK and Spain $\geq$ 95% and negative predictive value $\geq$ 99%, then information from the whole cohort would be used to estimate the incidence of diarrhoea and the incidence of SCD in the cohort of IBS-C patients and the relative risks of SCD and the exposures of interest (mainly linaclotide) as detailed below in Section 9.7.2 *Cohort analyses*. Otherwise, only ORs of SCD and the same exposures of interest will be estimated using data from cases and controls as detailed below in Section 9.7.3 *Nested Case-control Analyses*.

9.7.2 COHORT ANALYSES

9.7.2.1 CRUDE INCIDENCE OF DIARRHOEA AND CRUDE INCIDENCE OF SEVERE COMPLICATIONS OF DIARRHOEA

Exposure to linaclotide and other risk factors (e.g., laxatives) will be ascertained from the prescription information recorded in the databases. Person-time at risk (person-years and person-weeks) for developing complications of diarrhoea will be used to compute the incidence and incidence density rates among patients in the IBS-C cohort.

Crude incidence density rates (person-time incidence rates) for the full cohort of patients with IBS-C will be graphically displayed over the follow-up period since cohort entry date, to ascertain if rates are homogeneous over time. Crude incidence density rates for sub-cohorts, defined by exposure to potential risk factors for experiencing SCD (e.g., current users of linaclotide), will also be graphically displayed over time since the first treatment prescription. These figures will guide whether the follow-up periods should be broken into several intervals with different incidence density rates of diarrhoea complications (based on the clinical development programme of linaclotide, diarrhoea has been observed to be more frequent early in treatment) or not. Additionally, the first six months after linaclotide launch will be studied separately, since patients with prevalent IBS-C who are exposed to linaclotide during this period

could have more severe cases of IBS-C, have exhausted other treatment options, and have a different risk profile than incident patients with IBS-C.

The crude incidence of diarrhoea and the crude incidence of SCD in the full cohort of patients with IBS-C will be described by calculating the proportion of patients experiencing at least one episode of diarrhoea and the proportion of patients experiencing at least one episode of SCD, as well as their corresponding 95% CIs. The crude incidences of diarrhoea and of SCD in the sub-cohorts of patients with prescriptions of linaclotide will be described by calculating the proportions of patients experiencing diarrhoea or experiencing SCD, respectively, among those at risk for each of the time intervals (as determined graphically) since first treatment prescription, as well as the corresponding 95% CIs. Crude incidence density rates (person-time incidence rates) will also be computed with their corresponding 95% CIs. The incidence of SCD will be assessed separately for death subsequent to diarrhoea (≤45 days after diarrhoea diagnosis date) due to the seriousness of this complication (deadly SCD).

All incidence and incidence density rates will also be calculated separately for those groups of patients with increased risk of SCD as defined in the objectives: patients ≥65 years and patients with hypertension, diabetes, or cardiovascular disease diagnostic codes.

9.7.2.2 RISK OF SEVERE COMPLICATIONS OF DIARRHOEA

If the validation results of cases is satisfactory (positive predictive value of EMRs ≥ 95% and negative predictive value ≥ 99%), then information from the whole cohort would be used to estimate the incidence of SCD in the cohort of IBS-C patients, as well as the relative risks of SCD and the exposures of interest (mainly exposure to linaclotide) using the Cox proportional hazard model. Additionally, the nested case-control analysis will be conducted, and conditional logistic regression will be used as indicated in Section 9.7.3.1.

Alternatively, if the validation results show positive predictive value of EMRs < 95% or negative predictive value < 99%, then only the nested case-control analysis will be conducted, and conditional logistic regression will be used in place of Cox regression.

The corresponding regression models will be used to identify risk factors associated with risk of SCD. Multivariate regression models will be fitted to identify the effects of various baseline variables on the probability of having SCD. A set of 10 to 20 plausible candidate models will be proposed and fitted to the data. Models will be ranked according to Akaike's Information Criterion (AIC) and the best model will be selected. If several models prove to perform well, these will be averaged to produce a final model. Some iteration between choosing candidate models and data analysis will likely be necessary: in the case of Cox regression, due to the need to check that the proportional hazards assumption holds for each candidate model, and in all scenarios due to the iterative nature of the information theoretic model-building approach.

9.7.3 NESTED CASE CONTROL ANALYSES

9.7.3.1 RISK OF SEVERE COMPLICATIONS OF DIARRHOEA

Conditional logistic regression analyses will be used to estimate the relative risk (case control OR) of SCD among patients who were treated with linaclotide, had a prescription for laxatives, were ≥ 65 years old, and had a history of hypertension, diabetes or cardiovascular disease diagnostic codes (i.e., SCD occurrence is the outcome variable [yes/no], and the independent variables of main interest are whether the patient has a prescription for linaclotide, a prescription for laxatives, the patient is ≥ 65 years old, and the patient has hypertension, diabetes or cardiovascular disease diagnostic codes, all of them at index date, or not). The same multivariate regression modelling approach (as described in Section 9.7.2.2) will be followed.

For the algorithm-identified cases and controls that are not validated, sensitivity analyses will be performed to test different scenarios by treating these unconfirmed SCD events as either missing, cases or controls, respectively.

Statistical analyses will be conducted using SAS® statistical software.

9.8 QUALITY CONTROL

Standard operating procedures at each research centre will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

Aggregate results will be presented in accordance with data privacy policy and small numbers ($n < 5$) will be blinded.

All work will be subject to quality-control and documentation procedures to make certain that the final report is accurate and thorough, and the analyses can be reproduced. If the data do not permit an analysis as planned (e.g., through insufficient sample size in a subgroup analysis) or if clarifying analyses are required (e.g., an unexpected result that could be explained by a subgroup analysis), Evidera staff will inform AbbVie and include the additional information and results in the report. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

A quality-assurance audit of this study may be conducted.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Categorisation of patients with IBS into IBS-C, IBS-D, or IBS-M might be challenging. Similarly, the classification into mild, moderate, and severe IBS-C is not recorded in the databases and is expected to be available only for a fraction of patients. Differentiation between IBS-C and chronic constipation will also be challenging. As a consequence, some degree of misclassification is to be expected.

In the databases, we may miss some occurrences of safety endpoints (e.g., electrolyte imbalance) if they are not explicitly recorded; however, this is expected to affect only patients with complications of diarrhoea of milder severity.

The use of over-the-counter medications for the treatment of IBS-C-related symptoms, constipation, and diarrhoea is acknowledged as another study limitation. We will include over-the-counter medications, such as laxatives, when this information is recorded in the databases and reported by PCPs answering the study validation questionnaire. However, we expect under-recording of over-the-counter medications in the databases, and therefore the overall use of laxatives will be incompletely reflected. If the extent of misclassification of laxative exposure is different among cases and controls then some of the odds ratios could be biased and this limitation should be taken into account when the results are interpreted.

The CPRD provides a large, diverse, and representative sample of UK people using primary care services, which allows for generalizability of the study findings to the broader UK population. The General Practice Research Database (GPRD), predecessor to CPRD, has been widely used for observational studies, with over 890 studies published to date in peer-reviewed journals. The SIDIAP database includes information for 90% of the population in Catalonia, a region in northeast Spain, and resembling the data collected by the UK databases. One limitation is that date of prescription is only available for the first prescription and, thereafter, only an approximate date of dispensation is available. For Sweden, the NPR and PDR cover the entire Swedish population and have been previously use in observational studies including drug utilisation ones. However, no primary care data will be available, so diagnoses will be those determined by a specialist, which are expected to be required for the variables of interest for this study. The PDR is not complete with regard to drugs used in nursing homes.

According to the National Board of Health and Welfare, about 1% of people aged 65−79 years live in nursing homes, and about 20% of people aged 80 or more years live in nursing homes in Sweden [Socialstyrelsen]. This may be reflected in potential lower numbers of elderly patient using linaclotide identified in Sweden.

The validity of research findings based on CPRD data and data from the other databases depends on the quality and completeness of the data recorded. We are only able to identify comorbidities for which the patient has consulted their GP. Referrals are not always uniformly coded and may appear as free-hand text or letters within the database.

Interval censoring might have an impact on the precision of the results.

Additionally, the proposed linked data sources (i.e., HES OP, HES AE and HES APC) have different linkage coverage periods. In particular, HES OP and HES AE linkage periods are considerably shorter than that of HES APC. This might increase the risk of SCD cases being underestimated. Finally, potential SCD are not classified by severity.

9.10 OTHER ASPECTS

No further aspects to be considered.

10 PROTECTION OF HUMAN SUBJECTS

Institutional review board approval and/or any other required reviews of the study protocol by specific committees will be obtained in accordance with applicable national and local regulations.

The study will be conducted in accordance with the International Society for Pharmacoepidemiology's (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP)* (2007), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance's (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2011a). The ENCePP *Checklist for Study Protocols* (ENCePP, 2011b) will be completed.

The study will be registered in the ENCePP *Electronic Register of Studies* (ENCePP, 2010) after regulatory endorsement of the protocol.

The study will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/European Commission and its refinement provided in Chapter I.7 Section 1 of *Volume 9A of the Rules Governing Medicinal Products in the EU: Guidelines on Pharmacovigilance for Medicinal Products for Human Use* (European Commission, 2008), and referred to in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use's *Pharmacovigilance Planning* (ICH, 2004) and the *Guideline on Good Pharmacovigilance Practices, Module VIII—Post-Authorisation Safety Studies* (European Medicines Agency [EMA], 2012a).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS (AE)/ADVERSE REACTIONS

For studies in which the research team uses only data from automated healthcare databases, the ISPE provides the following guidance:

> *'Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines.'* (ISPE, 2007, Section VI)

The EMA *Guideline on Good Pharmacovigilance Practices, Module VI*, provides the following guidance:

'For non-interventional study designs which are based on secondary use of data, such as studies based on medical chart reviews or electronic healthcare records, systematic reviews or meta-analyses, adverse reactions reporting is not required. Reports of adverse events/reactions should only be summarised in the study report, where applicable.'
(EMA, 2012b, Section C.1.2.1)

The linaclotide PASS does not require adverse events (AEs) to be reported in an expedited manner to European authorities. Identified AEs/reactions will be summarised in the final study report.

AEs that are communicated in response to the physician questionnaires will be reported according to the *European Good Pharmacovigilance Practices, Module VI* (EMA, 2012b). Procedures for the collection and reporting to AbbVie of AEs/reactions identified during the study conduct will be agreed upon with AbbVie and put in place in accordance with the provisions of *Module VI, Management and Reporting of Adverse Reactions to Medicinal Products*, from the EMA.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 REGULATORY COMMUNICATION PLAN

The study protocol, study status, and report(s) will be included in regulatory communications in line with the RMP, PSUR, and other regulatory milestones and requirements.

12.2 PUBLICATION AND COMMUNICATION PLAN

Any publication resulting from the work outlined in this proposal will be discussed with AbbVie. Evidera will ensure AbbVie has adequate time to review and comment on any manuscript or abstract developed. For all publications of Evidera project work, Evidera adheres to the authorship definitions and requirements as stated in the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* from the International Committee of Medical Journal Editors (ICMJE) 2013, repeated in part, as follows:

- Authorship credit should be based on: 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2 and 3.
- All persons designated as authors should qualify for authorship and all those who qualify should be listed
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship

Study results will be published following guidelines of the ICMJE (2010) and communication in appropriate scientific venues (e.g., ISPE) will be considered. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (STROBE, 2007).

In its *Guidelines for Good Pharmacoepidemiology Practices*, ISPE contends that '*there is an ethical obligation to disseminate findings of potential scientific or public health importance*' (ISPE, 2007, Section V). This would include results pertaining to the safety of a marketed medication. Study results will be published following guidelines, including those for authorship, established by the ICMJE (2010).

The marketing authorisation holder and the investigator have agreed on a publication policy allowing the principal investigator to prepare publications independently based on the study results, irrespective of data ownership. The marketing authorisation holder will be entitled to view the results and

interpretations included in the manuscript, and provide comments prior to submission of the manuscript for publication (EMA, 2012a, Section VIII.B.7).

13 REFERENCES

Becher H, Kostev K, Schröder-Bernhardi D. Validity and representativeness of the "Disease Analyzer" patient database for use in pharmaco -epidemiological and pharmacoeconomic studies. *Int J Clin Pharmacol Ther*. 2009 Oct;47(10):617-626.

Bolíbar B, Fina Avilés F, Morros R, et al. [SIDIAP database: electronic clinical records in primary care as a source of information for epidemiologic research].[Article in Spanish] *Med Clin (Barc).* 2012 May 19;138(14):617-621.

British Heart Foundation (2012). Heart Statistics. Available from: http://www.bhf.org.uk/research/heart-statistics.aspx. Accessed 14 May 2013.

Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for Irritable Bowel Syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012;107(11):1702-1712.

Clinical Practice Research Datalink (2013). Available from: http://www.cprd.com/intro.asp. Accessed 23 April 2013.

Clinical Practice Research Datalink. (2022a). CPRD Aurum October 2022 (Version 2022.10.001) [Data set]. Available from: https://cprd.com/sites/default/files/2022-10/2022-10%20CPRD%20Aurum%20Release%20Notes.pdf. Accessed 7 November 2022.

Clinical Practice Research Datalink. (2022b). CPRD linked data: HES Admitted Patient Care data. Available from: https://cprd.com/cprd-linked-data#HES%20Admitted%20Patient%20Care%20data. Accessed 7 November 2022.

Clinical Practice Research Datalink. (2022c). CPRD GOLD October 2022 (Version 2022.10.001) [Data set]. Available from: https://cprd.com/sites/default/files/2022-10/2022-10%20CPRD%20GOLD%20Release%20Notes.pdf. Accessed 7 November 2022.

Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002;123(6):2108-2131.

European Commission. (2008) Volume 9A of the rules governing medicinal products in the European Union: Guidelines on pharmacovigilance for medicinal products for human use. Available at: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a 09-2008 en.pdf. Accessed 14 March 2013.

European Medicines Agency (2012a). Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies. Available at: http://www.emea.europa.eu/docs/en GB/document library/Scientific guideline/2012/06/WC500129137.pdf. Accessed 14 March 2013.

European Medicines Agency (2012b). Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. Available at: http://www.emea.europa.eu/docs/en GB/document library/Scientific guideline/2012/06/WC500129135.pdf. Accessed 14 March 2013.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Electronic Register of Studies (2010). Version 3.0.46. Available at: http://www.encepp.eu/encepp/studiesDatabase.jsp. Accessed 14 March 2013.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (2011a). Guide on methodological standards in pharmacoepidemiology. Available at: http://www.encepp.eu/standards and guidances/. Accessed 19 March 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (2011b). ENCePP checklist for study protocols (revision 1). Available at: http://www.encepp.eu/standards and guidances/. Accessed 19 March 2012.

Eurostat. Accessed on 17th March 2014. http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&language=en&pcode=tps00002&plugin=1

Fleiss JL, Levin B, Cho Pail M. (2003). *Statistical Methods for Rates and Proportions*, 3rd Edition. John Wiley & Sons: Holboken, New Jersey.

Fortea J, Prior M. Irritable bowel syndrome with constipation: a European-focused systematic literature review of disease burden. *J Med Econ* 2013;16(3):329-341.

Goettsch WG, van den Boom G, Breekveldt-Postma S, et al. Treatment patterns and health care cost of mebeverine-treated IBS patients: a case control study. *Pharmacoepidemiology and Drug Safety* 2004;13:803-810.

Harkness EF, Grant L, O'Brien SJ, Chew-Graham CA, Thompson DG. Using read codes to identify patients with irritable bowel syndrome in general practice: a database study. *BMC Family Practice* 2013;14:183 (a).

Harkness EF, Harrington V, Hinder S, O'Brien SJ, Thomson DG, Beech P, Chew-Graham CA. GP perspectives of irritable bowel syndrome – an accepted illness but management deviates from guidelines: a qualitative study. *BMC Family Practice* 2013;14:92 (b).

Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment Pharmacol Ther* 2003;17(5):643-650.

IBS Global (2009). Irritable bowel syndrome: a global perspective. Available at: http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/20 irritable bowel syndro me.pdf. Accessed on 14 March 2013.

ICD9DATA (2012). ICD-9-CM diagnosis codes: diarrhoea. Available at: http://www.icd9data.com/. Accessed 14 March 2013.

ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use (2004). Pharmacovigilance planning. Available at: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/pharmacovigilance-planning.html. Accessed 14 March 2013.

International Committee of Medical Journal Editors (ICMJE) (2010). Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. Available at: http://www.icmje.org/urm main.html. Accessed 14 March 2013.

International Society for Pharmacoepidemiology (ISPE) (2007). Guidelines for good pharmacoepidemiology practices (GPP). Available at: http://www.pharmacoepi.org/resources/guidelines 08027.cfm. Accessed 19 March 2012.

Keeling PWN, Fielding JF. The irritable bowel syndrome: a review of 50 consecutive cases. *J Irish Coll Phys Surg* 1975;4(91).

Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spliler RC. Functional bowel disorders. *Gastroenterol* 2006;130:1480-1491.

Longstreth GF, Wolde-Tsadik G. Irritable-bowel-type symptoms in HMO examinees. Prevalence, demographics, and clinical correlates. *Dig Dis Sci* 1993;38(9):1581-1589.

Masclee GMC, Valkhoff VE, van Soest EM, Schade R, Mazzaglia G et al. Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus protective agents: what to prescribe in daily practice? *Aliment Pharmacol Ther* 2013;38:178-189.

National Board of Health and Welfare (Sweden). The National Patient Register. Aug 2012. Available at: http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish. Accessed 16 April 2015.

Pang D. A relative power table for nested matched case-control studies. *Occup Environ Med* 1999;56:67-69.

Peterson AM, Nau DP, Cramer JA, et al. A Checklist for Medication Compliance and Persistence Studies Using Retrospective Databases *Value in Health* 2007;10(1): 3-12.

Prezioso D, Illiano E, Piccinocchi G, Cricelli C, Piccinocchi R et al. Urolithiasis in Italy: An epidemiological study. *ArchivioItaliano di Urologia e Andrologia*2014;86(2):99-102.

Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol* 2012;107(11):1714-1724.

Saito Y, Schoenfeld P, Locke GR. The epidemiology of irritable bowel syndrome in North America: A systematic review. *Am J Gastroenterol* 2002;97(8):1910–1915.

Sikka R, Xia F, Aubert RE. Estimating Medication Persistency Using Administrative Claims Data *Am J Manag Care* 2005;11:449-457.

Socialstyrelsen. Statistikdatabas för äldreomsorg [Statistics database for the elderly]. Available at: http://www.socialstyrelsen.se/statistik/statistikdatabas/aldreomsorg. Accessed April 20, 2015.

Spiller R, Aziz Q, Creed F, et al. Clinical Services Committee of The British Society of Gastroenterology. Guidelines on the irritable bowel syndrome: mechanisms and practical management. *Gut*. 2007;56(12):1770-1798.

STROBE Statement (2007). Strengthening the Reporting of Observational Studies in Epidemiology. STROBE checklists. Available at: http://www.strobe-statement.org/index.php?id=available-checklists. Accessed 14 March 2013.

Thompson WG. Gender differences in irritable bowel symptoms. *Eur J Gastroenterol Hepatol* 1997; 9(3):299-302.

Thompson WG. The irritable bowel. *Gut* 1984;25(3):305-320.

Tillisch K, Labus JS, Naliboff BD, et al. Characterization of the alternating bowel habit subtype in patients with irritable bowel syndrome. *Am J Gastroenterol* 2005;100:896-904.

Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007 Jul;16(7):726-35.

Wilson S, Roberts L, Roalfe A, et al. Prevalence of irritable bowel syndrome: a community survey. *British Journal of General Practice* 2004;54:495-502.

Wood P. Tegaserod in the treatment of constipation-predominant irritable bowel syndrome. Do the risks outweigh the benefits? *Naunyn-Schmiedeberg's Arch Pharmacol* 2012;385:1-3.

Wooltorton E. Tegaserod (Zelnorm) for irritable bowel syndrome: reports of serious diarrhea and intestinal ischemia. *CMAJ* 2004;170(13):1908. Correction in CMAJ 2004;171(7):712.

World Health Organization (2012). Health topics: diarrhoea. Available at: http://www.who.int/topics/diarrhoea/en/. Accessed 14 March 2013.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	SAP version identifier: 2.1	07/06/2016	Linaclotide Safety Study for the Assessment of Diarrhoea—Complications and Associated Risk Factors in Selected European Populations with IB-C Statistical Analyses Plan

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:

Linaclotide Safety Study for the Assessment of Diarrhoea Complications and Associated Risk Factors in Selected European Populations with IB C

Study reference number:

EUPAS15353

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[3]	☒	☐	☐	4.10,6
1.1.2 End of data collection[4]	☒	☐	☐	4.10,6
1.1.3 Study progress report(s)	☒	☐	☐	4.10,6
1.1.4 Interim progress report(s)	☒	☐	☐	4.10,6
1.1.5 Registration in the EU PAS register	☒	☐	☐	4.10,6
1.1.6 Final report of study results.	☒	☐	☐	4.10,6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1

[3] 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.
[4] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2,9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7
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)	☒	☒	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:	☒	☐	☐	9.2.1.4
4.2.1 Study time period?	☒	☐	☐	8.2
4.2.2 Age and sex?	☒	☐	☐	9.2.1
4.2.3 Country of origin?	☒	☐	☐	9.2.1
4.2.4 Disease/indication?	☒	☐	☐	9.2.1.4
4.2.5 Duration of follow-up?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1.1

Comments:

No sex or seasonality limitations. Patients ≥65 years and those with hypertension, diabetes, or cardiovascular disease diagnostic codes will be subgroups of interest for the analysis.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.4

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.2
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.2.1.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.2.1.2
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)	☒	☐	☐	9.3.4
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:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.3.2
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)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.3.4

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.2

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	4.7
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	4.7
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	4.7
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	4.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	4.7
9.3.3 Covariates?	☒	☐	☐	4.7
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	4.7

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	4.9
10.2 Are descriptive analyses included?	☒	☐	☐	4.9
10.3 Are stratified analyses included?	☒	☐	☐	4.9
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	4.9

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	4.9
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	4.8

Comments:

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

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.3.3

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.8

Comments:

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

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.2

Comments:

Name of the main author of the protocol: [redacted]

Date: 8/Nov/2022

Signature: [redacted]

ANNEX 3. ADDITIONAL INFORMATION

List of Read, ICD and SNOMED Codes to Identify Patients with IBS-C

Table 4. Read Codes fo the Identification of IBS and Constipation

Read Code	Description	Comments
J521100	Irritable bowel syndrome characterised by constipation	Preferred code.
J521000	IBS with diarrhoea	To be used as exclusion criteria
14CF.00	History of irritable bowel syndrome (IBS)	To identify potential prevalent cases
Eu45324	Psychogenic IBS	Unfrequently used, check for constipation
J521.00	Irritable colon–IBS	Preferred code, check for constipation
J521.13	Spastic colon	Unfrequently used, check for constipation
J521.11	Irritable bowel syndrome	Preferred code, check for constipation
J521200	IBS characterized by alternating bowel habit	Preferred code, check for constipation
19C..11	Constipation symptom	Preferred code, combined with IBS
19C..00	Constipation	Preferred code, combined with IBS
19C2.00	Constipated	Unfrequently used, combined with IBS
19CZ.00	Constipation NOS	Unfrequently used, combined with IBS
J520z00	Constipation NOS	Third choice, combined with IBS
J520.00	Constipation – functional	Second choice, combined with IBS
J520100	Chronic constipation with overflow	Unfrequently used, combined with IBS
J520000	Acute constipation	Unfrequently used, combined with IBS
J520200	Chronic constipation without overflow	Unfrequently used, combined with IBS
J520300	Drug induced constipation	Unfrequently used, combined with IBS
E264500	Psychogenic constipation	Unfrequently used, combined with IBS
J520y00	Other specified constipation	Unfrequently used, combined with IBS
1962.00	Colicky abdominal pain	Second choice as code in IBS
1971.00	Central abdominal pain	Third choice as code in IBS
1972.00	Epigastric pain	Third choice as code in IBS
196..00	Type of GIT pain	Unfrequently used
196..11	Abdominal pain type	Unfrequently used
1968.00	Abdominal discomfort	Third choice as code in IBS
1969.00	Abdominal pain	Second choice as code in IBS
197..13	Site of abdominal pain	Unfrequently used
197A.00	Generalised abdominal pain	Second choice as code in IBS
197C.00	Lower abdominal pain	Third choice as code in IBS
197Z.00	Site of GIT pain NOS	Unfrequently used
1963.00	Non-colicky abdominal pain	Unfrequently used

196Z.00	Type of GIT pain NOS	Unfrequently used
196..12	Type of GIT pain - symptom	Unfrequently used
1976.00	Right flank pain	Unfrequently used
1975.00	Left flank pain	Unfrequently used
197..11	Flank pain	Unfrequently used
197..12	Iliac fossa pain	Unfrequently used
1977.00	Right iliac fossa pain	Unfrequently used
1978.00	Left iliac fossa pain	Unfrequently used
197B.00	Upper abdominal pain	Unfrequently used
197D.00	Right upper quadrant pain	Unfrequently used
1974.00	Right subcostal pain	Unfrequently used
197..00	Site of GIT pain	Unfrequently used
197..14	Subcostal pain	Unfrequently used
1973.00	Left subcostal pain	Unfrequently used
197A.11	General abdominal pain symptom	Unfrequently used
R090400	[D] Abdominal cramps	Unfrequently used
R090.00	[D] Abdominal pain	Unfrequently used
R090500	[D] Epigastric pain	Unfrequently used
R09E00	[D] Recurrent acute abdominal pain	Unfrequently used
R090z00	[D] Abdominal pain NOS	Unfrequently used
R090100	[D] Abdominal colic	Unfrequently used
R090700	[D] Hypocondrial pain	Unfrequently used
R090400	[D] Abdominal cramps	Unfrequently used
R090N00	[D] Nonspecific abdominal pain	Unfrequently used
R090J00	[D] Right upper quadrant pain	Unfrequently used
R090H00	[D] Upper abdominal pain	Unfrequently used
R090900	[D] Pain in right iliac fossa	Unfrequently used
R090600	[D] Umbilical pain	Unfrequently used
R090A00	[D] Pain in left iliac fossa	Unfrequently used
R090000	[D] Abdominal tenderness	Unfrequently used
R090K00	[D] Left upper quadrant pain	Unfrequently used
R090y00	[D] Other specified abdominal pain	Unfrequently used
R090L00	[D] Left lower quadrant pain	Unfrequently used
R090311	[D] Right lower quadrant pain	Unfrequently used
1961.00	No abdominal pain	To be used as exclusion criteria
19A..00	*Abdominal distension symptom*	*Second choice as code in IBS*
19A3.00	*Abdomen feels distended*	*Unfrequently used*
19A2.00	*Abdomen feels bloated*	*Unfrequently used*
19AZ.00	*Abd. Distension symptom NOS*	*Unfrequently used*

19A4.00	*Abdomen feels swollen*	*Unfrequently used*
19B..12	*Bloating symptom*	*Second choice as code in IBS*
19B..15	*Wind symptom*	*Unfrequently used*
19B2.00	*Excessive flatulence*	*Unfrequently used*
19B..14	*Flatulence symptom*	*Unfrequently used*
19B..00	*Flatulence/wind*	*Unfrequently used*
19BZ.00	*Wind NOS*	*Unfrequently used*
R073400	*[D] Bloating*	*Third choice as code in IBS*
R073000	*[D]Flatulence*	*Unfrequently used*
R073.00	*[D] Flatulence, eructation, and gas pain*	*Third choice as code in IBS*
R073300	*[D] Abdominal distension, gaseous*	*Unfrequently used*
R073z11	*[D] Wind*	*Unfrequently used*
R073200	*[D] Gas pain (abdominal)*	*Unfrequently used*
R073z00	*[D] Flatulence, eructation and gas pain NOS*	*Unfrequently used*
19EA.00	*Change in bowel habit*	*Unfrequently used*
19EA.11	*Altered bowel habit*	*Unfrequently used*
R078.00	*[D] Change in bowel habit*	*Unfrequently used*
R121200	*[D] Mucus in stool*	*Unfrequently used*
4763.00	*Faeces: mucous present*	*Unfrequently used*
19EH.00	*Mucus in faeces*	*Unfrequently used*
198..00	*Nausea*	*Second choice as code in IBS*
1982.00	*Nausea present*	*Unfrequently used*
198..12	*Nausea symptoms*	*Third choice as code in IBS*
198..11	*C/O - nausea*	*Unfrequently used*
198Z.00	*Nausea NOS*	*Unfrequently used*
R070000	*[D] Nausea*	*Unfrequently used*
R070.00	*[D] Nausea and vomiting*	*Unfrequently used*
R093000	*[D] Abdominal swelling*	*Unfrequently used*
J16y411	*Flatulent dyspepsia*	*Unfrequently used*
19D..12	*Anal symptoms*	*Unfrequently used*
19D..11	*Tenesmus symptom*	*Unfrequently used*
19D..00	*Tenesmus*	*Unfrequently used*
19D2.00	*Tenesmus present*	*Unfrequently used*
19DZ.00	*Tenesmus NOS*	*Unfrequently used*
19E..11	*Faeces symptom*	*Unfrequently used*
19E..12	*Motions – symptom*	*Unfrequently used*
19E..00	*Faeces/motions – symptoms*	*Unfrequently used*

Abbreviations: IBS irritable bowel syndrome; IBS C IBS predominately with constipation; NOS unspecified

Patients with IBS will be identified through the following criteria:

- Code J521100 (Irritable bowel syndrome characterised by constipation)
- One or more codes for IBS among the following: J521.00, J521.11, J521.13, Eu45324, 14CF.00.
- Alternatively, a combination of a code of abdominal pain or discomfort (in gray background and regular font) and at least two codes among those reported as "second choice as code in IBS", "third choice as code in IBS" or "unfrequently used" (in *italics* and gray background).

Patients with only 14CF.00 will identify as prevalent IBS-C patients since the diagnosis date is uncertain.

In addition to patients with code J521100, patients with IBS-C will be identified through the following criteria:

- Patient with IBS as specified above and one preferred code including the term "constipation"

Table 5. ICD-10 Codes for the Identification of IBS and Constipation

ICD-10 Code	Description	Comments
K58	Irritable bowel syndrome (IBS), irritable colon	Preferred code, check for constipation
K58.0	IBS with diarrhoea	To be used as exclusion criteria
K58.9	IBS without diarrhoea; IBS NOS	Preferred code, check for constipation
K59.9	Functional intestinal disorder, unspecified	Not specific
K59.0*	Constipation	To be used in combination with K58, K58.9, and K59.9 to identify IBS predominantly with constipation (IBS-C

Abbreviations: IBS irritable bowel syndrome; IBS C IBS predominately with constipation; NOS unspecified

Patients with IBS will be identified through the following criteria:

- At least one code K58, K58.9 or K59.9 without code K58.0

Patients with IBS-C will be identified through the following criteria:

- Patient with IBS as specified above and code K.59.0

Table 6. ICD-9 Codes for the Identification of IBS and Constipation

ICD-9 Code	Description	Comments
564.1	Irritable bowel syndrome (IBS); irritable colon; spastic colon	Preferred code, check for constipation
564.0, 564.00, 564.01, 564.09	Constipation	To be used in combination with 564.1 to identify IBS predominantly with constipation (IBS-C)

Abbreviations: IBS irritable bowel syndrome; IBS C IBS predominately with constipation

Patients with IBS will be identified through the following criteria:

- Code 564.1

Patients with IBS-C will be identified through the following criteria:

- Patient with IBS as specified above and code at least one code among 564.0, 564.00, 564.01, 564.09

A brief questionnaire will be sent to a sample of physicians treating the IBS-C patients included in this study (cases and controls) to confirm the diagnosis of the patient identified with IBS and constipation codes.

Table 7. SNOMED Code List for IBS-1: IBS Diagnoses in CPRD Aurum

MedCodeId	Description
1101501000006115	Adverse reaction to Colpermin Ibs Relief
1495560015	[X]Psychogenic IBS
18665016	Spastic colon
18666015	Irritable bowel syndrome
1927491000006111	IBS characterised by alternating bowel habit
7238961000006111	Irritable bowel syndrome characterised by alternating bowel habit
2018751000006112	Adverse reaction to Imodium Ibs Relief
2346441000000118	Dietary education for irritable bowel syndrome
2361431000033115	Imodium Ibs Relief
2670821000006113	Irritable colon
2670831000006111	Adaptive colitis
2670841000006118	Membranous colitis
2670871000006114	Mucous colitis
2670881000006112	Colon spasm
2670891000006110	Functional bowel disease
2670901000006114	Nervous colitis
2670911000006112	IBS - Irritable bowel syndrome
2670921000006116	Irritable bowel
2670931000006118	Spastic colitis
2670941000006111	Irritable colon syndrome
2670951000006113	IC - Irritable colon
2791650019	Irritable bowel syndrome characterised by constipation
303071000000118	History of irritable bowel syndrome
303172010	Irritable bowel syndrome with diarrhoea
4786241000006112	Irritable bowel syndrome with diarrhea

5086151000006112	Irritable bowel syndrome variant of childhood
5086161000006114	Irritable bowel syndrome variant of childhood with diarrhoea
696071000006114	Mucous colitis and/or proctitis
7238961000006111	Irritable bowel syndrome characterized by alternating bowel habit
7240101000006111	Constipation predominant irritable bowel syndrome
7240111000006114	Irritable bowel syndrome characterized by constipation
742351000006119	Irritable colon - Irritable bowel syndrome
8022171000006115	H/O irritable bowel syndrome
886361000006114	Irritable bowel - IBS
906181000006110	[RFC] Irritable bowel syndrome (IBS)
2129721000000119	Management of irritable bowel syndrome
8435781000006117	Dietetic Intervention for Irritable Bowel Syndrome TOM (Therapy Outcome Measure) activity score
8460301000006111	Irritable Bowel Syndrome - Symptom Severity Scale score

Table 8. SNOMED Code List for IBS-2

MedCodeId	Description
1218836019	General abdominal pain-symptom
1236016018	Abdominal colic
132601013	Epigastric pain
137890011	Upper abdominal pain
1786591000006112	[D]Functional abdominal pain syndrome
1858471000006119	Abdominal pain score
1983911000006113	Manchester triage - Abdominal pain in adult
1983921000006117	Manchester triage - Abdominal pain in child
252305018	Generalised abdominal pain
252571013	Non-colicky abdominal pain
252577012	Type of GIT pain NOS
252584016	Central abdominal pain
252585015	Left subcostal pain
252586019	Right subcostal pain

252587011	Left flank pain
252588018	Right flank pain
252589014	Right iliac fossa pain
252594014	Left iliac fossa pain
252597019	Site of GIT pain NOS
254352011	On examination - abdominal pain - right hypochondrium
254353018	On examination - abdominal pain - epigastrium
254354012	On examination - abdominal pain - left hypochondrium
254355013	On examination - abdominal pain - right lumbar
254356014	On examination - abdominal pain - umbilical
254357017	O/E - umbilical pain on palp.
254358010	On examination - abdominal pain - left lumbar
254359019	On examination - abdominal pain - right iliac
254360012	On examination - abdominal pain - hypogastrium
254361011	On examination - abdominal pain - left iliac
254362016	On examination - abdominal pain on palpation
2659101000006115	Intestinal colic
2659121000006113	Spasmodic abdominal pain
2659131000006111	Colicky abdominal pain
2842251000006112	AP - Abdominal pain
299171000006116	[D]Left upper quadrant pain
301981000006114	[D]Right upper quadrant pain
303651000006110	[D]Upper abdominal pain
317562013	[D]Abdominal pain
317563015	[D]Abdominal tenderness
317564014	[D]Abdominal colic
317567019	[D]Abdominal cramps
317568012	[D]Epigastric pain
317569016	[D]Umbilical pain
317572011	[D]Pain in right iliac fossa

317573018	[D]Pain in left iliac fossa
317586010	[D]Other specified abdominal pain
317587018	[D]Abdominal pain NOS
318001012	[X]Pain localized to other parts of lower abdomen
318003010	[X]Other and unspecified abdominal pain
3329721000006110	Stomach gripes
36112013	Abdominal pain
369360011	Subcostal pain
369361010	Site of abdominal pain
369362015	Iliac fossa pain
369363013	Flank pain
369364019	Type of GIT pain - symptom
369368016	Abdominal pain type
3714121000006115	Abdominal pain through to back
397910011	Site of GIT pain
402478014	O/E - abdomen tender
402479018	O/E - abdo. pain on palpation
4077741000006111	Localized abdominal pain
4077761000006110	Generalized abdominal pain
411281013	O/E - iliac pain on palpation
411282018	O/E - lumbar pain on palpation
4202081000006115	Chronic abdominal pain
443112015	Right upper quadrant pain
452290019	On examination - epigastric pain on palpation
4546201000006117	RIF - Right iliac fossa pain
4546241000006115	LIF - Left iliac fossa pain
455441012	[D]Left lower quadrant pain
455442017	[D]Right lower quadrant pain
455443010	[D]Nonspecific abdominal pain
5086191000006118	Chronic nonspecific abdominal pain

5243121000006113	Type of abdominal pain
5497951000006119	Site of gastrointestinal tract pain
5516891000006111	Type of gastrointestinal tract pain
5561471000006117	C/O right iliac fossa pain
5561481000006119	Complaining of right iliac fossa pain
5561491000006116	C/O left iliac fossa pain
5561501000006112	Complaining of left iliac fossa pain
5561641000006110	O/E - abdominal pain
5561651000006112	On examination - abdominal pain
5561661000006114	O/E - epigastric pain
5700651000006115	Left sided abdominal pain
5700661000006118	Right sided abdominal pain
5965591000006114	Psychosomatic abdominal pain
6043821000006114	Abdominal pain - cause unknown
6043831000006112	Unexplained abdominal pain
7223421000006117	Recurrent abdominal pain
7234071000006113	Generalised abdominal tenderness
72350017	Abdominal discomfort
7278501000006115	Periumbilical pain
7278511000006117	Periumbilical abdominal pain
7297231000006117	Acute exacerbation of chronic abdominal pain
85031000006113	Type of GIT pain
90723010	Lower abdominal pain
958281000006114	Colicky abdominal pain control
958291000006112	Colicky abdominal pain present
958301000006113	Colicky abdominal pain absent
961961000006110	Cramping/abdominal discomfort
5273021000006113	Bowel spasm
252575016	Abdominal wall pain
3475231000006112	Midabdominal crampy pain

4317181000006113	Epigastric discomfort
442693019	Tenderness of epigastrium
4546261000006116	Pain of hypogastrium
4546271000006111	Hypogastric pain
5527711000006117	Stomach discomfort
5561681000006116	On examination - iliac pain - abdominal
5561691000006118	On examination - lumbar pain abdominal
5561701000006118	O/E left iliac fossa tender
5893241000006114	Tenderness of hypogastrium
5893251000006111	Tenderness of right iliac fossa
5893261000006113	RIF - Tenderness of right iliac fossa
5893271000006118	Tenderness of left iliac fossa
5893281000006115	LIF - Tenderness of left iliac fossa
7050521000006116	Pain radiating to lower abdomen
7068601000006119	Pain radiating to upper abdomen
7077301000006119	Pain radiating to middle abdomen
1222526011	Perineal pain
1222528012	[D] Pelvic pain
1807411000006116	Suprapubic tenderness
252595010	Suprapubic pain
252841013	C/O pelvic pain
252842018	C/O perineal pain
3133971000006116	Pelvic pain syndrome
3133981000006118	PPS - Pelvic pain syndrome
317570015	Hypochondrial pain
317571016	[D]Suprapubic pain
317579019	Pelvic and perineal pain
3507421013	Chronic female pelvic pain syndrome
4546871000006112	Complaining of pelvic pain
4546891000006113	Complaining of perineal pain

5024161000006112	Hypochondriacal pain
5103011000006112	Chronic pelvic pain of female
5620581000006113	Chronic pelvic pain without obvious pathology
5892741000006113	Right hypochondrial pain
5892751000006110	Left hypochondrial pain
5893191000006114	Tenderness of right hypochondrium
5893201000006112	Tenderness of left hypochondrium
7129211000006113	Male perineal pain
7761481000006119	Non-cyclic pelvic pain
7812951000006111	Cyclic pelvic pain
14233141000006110	Pain relieved by opening bowels
302649018	Gastric spasm
4943861000006119	Bowel action painful

Table 9. SNOMED Code List for IBS-3

MedCodeId	Description
103578017	Diarrhoea
109071000006118	Tenesmus symptom
1216044011	Faeces symptom
1221314019	Motions - symptom
1222516016	[D]Wind
1233452016	Bowels: incontinent
12717761000006112	[D]Mucus in stool
131671000006119	Spurious (overflow) diarrhoea
13636751000006116	Vesical tenesmus
140077016	Retching
14233121000006115	Pain relieved by breaking wind
14233131000006117	Pain relieved by passing flatus
14841441000006111	Bloated abdomen
1490285011	[X]Psychogenic diarrhoea

1494941012	[X]Psychogenic dyspepsia
1776591000006119	Reason for referral: Diarrhoea and Vomiting
1777091000006111	Reason for referral: Vomiting/Nausea
1786047017	Loose stool
1936821000006111	Functional incontinence of faeces
1936881000006110	Incontinent of faeces - whole formed stool
196858012	Spurious diarrhoea
199373016	Removal of impacted faeces
2474996011	Mucus in faeces
2475423012	Abdomen feels bloated
2475503014	Abdomen feels distended
2519801000006111	Removal of impacted feces
252559019	Indigestion
252560012	Dyspepsia
252565019	Indigestion symptom NOS
252600018	Nausea present
252604010	Nausea NOS
252623015	Abdominal distension symptom
252628012	Abd. distension symptom NOS
252640012	Excessive belching
252642016	Wind NOS
252655015	Tenesmus present
252656019	Tenesmus NOS
252657011	Faeces/motions - symptoms
252725016	Faeces symptom
252725016	Faeces symptoms NOS
2545501000006118	Nausea, vomiting and diarrhoea
2545511000006115	Nausea, vomiting and diarrhea
260397014	Faeces: mucous present
2604541000006115	Rectal tenesmus

2607741000006117	Vesical tenesmus
2607751000006115	Tenesmus - bladder
2620502012	Wind symptom
2643930014	Nausea
270035013	Manual removal of impacted faeces from rectum
2768791000006115	N&V - Nausea and vomiting
2768801000006119	N+V - Nausea and vomiting
2845201000006119	Rectal mucus
2945081000006110	Semisolid stools
2945091000006113	Soft faeces
2945101000006119	Soft feces
317456018	[D]Nausea and vomiting
317457010	[D]Nausea
317462011	[D]Nausea and vomiting NOS
317470018	[D]Flatulence, eructation and gas pain
317470018	Flatulence, eructation and gas pain
317471019	[D]Flatulence
317472014	[D]Eructation
317473016	[D]Gas pain (abdominal)
317474010	[D]Abdominal distension, gaseous
317475011	[D]Bloating
317477015	[D]Flatulence, eructation and gas pain NOS
317486013	[D]Incontinence of faeces
317489018	[D]Incontinence of faeces NOS
317494018	[D] Stools loose
317497013	[D]Change in bowel habit
317503017	[D]Tenesmus
317558019	[D]Vesical tenesmus
3175721000006116	Abdominal distension
317595019	[D]Abdominal swelling

317725013	[D]Mucus in stool
3219651000006110	Fecal impaction of rectum
3219661000006112	Faecal impaction of rectum
3219671000006117	Impacted stool in rectum
3219681000006119	Impacted feces
3219691000006116	Impacted faeces
3219701000006116	Fecal impaction
3219711000006118	Faeces - impacted
3219721000006114	Feces - impacted
3219731000006112	Fecal impaction in rectum
3242511000006110	Abdominal wind pain
3242521000006119	Gas pain - abdominal
3270801000006114	Colonic mucus
3486481000006112	Swollen abdomen
3486491000006110	Meteorism
3486501000006119	Bloat
3486511000006116	Bloating
3486521000006112	Swelling of abdomen
3486531000006110	Bloated abdomen
3486541000006117	Abdominal distention
3486561000006118	Abdomen distended
3512721000006112	Diarrhea
3512731000006110	D - Diarrhoea
3512741000006117	D - Diarrhea
3636304012	Functional nausea
3671971000006116	Bowel incontinence
3671981000006118	Incontinence of feces
3671991000006115	Involuntary stool
3672011000006115	Incontinent of feces
3672021000006111	Incontinent of faeces

3692541000006117	Increased nausea and vomiting
370924017	Bloating symptom
372267012	Indigestion NOS
372268019	Flatulent dyspepsia
372283012	Diarrhoea and vomiting
3724321000006111	Hard stools
3724331000006114	Hard feces
3724341000006116	Hard faeces
3931931000006117	Altered bowel function
3931941000006110	Altered bowel habits
3931971000006119	Change in bowel pattern
3971851000006118	Wind
397913013	Flatulence/wind
397914019	Tenesmus
397927015	Diarrhoea symptoms
397928013	Diarrhoea symptom
401804015	Psychogenic diarrhoea
411263010	Belching symptom
4270371000006111	Abdominal bloating
436421000006112	Abdomen feels swollen
452022012	Flatulence symptom
4546441000006119	Faeces/motions - symptoms
4546451000006117	Feces/motions - symptoms
4546471000006110	Feces symptom
4546481000006113	Motions - symptom
4546571000006114	Spurious diarrhea - overflow
4546581000006112	Overflow incontinence - faeces
4546591000006110	Faecal overflow
4660891000006112	Manual removal of impacted feces from rectum
493967017	Faecal impaction

504392014	Excessive flatus
507901013	Change in bowel habit
507902018	Altered bowel habit
5272591000006114	Passing flatus
5272611000006115	Flatus
5272821000006110	D+V - Diarrhoea and vomiting
5272831000006113	D&V - Diarrhoea and vomiting
531181000006118	C/O - nausea
5530091000006110	Belching
5530371000006112	Mucus in feces
5571851000006116	Diarrhea and vomiting, symptom
619741000006114	Diarrhoea
619771000006118	Diarrhoea & vomiting, symptom
6270131000006115	Feces/motions - symptoms
648081000006117	Burping
648081000006117	Eructation symptom
650681000006114	Excessive eructation
650701000006112	Excessive flatulence
6596461000006117	LS - Loose stools
6596501000006117	Loose feces
6596511000006119	Loose faeces
6599731000006113	Fluid stool
6599741000006115	Liquid faeces
6599751000006118	Liquid feces
6599761000006116	Watery stool
661971000006116	Faeces consistency: dry
661981000006118	Faeces consistency: fluid
661991000006115	Faeces consistency: hard
662021000006111	Faeces consistency: semi-fluid
662031000006114	Faeces consistency: soft

681151000006114	Nausea symptoms
7023271000006113	Dry feces
7023281000006111	Dry faeces
781171000006111	Indigestion symptoms
781761000006117	Incontinent of faeces
781771000006112	Incontinent of faeces symptom
7837471000006115	Functional bloating
8136181000006110	[D]Flatulence NOS
8261721000006113	Minimal nausea
854661000006115	Diarrhoea & vomiting
886051000006110	Dyspepsia, indigestion NOS
894791000006113	Stool mucus abnormal [D]
982741000006119	Change in bowel habit
1228728015	Functional dyspepsia
1228729011	Non-ulcer dyspepsia
14438511000006112	Faecal impaction of rectum
14438521000006116	Impacted stool in rectum
14438531000006118	Faecal impaction in rectum
1819581000006115	History of dyspepsia
1935661000006114	Initial bowel incontinence bothersome rating score
1935671000006119	Follow-up bowel incontinence bothersome rating score
1935741000006116	Initial bowel incontinence quality of life score
1935761000006117	Follow-up bowel incontinence quality of life score
1936411000006118	Bowels: incontinence protection worn
1936431000006112	Bowels: incontinence protection not worn
1936561000006119	Degree of bowel incontinence
1936571000006114	Degree of bowel incontinence: mild
1936581000006112	Degree of bowel incontinence: moderate
1936591000006110	Degree of bowel incontinence: severe
1936601000006119	Total bowel incontinence

1936891000006113	Frequency of faecal incontinence
1937401000006118	Patient advised to take antidiarrhoeal medication
217981000000118	Bowels incontinence assessment
2373691000000119	Functional urinary and faecal incontinence
2548704017	Under care of dyspepsia specialist nurse
2549912010	Discharged from care of dyspepsia specialist nurse
2557701000006116	Nonulcer dyspepsia
2557741000006119	Non ulcer dyspepsia
2748991000006113	Secretory diarrhoea
2749001000006113	Secretory diarrhea
2778501000006114	Chronic diarrhoea of unknown origin
295381013	Psychogenic dyspepsia
2968861000006110	Fecal impaction of colon
3007451000006112	Spurious diarrhoea
3007461000006114	Overflow diarrhoea
3007471000006119	Overflow diarrhea
311291000000114	Undiagnosed dyspepsia
3143951000006113	Flatus
353856013	Chronic diarrhoea
3596741000006115	Faecal impaction
3596751000006118	Fecal impaction
3617831000006110	Belching
3668121000006116	Defaecation urgency
3668151000006113	Fecal urgency
3668161000006110	Faecal urgency
3776311000006113	Double incontinence - urine and stool
406291000000114	Referral to dyspepsia specialist nurse
4407381000006116	Diarrhoeal disorder
4407401000006116	Diarrheal disorder
501970016	Urgent desire for stool

5089171000006111	Chronic diarrhea
5089341000006117	Protracted diarrhoea
5272631000006114	Passing loud flatus
5272641000006116	Passing offensive flatus
5272651000006119	Unable to control flatus
5272771000006119	Constipation alternates with diarrhoea
5272781000006116	Constipation alternates with diarrhea
5272911000006114	Unaware of passing flatus
5272981000006119	Unable to distinguish stool and flatus
5697641000006111	Burping in public
5878721000006114	Finding of flatus
5879481000006110	Uniform abdominal distention
6028331000006114	Disimpaction of feces
6459921000006114	Idiopathic faecal incontinence
6780951000006113	Severe diarrhoea
6787651000006116	Acute diarrhoea
6787661000006119	Acute diarrhea
6987261000006113	Number of bowel incontinence episodes
7219391000006117	Faecal fluid leakage
7219401000006115	Fecal fluid leakage
7821851000006118	Non-retentive fecal incontinence
7837461000006110	Functional belching disorder
7837491000006119	Functional faecal incontinence
796791000006115	Functional diarrhoea
8045121000006113	Faecal soiling co-occurrent and due to faecal incontinence
8045131000006111	Fecal soiling co-occurrent and due to fecal incontinence
8045141000006118	Faecal incontinence with faecal urgency
8045151000006116	Fecal incontinence with fecal urgency
8263411000006112	Daytime faecal incontinence
8263501000006110	Night time faecal incontinence

8465811000006112	Complete faecal incontinence
8465821000006116	Complete fecal incontinence
886331000006117	Faecal and other impaction
908931000006111	[RFC] Incontinence both urinary & bowel
909041000006112	[RFC] Bowel incontinence
909311000006110	[RFC] Loose stools
917541000006111	Bladder: faecal incontinence
926021000006116	Bowels: incontinent
960251000006111	Indigestion
961971000006115	Incontinent of stool
982731000006112	Diarrhoea/loose stools
317493012	Bulky stool
317604019	Umbilical swelling
295383011	Psychogenic gastrointestinal tract symptom NOS
317488014	Sphincter ani incontinence
6342731000006111	Urinary sphincter weakness incontinence

Table 10. SNOMED Codes for the Identification of Constipation

MedCodeId	**Description**
1726521000006115	Chronic constipation
1779381000000111	Education for constipation care
1824011000006112	Paediatric constipation clinical pathway protocol followed
1824121000006115	Paediatric constipation clinical pathway protocol not followed
2162207016	Constipated
2197541000000118	Constipation in children clinical pathway
25076018	Constipation
255196012	On examination - defaecation reflex abnormal - constipated
2733831000006110	Costiveness
2733841000006117	Difficulty defaecating
2733851000006115	Difficulty defecating

2733861000006118	Difficulty passing stool
2733871000006113	Difficulty opening bowels
2733891000006114	CN - Constipation
2733901000006113	Difficult passing motion
295382018	Psychogenic constipation
3007441000006110	Spurious diarrhea
3007451000006112	Spurious diarrhoea
3007461000006114	Overflow diarrhoea
3007471000006119	Overflow diarrhea
3007481000006116	Overflow incontinence due to constipation
303161017	Constipation - functional
303162012	Acute constipation
303163019	Chronic constipation without overflow
303165014	Other specified constipation
303166010	Constipation NOS
3068881000006119	Slow transit constipation
3068901000006117	Constipation by delayed colonic transit
3446061000006115	Intermittent constipation pattern
353853017	Chronic constipation
3689851000006111	Encopresis with constipation AND overflow incontinence
3849221000006117	Chronic idiopathic constipation
4786191000006112	Functional constipation
4786201000006110	Constipation-functional
484894013	Chronic constipation with overflow
5089151000006118	Simple constipation
5272771000006119	Constipation alternates with diarrhoea
5272781000006116	Constipation alternates with diarrhea
590101000006113	Constipation NOS
590111000006111	Constipation symptom
598301000006114	Costive symptom

630451000006116	Drug induced constipation
6511391000006113	Constipation care
6511401000006110	Constipation management
7159921000006114	Atonic constipation
7171761000006117	Neurogenic constipation
7275421000006117	Dietary education for constipation
8042951000006113	Therapeutic opioid induced constipation
906171000006112	[RFC] Constipation
909031000006119	[RFC] Constipation
982721000006114	Constipation
131671000006119	Spurious diarrhoea - overflow
196858012	Spurious diarrhoea
441433010	Difficulty in ability to defaecate
5878931000006114	Difficult defaecation
5878951000006119	Difficulty in defaecating

A Patient will be said to have IBS if there is a SNOMED code from IBS 1 code lists in the medical records OR if there is a SNOMED code from IBS 2 code lists AND 2 or more codes from IBS 3 code lists ever.

A patient with IBS identified from the SNOMED code lists above will be said to have IBS-C if they have any of the codes from Table 10.

List of Read Codes, ICD codes and SNOMED codes to Identify the Safety Endpoint: SCD

Published literature from the candidate databases on diarrhoea and its complications is limited. Still, the identification of these endpoints is possible using a set of codes to capture diarrhoea, electrolyte imbalances, etc. One concern is that conditions such as electrolyte imbalances are not necessarily only complications of diarrhoea; the International Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification (ICD-10-CM) and Read codes to identify these conditions are unspecific in this respect (i.e., codes for electrolyte imbalance and others do not reflect whether the condition is secondary to diarrhoea). We suggest using combinations of codes for diarrhoea and each of these conditions to ensure that diarrhoea-related events are identified as such (we will only consider those diarrhoea complications occurring between the diarrhoea diagnosis date and 45 days afterwards). Below is a preliminary list of codes to be used.

Diarrhoea

Diarrhoea is the condition of passing three or more loose or liquid bowel movements per day, or more than is normal for the individual (World Health Organization [WHO], 2012). Loss of fluids through diarrhoea can cause dehydration and electrolyte imbalances.

Lists of Read (Table 11), ICD-9 (Table 12) and SNOMED (Table 13) codes to identify diarrhoea episodes are included below.

Table 11. Read Codes to Identify Episodes of Diarrhoea

Read Code	Description	Specific
19F..11	Diarrhoea	
19F..00	Diarrhoea symptoms	
19FZ.11	Diarrhoea and vomiting, symptom	
19F2.00	Diarrhoea	
19G..00	Diarrhoea and vomiting	
A083.11	Diarrhoea and vomiting -? infect	No
A083.00	Diarrhoea of presumed infectious origin	No
19FZ.00	Diarrhoea symptom NOS	
J525.00	Functional diarrhoea	
A076.11	Viral diarrhoea	No
19F4.00	Toddlers diarrhoea	No
A082.00	Infectious diarrhoea	No
A082z00	Infectious diarrhoea NOS	No
J4...13	Non-infective diarrhoea	
A074311	Diarrhoea due to campylobacter jejuni	No
E264300	Psychogenic diarrhoea	
J4zz.11	Diarrhoea – presumed non-infectious	
J4z..11	Presumed non-infectious diarrhoea	
J4z..00	Non-infective gastroenteritis NOS	
A082100	Epidemic diarrhoea	No
Eu45317	[X] Psychogenic diarrhoea	
A074011	Diarrhoea due to staphylococcus	No
Ayu0H00	[X] Diarrhoea and gastroenteritis of presumed infectious origin	No
A074012	Diarrhoea due to staphylococcal toxin	No
A074111	Diarrhoea due to pseudomonas pyocyanea	No
19F. 12	Loose stools	
R077100	[D] Stools loose	
4743.00	Faeces consistency: semi-fluid	
4744.00	Faeces consistency: fluid	
E264311	Spurious diarrhoea	
19F3.00	Spurious (overflow) diarrhoea	
J43z.11	Chronic diarrhoea	
J43z.00	Other non-infective gastroenteritis and colitis NOS	
A082000	Dysenteric diarrhoea	No
J433.11	Dietetic diarrhoea	No
J432.11	Allergic diarrhoea	No

Abbreviations: NOS unspecified

Table 12. ICD Codes to Identify Episodes of Diarrhoea

ICD-9-CM	2013 ICD-9-CM Additional Description	Direct or Approximate Conversion to ICD-10-CM
787.91 Diarrhoea	Abnormal frequency and fluidity of faeces Increased liquidity or decreased consistency of faeces, such as running stool; faecal consistency is related to the ratio of water-holding capacity of insoluble solids to total water, rather than the amount of water present; diarrhoea is not hyperdefecation or increased faecal weight. Passage of loose, unformed stools, a condition of frequent and watery bowel movements	K52.2 Allergic and dietetic gastroenteritis and colitis K52.89 Other specified non-infective gastroenteritis and colitis R19.7 Diarrhoea, unspecified
009.2 Infectious diarrhoea		A09 Infectious gastroenteritis and colitis, unspecified
009.3 Diarrhoea of presumed infectious origin		A09
564.5 Functional diarrhoea		K59.1 Functional diarrhoea
558.9 Other and unspecified non-infectious gastroenteritis and colitis		K52.9 Non-infective gastroenteritis and colitis, unspecified
558.2 Toxic gastroenteritis and colitis		K52.1 Toxic gastroenteritis and colitis

ICD-9-CM	2013 ICD-9-CM Additional Description	Direct or Approximate Conversion to ICD-10-CM
558.42 Eosinophilic colitis 535.70 Eosinophilic gastritis, without mention of haemorrhage 535.71 Eosinophilic gastritis, with haemorrhage 558.41 Eosinophilic gastroenteritis 558.9 787.91		K52.8 Other specified non-infective gastroenteritis and colitis

Abbreviations: ICD 9 CM International Classification of Diseases and Related Health Problems (Ninth Revision) Clinical Modification; ICD 10 CM International Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification

Table 13. SNOMED Codes to Identify Episode of Diarrhoea

MedCodeId	MedCodeId Description
1786047017	Loose stool
103081000006118	Toddler diarrhoea
103578017	Diarrhoea
106758018	Colitis
118918011	Toxic gastroenteritis
120502010	Dietetic colitis
1227776017	[V]Dietary counselling in colitis
12705101000006115	Ischaemic colitis
14542421000006112	Giardia lamblia colitis
14615831000006119	Noninfectious enteritis of intestine
14627891000006119	Drug-induced enteritis of intestine
14655241000006116	Noninfective enteritis and colitis
147185013	Pericolitis
1490285011	[X]Psychogenic diarrhoea
1566381000006119	Bloody diarrhoea
1776591000006119	Reason for referral: Diarrhoea and Vomiting
1785915017	Pseudomembranous colitis
1816481000006111	Gastroenteritis and colitis of unknown origin
1937401000006118	Patient advised to take antidiarrhoeal medication
198185014	Allergic diarrhoea

1984091000006117	Manchester triage - Diarrhoea and vomiting
198411000006113	Pseudomembranous colitis
198421000006117	Pseudomembranous colitis
201288012	Epidemic diarrhoea
208361000006117	Presumed non-infectious diarrhoea
221051000000112	Non-infective diarrhoea
2238751000000119	Time since last episode of diarrhoea
234701000006118	Perinatal necrotising enterocolitis
252734014	Diarrhoea not present
2532959018	Exacerbation of non-infective colitis
2545501000006118	Nausea, vomiting and diarrhoea
2545511000006115	Nausea, vomiting and diarrhea
2748991000006113	Secretory diarrhoea
2778501000006114	Chronic diarrhoea of unknown origin
281111000006111	Noninfectious gastroenteritis
2905891000006110	GE - Gastroenteritis
2968281000006118	Eosinophilic colitis
299711000000117	Ischemic colitis
3006581000006119	Lymphocytic-plasmacytic colitis
302946010	Regional ileocolitis
303009019	Toxic enteritis
303010012	Toxic enterocolitis
303014015	Toxic gastroenteritis NOS
303024011	Allergic enterocolitis
303026013	Allergic gastroenteritis NOS
303034019	Dietetic enterocolitis
303036017	Dietetic gastroenteritis NOS
303051014	Non-infective colitis NOS
303172010	Irritable bowel syndrome with diarrhoea
303183018	Diarrhoea after gastrointestinal tract surgery
3143081000006116	Toddler diarrhea
317494018	Loose stools
32563019	Collagenous colitis
3273421000006113	Functional diarrhea
3296661000006115	Allergic diarrhea
3331221000006119	Diversion colitis
3386111000006115	Chronic colitis
3512083018	Diarrhoea co-occurrent and due to carcinoid syndrome
3512721000006112	Diarrhea
3512731000006110	D - Diarrhoea
3512741000006117	D - Diarrhea
3512751000006115	Observation of diarrhoea
3512761000006118	Observation of diarrhea
353407019	Indeterminate colitis
353418019	Microscopic colitis

353856013	Chronic diarrhoea
3550901000006110	Enteritis of small intestine
3550911000006113	Enteritis
356111014	Insulin-dependent diabetes mellitus secretory diarrhoea syndrome
360012013	Infantile gastroenteritis
3634541000006115	Acute gastroenteritis
3637781000006111	Non-infective diarrhea
3637801000006110	Presumed non-infectious diarrhea
372283012	Diarrhoea and vomiting
37319017	Allergic enteritis
3852941000006114	Dietetic diarrhea
3908451000006116	Epidemic diarrhea
396361018	Noninfectious enteritis
396363015	Allergic gastroenteritis and colitis
396366011	Other non-infective gastroenteritis and colitis NOS
396367019	Non-infective gastroenteritis NOS
397834017	H/O: colitis
397927015	Diarrhoea symptoms
397928013	Diarrhoea symptom
400051000006118	[X]Noninfective enteritis and colitis
401804015	Psychogenic diarrhoea
402244018	Neonatal diarrhoea
4058311000006112	Haemorrhagic diarrhoea
4058321000006116	Hemorrhagic diarrhea
4058331000006118	Bloody diarrhea
415991000006119	[X]Other specified noninfective gastroenteritis+colitis
42550011	Gastroenteritis
43567011	Allergic gastroenteritis
4407381000006116	Diarrhoeal disorder
4786241000006112	Irritable bowel syndrome with diarrhea
483467010	Chronic ischaemic colitis
494676019	Chronic ischaemic enterocolitis
502379012	Chronic ischaemic enteritis
503091015	Acute ischaemic colitis
505456018	Dietetic diarrhoea
50729018	Allergic colitis
5084481000006118	Drug-induced enteritis
5086161000006114	Irritable bowel syndrome variant of childhood with diarrhoea
5089171000006111	Chronic diarrhea
5089181000006114	Diarrhoea due to laxative abuse
5089301000006119	Diarrhoea due to ingestion of unabsorbable substances
5089341000006117	Protracted diarrhoea
51411016	Dietetic enteritis
52549017	Lymphocytic colitis
5272771000006119	Constipation alternates with diarrhoea

5272781000006116	Constipation alternates with diarrhea
5272811000006119	Diarrhea and vomiting
5272821000006110	D+V - Diarrhoea and vomiting
5272831000006113	D&V - Diarrhoea and vomiting
5395541000006110	Faecal fluid sample
5498121000006114	Diarrhea symptom
5506591000006111	Psychogenic diarrhea
554971000006116	Chronic ischaemic colitis and/or enteritis
5571851000006116	Diarrhea and vomiting, symptom
56238012	Dietetic gastroenteritis
56770011	Granulomatous enteritis
572031000006114	Giardial colitis
572041000006116	Noninfectious colitis
5730511000006110	Diarrhoea and vomiting after gastrointestinal tract surgery
585591000006118	Non-infective enteritis and colitis
5894121000006114	Antibiotic-associated diarrhoea
5894131000006112	Antibiotic-associated diarrhea
601031000006119	CC - Crohn's colitis
619741000006114	Diarrhoea
619771000006118	Diarrhoea and vomiting, symptom
619781000006115	Diarrhoea - presumed non-infectious
6342471000006119	Coccidial enteritis
6383601000006112	Distal colitis
6568001000006112	Acute and chronic colitis
6596461000006117	LS - Loose stools
6596471000006112	Loose motion
6596481000006110	Loose bowel motions
6596491000006113	Loose bowel movement
6596501000006117	Loose feces
6596511000006119	Loose faeces
662021000006111	Faeces consistency: semi-fluid
6703931000006110	Non-specific colitis
6780951000006113	Severe diarrhoea
6787651000006116	Acute diarrhoea
6787661000006119	Acute diarrhea
696071000006114	Mucous colitis and/or proctitis
70682016	Toxic colitis
7094811000006114	Drug-induced diarrhea
7094821000006118	Drug-induced diarrhoea
7219391000006117	Faecal fluid leakage
72962011	Enterocolitis
7375121000006118	Stercoral colitis
796791000006115	Functional diarrhoea
8467221000006112	Sclerosing mesenteritis
854661000006115	Diarrhoea & vomiting

886281000006114	Noninfective enteritis/colitis
906161000006117	[RFC] Gastroenteritis
909311000006110	[RFC] Loose stools
970741000006111	Misuse of anti-diarrhoea/anti-emetic
982731000006112	Diarrhoea/loose stools

Diarrhoea Complications

Table 14. Read Codes to Identify Severe Complications of Diarrhoea (SCD)

Read Code	Description	Specific
Dehydration		
C365200	Dehydration NEC	
2225.00	O/E – dehydrated	
C365000	Isonatraemic dehydration	
2587.00	O/E – abdo. skin dry-dehydration	
2587.11	O/E - abdo. skin – dehydrated	
8A14.00	Dehydration monitoring	
1A42.00	Urine looks dark	No
4622.00	Urine: dark/concentrated	No
Electrolyte imbalance: potassium and sodium		
C368.00	Hypokalaemia	
44I4200	Low serum potassium level	
ZC61c00	Potassium supplementation	
F393.11	Familial hypokalaemic periodic paralysis	
C368.11	Hypopotassaemia	
K08y000	Hypokalaemic nephropathy	
C360.11	Hypernatraemia	
C360.00	Hyperosmolality and or hypernatraemia	
Oliguria		
R085000	[D]Oliguria	
SP15200	Oliguria as a complication of care	
R085.00	[D]Oliguria and anuria	
L093000	Oliguria following abortive pregnancy	No
R085z00	[D]Oliguria and anuria NOS	
Anuria		
1AC0.00	Anuria	
R085100	[D]Anuria	
SP15300	Anuria as a complication of care	
Thromboembolism		
7929100	Percut transluminal coronary thrombolysis with streptokinase	
7929111	Percut translum coronary thrombolytic therapy- streptokinase	

Read Code	Description	Specific
7A4B800	Percut translum thrombolysis femoral graft streptokinase	
7A54700	Percutaneous transluminal thrombolysis of artery	
7A56000	Percutaneous transluminal arterial thrombolysis reconstruct	
7A6Q000	Percutaneous mechanical thromboembolectomy	
7A6Q100	Percutaneous aspiration thromboembolectomy	
7L10500	Continuous infusion of antithrombolytic NEC	
88A8.00	Thrombolytic therapy	
8B3g.00	Pain to thrombolysis time	
8I3L.00	Thrombolytic therapy refused	
F161500	Anterior spinal artery thrombosis	
G30..12	Coronary thrombosis	
G30..16	Thrombosis - coronary	
G30A.00	Mural thrombosis	
G312.00	Coronary thrombosis not resulting in myocardial infarction	
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI	
G631.12	Thrombosis, carotid artery	
G63y000	Cerebral infarct due to thrombosis of precerebral arteries	
G640.00	Cerebral thrombosis	
G640000	Cerebral infarction due to thrombosis of cerebral arteries	
G74..00	Arterial embolism and thrombosis	
G74..11	Arterial embolus and thrombosis	
G74..12	Thrombosis - arterial	
G74..13	Arterial embolic and thrombotic occlusion	
G740.00	Embolism and thrombosis of the abdominal aorta	
G741.00	Embolism and thrombosis of the thoracic aorta	
G742.00	Embolism and thrombosis of an arm or leg artery	
G742000	Embolism and thrombosis of the brachial artery	
G742100	Embolism and thrombosis of the radial artery	
G742200	Embolism and thrombosis of the ulnar artery	
G742300	Embolism and thrombosis of an arm artery NOS	
G742400	Embolism and thrombosis of the femoral artery	
G742500	Embolism and thrombosis of the popliteal artery	
G742600	Embolism and thrombosis of the anterior tibial artery	
G742700	Embolism and thrombosis of the dorsalis pedis artery	
G742800	Embolism and thrombosis of the posterior tibial artery	
G742900	Embolism and thrombosis of a leg artery NOS	
G742z00	Peripheral arterial embolism and thrombosis NOS	
G743.00	Embolism and thrombosis of other and unspec parts aorta	

Read Code	Description	Specific
G74y.00	Embolism and thrombosis of other specified artery	
G74y000	Embolism and/or thrombosis of the common iliac artery	
G74y100	Embolism and/or thrombosis of the internal iliac artery	
G74y200	Embolism and/or thrombosis of the external iliac artery	
G74y300	Embolism and thrombosis of the iliac artery unspecified	
G74y500	Embolism and thrombosis of the subclavian artery	
G74y600	Embolism and thrombosis of the splenic artery	
G74y700	Embolism and thrombosis of the axillary artery	
G74y800	Embolism and thrombosis of the coeliac artery	
G74y900	Embolism and thrombosis of the hepatic artery	
G74yz00	Embolism and thrombosis of other arteries NOS	
G74z.00	Arterial embolism and thrombosis NOS	
G82y.00	Other embolism and thrombosis	
G82z.00	Embolism and thrombosis NOS	
G82zz00	Embolism and thrombosis NOS	
J420.18	Mesenteric thrombosis	
K138200	Renal artery thrombosis	
Orthostatic hypotension		
G870.11	Postural hypotension	
G870.00	Orthostatic hypotension	
G87..00	Hypotension	
G87z.00	Hypotension NOS	
G873.00	Hypotension due to drugs	
F130300	Parkinsonism with orthostatic hypotension	
G872.00	Idiopathic hypotension	
Gyu9000	[X] Other hypotension	
Syncope		
R002100	[D] Fainting	
1B68.00	Felt faint	No
1B6..11	Faint symptom	
R002.11	[D] Syncope	
1B6..12	Syncope symptom	
R000311	[D] Loss of consciousness	
1B62.00	Syncope/vasovagal faint	
R002z00	[D] Syncope and collapse NOS	
R002.00	[D] Syncope and collapse	
R000300	[D] Unconsciousness	
1B6Z.00	Consciousness disturbance NOS	

Read Code	Description	Specific
1B6..00	Disturbance of consciousness	
R002400	[D] Micturition syncope	No
2236.12	O/E – loss of consciousness	
2244.00	O/E –collapse - syncope	
2236.13	O/E – unconscious	
R002600	[D] Asystolic vasovagal syncope	
SN21.12	Heat syncope or collapse	No
SN21.00	Heat syncope or collapse	No
Eu46y16	[X] Psychogenic syncope	
2239.00	O/E – decreased level of consciousness	
R002500	[D] Defaecation syncope	No
2238.00	O/E – clouded consciousness	No
Dizziness		
1B5..11	Dizziness symptom	
R004000	[D]Dizziness	
1B53.00	Dizziness present	
R004.00	[D]Dizziness and giddiness	
R004z00	[D]Dizziness and giddiness NOS	
1B55.00	Dizziness on standing up	
Vertigo		
R004300	[D]Vertigo NOS	
F561100	Benign paroxysmal positional vertigo or nystagmus	
1491.12	H/O: vertigo	
R004400	[D]Acute vertigo	
F561.00	Other and unspecified peripheral vertigo	
F561400	Otogenic vertigo	
1491.00	H/O: vertigo/Meniere's disease	
F562.00	Vertigo of central origin	No
A78y000	Epidemic vertigo	
F561000	Unspecified peripheral vertigo	
F561z00	Other peripheral vertigo NOS	
F561500	Benign paroxysmal positional vertigo	
F562z00	Vertigo of central origin NOS	No
F561411	Aural vertigo	
F562100	Malignant positional vertigo	
FyuQ100	[X]Other peripheral vertigo	
Acute kidney injury		
K04..00	Acute renal failure	

Read Code	Description	Specific
K00..00	Acute glomerulonephritis	No
K00..11	Acute nephritis	No
K08y500	Acute interstitial nephritis	No
K04z.00	Acute renal failure NOS	
K040.00	Acute renal tubular necrosis	No
K00z.00	Acute glomerulonephritis NOS	No
SK08.00	Acute renal failure due to rhabdomyolysis	No
K0A0.00	Acute nephritic syndrome	No
K000.00	Acute proliferative glomerulonephritis	No
K04y.00	Other acute renal failure	
K0E..00	Acute-on-chronic renal failure	
K042.11	Necrotising renal papillitis	No
K00y000	Acute glomerulonephritis in diseases EC	No
K043.00	Acute drug-induced renal failure	
K042.00	Acute renal medullary necrosis	No
K00y.00	Other acute glomerulonephritis	No
K00yz00	Other acute glomerulonephritis NOS	No
K00y300	Acute diffuse nephritis	No
K0A0200	Acute nephritic syndrome, diffuse membranous glomerulonephritis	No
L393.00	Acute renal failure following labour and delivery	
K041.00	Acute renal cortical necrosis	
Kyu2000	[X] Other acute renal failure	
K0A0100	Acute nephritic syndrome, focal, and segmental glomerular lesions	No
K0A0500	Acute nephritic syndrome, diffuse mesangiocapillary glomerulonephritis	No
K044.00	Acute renal failure due to urinary obstruction	No
K0A0600	Acute nephritic syndrome, dense deposit disease	No
L393200	Post-delivery acute renal failure with postnatal problem	
L393000	Post-delivery acute renal failure unspecified	
L393100	Post-delivery acute renal failure – delivered with postnatal problem	
K0A0400	Acute nephritic syndrome diffuse endocapillary proliferative glomerulonephritis	No
Hypovolaemic shock		
C365100	Hypovolaemia	
R055400	[D] Hypovolaemic shock	
Stupor		
R000.12	[D]Stupor	
E282.00	Acute stupor state due to acute stress reaction	No
Eu20211	[X]Catatonic stupor	

Read Code	Description	Specific
R000500	[D] Stupor	
E13y000	Psychogenic stupor	
Eu44200	[X]Dissociative stupor	
Coma		
R000400	[D] Coma	
R000.11	[D]Coma	
R000z00	[D]Coma and stupor NOS	
R000.00	[D]Coma and stupor	

Abbreviations: NEC necrotizing enterocolitis; NOS unspecified; O/E on examination

Table 15. ICD Codes to Identify SCD

2013 ICD-9-CM	2013 ICD-9-CM Additional Description	Direct or approximate conversion to 2013 ICD-10-CM
Dehydration		
276.51 Dehydration	Condition that results from excessive loss of water from a living organism A condition caused by the loss of too much water from the body; severe diarrhoea or vomiting can cause dehydration. Decreased intravascular, interstitial, and/or intracellular fluid; this refers to dehydration, water loss alone without change in sodium. State of excessively reduced body water or water deficit	E86.0 Dehydration

2013 ICD-9-CM	2013 ICD-9-CM Additional Description	Direct or approximate conversion to 2013 ICD-10-CM
Electrolyte imbalance: potassium and sodium		
276.8 Hypopotassaemia	Abnormally low potassium concentration in the blood; may result from excessive potassium loss by the renal or gastrointestinal route, from decreased intake, or from transcellular shifts; manifested clinically by neuromuscular disorders ranging from weakness to paralysis, by electrocardiographic abnormalities, and by renal and gastrointestinal disorders Hypokalaemia; lower than normal levels of potassium in the circulating blood Condition due to decreased dietary intake of potassium, as in starvation or failure to administer in intravenous solutions, or to gastrointestinal loss; severe potassium deficiency may produce muscular weakness and lead to paralysis and respiratory failure; muscular malfunction may result in hypoventilation, paralytic ileus, hypotension, muscle twitches, tetany, and rhabdomyolysis; nephropathy from potassium deficit impairs the concentrating mechanism.	E87.6 Hypokalaemia
276.0 Hyperosmolality and/or hypernatraemia	Excessive amount of sodium in the blood	E87.0 Hyperosmolality and hypernatraemia
Oliguria and anuria		
788.5 Oliguria and anuria	Absence of urine formation. It is usually associated with complete bilateral ureteral (ureter) obstruction, complete lower urinary tract obstruction, or unilateral ureteral obstruction when a solitary kidney is present.	R34 Anuria and oliguria
Thromboembolism		
434.0 Cerebral thrombosis		I66.09 Occlusion and stenosis of unspecified middle cerebral artery I66.19 Occlusion and stenosis of unspecified anterior cerebral artery I66.29 Occlusion and stenosis of unspecified posterior cerebral artery

2013 ICD-9-CM	2013 ICD-9-CM Additional Description	Direct or approximate conversion to 2013 ICD-10-CM
434.01 Cerebral thrombosis with cerebral infarction		I63.30 Cerebral infarction due to thrombosis of unspecified cerebral artery
437.6 Nonpyogenic thrombosis of intracranial venous sinus		I67.6 Nonpyogenic thrombosis of intracranial venous system
444 Arterial embolism and thrombosis		I74 Arterial embolism and thrombosis
446.6 Thrombotic microangiopathy		M31.1 Thrombotic microangiopathy
452 Portal vein thrombosis		I81 Portal vein thrombosis
453 Other venous embolism and thrombosis		I82 Other venous embolism and thrombosis
455.1 Internal thrombosed hemorrhoids		K64.8 Other hemorroids
455.4 External thrombosed hemorrhoids		K64.5 Perianal venous thrombosis
455.7 Unspecified thrombosed hemorrhoids		K64.5 Perianal venous thrombosis
593.81 Vascular disorders of kidney	Renal artery thromboembolism Thromboembolism of renal arteries Thromboembolism of renal artery	N28.0 Ischemia and infarction of kidney
Orthostatic hypotension		
458.0 Orthostatic hypotension	Fall in blood pressure associated with dizziness, syncope, and blurred vision occurring upon standing or when standing motionless in a fixed position	I95.1 Orthostatic hypotension
Dizziness		
780.4 Dizziness and giddiness		R42 Dizziness and giddiness
Vertigo		
078.81 Epidemic vertigo		A88.1 Epidemic vertigo

2013 ICD-9-CM	2013 ICD-9-CM Additional Description	Direct or approximate conversion to 2013 ICD-10-CM
386.0 Meniere's disease		H81.0 Ménière's disease
386.11 Benign paroxysmal positional vertigo		H81.1 Benign paroxysmal vertigo
386.1 Other and unspecified peripheral vertigo		H81.3 Other peripheral vertigo
386.9 Unspecified vertiginous syndromes and labyrinthine disorders		H81.9 Disorder of vestibular function, unspecified Incl.: Vertiginous syndrome NOS
Syncope		
780.2 Syncope and collapse	Fainting due to a sudden fall of blood pressure below the level required to maintain oxygenation of brain tissue Extremely weak; threatened with syncope	R55 Syncope and collapse
Acute renal failure		
584	Acute kidney failure: clinical syndrome characterised by a sudden decrease in glomerular filtration rate, usually associated with oliguria and always associated with biochemical consequences of the reduction in glomerular filtration rate such as a rise in blood urea nitrogen (BUN) and serum creatinine concentrations	N17 Acute kidney failure
Hypovolaemic shock		
785.59 Other shock without mention of trauma	Shock resulting from insufficient blood volume for the maintenance of adequate cardiac output, blood pressure, and tissue perfusion	R57.1 Hypovolaemic shock
276.52 Hypovolaemia	Abnormally decreased volume of circulating fluid (plasma) in the body Abnormally decreased volume of circulating fluid (plasma) in body	E86.1 Hypovolaemia
Stupor		
780.09 Other alteration of consciousness		R40.1 Stupor
Coma		
780.01 Coma		R40.2 Coma

Abbreviations: ICD 9 CM International Classification of Diseases and Related Health Problems (Ninth Revision) Clinical Modification; ICD 10 CM International Classification of Diseases and Related Health Problems (10th Revision) Clinical Modification

For available lab test results, the levels of sodium and potassium will be retrieved and patients with low levels following diarrhoea, as defined in the protocol, will be classified as having electrolyte imbalance.

Table 16. SNOMED Codes to Identify SCD

MedCodeId	MedCodeId Description
Dehydration	
293511017	Isonatraemic dehydration
4760401000006111	Isonatremic dehydration
492134010	Urine looks dark
881801000006112	Dehydration
Electrolyte imbalance: potassium and sodium	
1221390012	Low serum potassium level
13499041000006118	Hypernatraemia
2617791000006112	Acute hypernatraemia
2617801000006113	Acute hypernatremia
3133251000006116	Hypernatremia
3133261000006119	Na overload
3133271000006114	Na excess
3133281000006112	Sodium retention
3133291000006110	Sodium overload
3198231000006113	Hypokalemia
3198241000006115	Potassium depletion
3198251000006118	K deficiency
3198261000006116	Hypopotassemia syndrome
3198271000006111	Hypokalemic syndrome
3198281000006114	Hypokalaemic syndrome
3198311000006111	Hypopotassemia
3198321000006115	Hypopotassaemia syndrome
3390511000006114	Hypokalemic nephropathy
3390541000006113	Hypokalemic nephrosis
3390551000006110	Hypokalaemic nephrosis
3493151000006115	Acute hypokalaemia
3493161000006118	Acute hypokalemia
3597481000006116	Essential hypernatraemia
398883015	Hyperosmolality and or hypernatraemia
4599541000006118	Low serum potassium level - finding
492049017	Hypernatraemia
493576016	Hypokalaemia
493577013	Hypopotassaemia
5113441000006115	Drug-induced hypokalaemia
5113451000006118	Drug-induced hypokalemia
5500641000006116	Hyperosmolality and or hypernatremia
72310015	Potassium deficiency
881781000006113	Sodium overload
91216016	Hypokalaemic nephropathy

Oliguria	
1234791019	Oligouria
317535017	[D]Oliguria and anuria
317536016	[D]Oliguria
317540013	[D]Oliguria and anuria NOS
325089014	Oliguria as a complication of care
Anuria	
139055010	Indicanuria
2538411000006112	Passes no urine
317535017	[D]Oliguria and anuria
317537013	[D]Anuria
317540013	[D]Oliguria and anuria NOS
325090017	Anuria as a complication of care
354415011	Traumatic anuria - crush syndrome
5228011	Anuria
899241000006113	Traumatic anuria -crush syndr.
Thromboembolism	
100681000006116	Thrombosis atrium,auric append&vent/curr comp foll acute MI
100691000006118	Cerebral venous thrombosis of cavernous sinus
100701000006118	Thrombosis lateral sinus
100721000006111	Cerebral venous sinus thrombosis
100771000006112	Carotid artery thrombosis
100811000006112	Superior mesenteric artery thrombosis
100821000006116	Superior mesenteric vein thrombosis
1119161000000115	Deep vein thrombosis of peroneal vein
118689010	Cerebral thrombosis
12027691000006119	LVAD (left ventricular assist device) thrombosis
12107671000006115	Chronic deep vein thrombosis of left iliac vein
12107681000006117	Acute deep vein thrombosis of right iliac vein
12107691000006119	Acute deep vein thrombosis of left iliac vein
12122311000006110	Acute thrombosis of superficial vein of bilateral upper limbs
12126121000006117	Right iliac artery thrombosis
12126161000006111	Splenic artery thrombosis
12126511000006117	Thrombosis of artery of left upper limb
12126741000006111	Left popliteal artery thrombosis
12126751000006113	Thrombosis of right popliteal artery
12126781000006117	Left femoral artery thrombosis
12126831000006114	Thrombosis of left common femoral artery
12126841000006116	Left common femoral artery thrombosis
1221072019	Embolism of central nervous system venous sinus
12220791000006119	Thrombosis of atrium, auricular appendage, and ventricle due to and following acute myocardial infarction
1222321017	Embolism of vein NOS

1230092014	Corpus cavernosum thrombosis
1231107016	Corpus cavernosum embolism
1232993010	Testicular thrombosis
1235655012	Mural thrombosis
1235913017	Cerebral vein thrombosis
125470015	Cerebral embolism
12728641000006110	Thrombosis of vein NOS
12733151000006114	Peripheral arterial embolism and thrombosis NOS
12733161000006111	Arterial embolism and thrombosis NOS
12759341000006113	Embolism of vein NOS
14452791000006113	Embolism of left carotid artery
14457701000006115	Left posterior cerebral artery thrombosis
14457721000006113	Right posterior cerebral artery thrombosis
14457741000006118	Left cerebellar artery thrombosis
14457761000006119	Right cerebellar artery thrombosis
14457901000006117	Cerebral venous sinus thrombosis in puerperium
14496451000006117	Deep venous thrombosis in puerperium
14501081000006115	Cerebral venous thrombosis in puerperium
158317012	Renal artery thrombosis
158318019	Renal artery embolism
1729331000006116	Cerebral venous thrombosis
1786197015	Coronary thrombosis
1786198013	Thrombosis - coronary
1786921000006116	Recurrent deep vein thrombosis
1809151000006116	Renal artery stent thrombosis
1848121000006110	Renal artery stent thrombosis
200961000006116	Puerperal thrombosis NOS
2144741000000111	Recurrent deep vein thrombosis
215511000000110	Mesenteric thrombosis
216205019	Deep vein thrombosis of leg related to air travel
2162148012	Deep vein thrombosis
2162149016	Deep vein thrombosis
2162422011	Deep vein thrombosis of lower limb
216571000006116	Postoperative deep vein thrombosis
218541000000116	Arterial thrombosis
218551000000118	Deep vein thrombosis, leg
2210381000000117	Thrombosis of dialysis vascular access
2234371000000119	Thrombosis of internal jugular vein
2234411000000115	Thrombosis of external jugular vein
2238261000000112	Thrombosis of dialysis arteriovenous graft
2238301000000119	Thrombosis of dialysis arteriovenous fistula
2238341000000116	Thrombosis of dialysis arteriovenous shunt
2247661000000111	On deep vein thrombosis care pathway
2488341000000112	Unprovoked deep vein thrombosis

2488381000000116	Provoked deep vein thrombosis
2534187010	Deep vein thrombosis of leg related to intravenous drug use
2608401000000118	Perianal venous thrombosis
2674197014	Thrombolytic therapy
2725621000006114	Embolism of intracranial venous sinus
2730141000006117	Splenic vein thrombosis
2751251000006116	Thrombosis of renal vein
2751261000006119	Renal vein thrombosis
2784341000006116	Deep vein thrombosis of portal vein
2784351000006119	PVT - Portal vein thrombosis
2795114019	Thrombosis of subclavian vein
2837981000006113	Thrombosis of lateral venous sinus
2837991000006111	Thrombosis of transverse sinus
2838001000006118	Cerebral venous thrombosis of lateral sinus
296932010	Embolism cavernous sinus
296933017	Embolism superior longitudinal sinus
296934011	Embolism lateral sinus
296935012	Embolism transverse sinus
296936013	Embolism central nervous system venous sinus NOS
296938014	Thrombosis of superior longitudinal sinus
296939018	Thrombosis transverse sinus
296940016	Thrombosis of central nervous system venous sinus NOS
2981141000006112	Coronary artery embolism
299742017	Coronary thrombosis not resulting in myocardial infarction
300234010	Atrial thrombosis
300533017	Embolism and thrombosis of the thoracic aorta
300534011	Embolism and thrombosis of an arm or leg artery
300535012	Embolism and thrombosis of the brachial artery
300536013	Embolism and thrombosis of the radial artery
300537016	Embolism and thrombosis of the ulnar artery
300538014	Embolism and thrombosis of an arm artery NOS
300539018	Embolism and thrombosis of the femoral artery
300540016	Embolism and thrombosis of the popliteal artery
300541017	Embolism and thrombosis of the anterior tibial artery
300542012	Embolism and thrombosis of the dorsalis pedis artery
300543019	Embolism and thrombosis of the posterior tibial artery
300547018	Embolism and thrombosis of a leg artery NOS
300550015	Peripheral arterial embolism and thrombosis NOS

300552011	Embolism and thrombosis of other specified artery
300553018	Embolism and/or thrombosis of the common iliac artery
300554012	Embolism and/or thrombosis of the internal iliac artery
300555013	Embolism and/or thrombosis of the external iliac artery
300556014	Embolism and thrombosis of the iliac artery unspecified
300557017	Embolism and thrombosis of the subclavian artery
300558010	Embolism and thrombosis of the splenic artery
300559019	Embolism and thrombosis of the axillary artery
300561011	Embolism and thrombosis of the coeliac artery
300562016	Embolism and thrombosis of the hepatic artery
300563014	Embolism and thrombosis of other arteries NOS
300564015	Arterial embolism and thrombosis NOS
300704016	Other venous embolism and thrombosis
300710016	Embolism and thrombosis of the vena cava
300711017	Embolism and thrombosis of the renal vein
300712012	Other embolism and thrombosis
300713019	Embolism and thrombosis NOS
300714013	Embolus of vein NOS
3007901000006117	Thrombosis of arteries of upper extremity
30091013	Capillary thrombosis
300964011	[X]Embolism and thrombosis of other arteries
300975010	[X]Embolism and thrombosis of other specified veins
30273012	Portal vein thrombosis
302984016	Thrombosis of mesenteric vein
3040431000006114	Thrombosis of arteries of the extremities
304527018	Scrotal thrombosis
307782017	Cerebral venous thrombosis in the puerperium
3123551000006116	Hepatic vein thrombosis
3132081000006111	Embolism of renal vein
3215871000006116	Thrombosis of corpus cavernosum
3345371000006113	Femoral artery thrombosis
3347911000006112	Embolism of corpus cavernosum
3387371000006112	Arterial embolism
3439701000006113	Pulmonary artery thrombosis
3439711000006111	Pulmonary arterial thrombosis
345723011	Anterior spinal artery thrombosis
3462921000006119	PE - Pulmonary embolism
350892013	Arteriovenous fistula thrombosis
3511086012	Thrombosis of right vertebral artery
3511955015	Thrombosis of right middle cerebral artery

3511959014	Thrombosis of left middle cerebral artery
354495010	Cholesterol embolus syndrome
3553621000006119	Vertebral artery thrombosis
3627981000006110	Pulmonary thrombosis
3636257010	Iliac vein thrombosis
3636258017	Thrombosis of iliac vein
3648381000006112	Thrombosis of superior sagittal sinus
3648391000006110	Sagittal sinus thrombosis
3662311000006113	Thrombosis of cerebral arteries
3662321000006117	Cerebral arterial thrombosis
3662331000006119	CT - Cerebral thrombosis
3728451000006116	Cerebral arterial embolism
3745891000006115	Penile venous thrombosis
3767271000006119	Pulmonary venous thrombosis
3767281000006116	Pulmonary vein thrombosis
3805161000006114	Hepatic artery embolism
3807321000006113	Embolism of iliac artery
3841211000006114	Thrombosis of iliac artery
3865591000006112	Hepatic artery thrombosis
3870981000006117	Thrombosis of abdominal aorta
3918361000006110	Popliteal artery thrombosis
3932731000006114	Basilar artery thrombosis
395795012	Arterial embolus and thrombosis
395796013	Embolism and thrombosis of the abdominal aorta
395803017	Thrombosis of vein NOS
3962581000006110	Thrombosis of cavernous venous sinus
3978101000006118	Thrombosis of arteries of lower extremity
3978111000006115	Lower limb arterial thrombosis
3983941000006119	Endocardial thrombosis
4056781000006117	Thrombosis of pelvic vein
4056971000006118	Thrombosis of cerebral veins
4056981000006115	Cerebral venous thrombosis
4059051000006119	Thrombosis of renal artery
412652016	Mesenteric embolism
419640012	Thrombosis of inferior vena cava
437622013	Axillary vein thrombosis
4403261000006113	DVT - Deep vein thrombosis
4403291000006117	Deep venous thrombosis of pelvic vein
449993015	Thrombosis of renal artery bypass graft
4506441000006113	Paradoxical embolism
452963015	Right ventricular thrombosis
453210011	Thrombosis of vein of leg
4768491000006118	Thrombosis of intracranial venous sinus
4778981000006116	Embolism and thrombosis of the celiac artery
4778991000006118	Embolism and thrombosis of hepatic artery

4785671000006113	Deep venous thrombosis of the superior mesenteric vein
4802301000006116	Puerperal pulmonary embolism
491241000006118	Arterial embolism and thrombosis
5004981000006112	Intracranial septic embolism
5011651000006111	Cerebral venous thrombosis of sigmoid sinus
5011661000006113	Cerebral venous thrombosis of cortical vein
5057591000006116	Pulmonary thromboembolism
5057601000006112	PTE - Pulmonary thromboembolism
5057611000006110	PE - Pulmonary thromboembolism
5057621000006119	Acute massive pulmonary embolism
5057651000006111	Subacute massive pulmonary embolism
5057661000006113	SAMPE - Subacute massive pulmonary embolism
5057671000006118	Pulmonary fat embolism
5057691000006117	Pulmonary tumour embolism
5059251000006117	Inferior mesenteric vein thrombosis
5059271000006110	Thrombosis of vein of lower leg
5059291000006111	Below knee thrombosis
5059301000006112	Iliofemoral deep vein thrombosis
5059311000006110	IFVT - Iliofemoral vein thrombosis
5059321000006119	Ileofemoral deep vein thrombosis
5059381000006115	Embolus of vein
5477061000006113	Cardiac embolism
5477661000006119	Thrombosis
5560171000006116	Aortic thromboembolism
5574011000006113	Superficial vein thrombosis
5645781000006111	Pulmonary air embolism
5645871000006116	Arteriovenous graft thrombosis
5653431000006118	Thrombosis of superior vena cava
5653441000006111	Brachiocephalic vein thrombosis
5836801000006110	Brachial artery thrombosis
5836841000006112	Common femoral artery thrombosis
5836861000006111	Common iliac artery thrombosis
5836901000006116	Internal iliac artery thrombosis
5836921000006114	Subclavian artery thrombosis
5836951000006117	Intracranial venous thrombosis
586241000006116	Nonpyogenic venous sinus thrombosis
5886741000006110	Digital arterial thrombosis
5992311000006119	Thrombosis of vein of lower limb
6018491000006111	Thrombosis of vein of trunk
6018501000006115	Venous thrombosis, phlebitis and thrombophlebitis
632111000000118	Recurrent pulmonary embolism
638821000006113	Embolism and thrombosis NOS

638871000006114	Embolism and thrombosis of other and unspec parts aorta
64466019	Hepatic vein thrombosis
6601121000006118	Coronary artery thrombosis
6601131000006115	CT - Coronary thrombosis
6694741000006111	Deep venous thrombosis of lower extremity
6694751000006113	DVT - Deep vein thrombosis of lower limb
6694761000006110	Deep venous thrombosis of leg
6694771000006115	Deep venous thrombosis of lower limb
6765361000006119	Pontine artery thrombosis
6851821000006113	Embolism
6969941000006114	Coronary artery stent thrombosis
6977021000006119	Thrombosis prophylaxis
7070211000006112	Thrombosis of ulnar artery
7078561000006114	Deep venous thrombosis of profunda femoris vein
7078581000006116	Deep venous thrombosis of deep femoral vein
7078591000006118	Thrombosis of the popliteal vein
7078601000006114	Deep venous thrombosis of the popliteal vein
7103191000006117	Superficial venous thrombosis of leg
7218941000006118	Thrombosis
7273741000006119	Deep venous thrombosis of peroneal vein
748061000006117	Left ventricular thrombosis
7609581000006110	Acute pulmonary embolism
7665071000006116	Recurrent DVT (deep vein thrombosis)
7855891000006114	Microvascular embolism of arteriole
7966351000006118	Acute deep vein thrombosis of lower limb
7967281000006119	Pulmonary embolism with pulmonary infarction
7967291000006116	Pulmonary embolism with infarction
8041531000006117	Acute deep venous thrombosis of calf
8041571000006119	Acute deep venous thrombosis
8041581000006116	Acute deep venous thrombosis of femoral vein
8041601000006114	Acute deep venous thrombosis of ileofemoral vein
8042501000006117	Acute deep venous thrombosis of axillary vein
8042511000006119	Acute deep venous thrombosis of internal jugular vein
8361011000006114	Unprovoked DVT (deep vein thrombosis)
8361031000006115	Provoked DVT (deep vein thrombosis)
851241000006115	Axillary vein thrombosis
884141000006116	Coronary thrombosis
884631000006118	Arterial embolism/thrombosis
884641000006111	Embolus/thrombosis abd. aorta
884651000006113	Embolus/thrombosis aorta NOS
884661000006110	Peripheral arterial embolism
884721000006112	Superfic.venous thrombosis leg

884731000006110	Deep venous thrombosis - leg
884741000006117	Venous embolism NOS
884751000006115	Venous thrombosis NOS
887751000006110	Embolism
905451000006118	[RFC] Pulmonary embolism/pulmonary hypertension
905491000006112	[RFC] Venous thrombosis
905541000006119	[RFC] Arterial embolism of limbs
909471000006114	[RFC] Deep vein thrombosis
9652971000006111	Thrombosis of vein of upper limb
9652981000006114	Thrombosis of arm
98484016	Pulmonary embolism
989221000006110	Deep venous thrombosis - leg
Orthostatic hypotension	
2762731000006117	Orthostatic hypotension dysautonomic syndrome
297043014	Parkinsonism with orthostatic hypotension
300835018	Idiopathic hypotension
300837014	Hypotension NOS
300988013	[X]Other hypotension
3226201000006112	Arterial hypotension
350841017	Hypotension due to drugs
3873661000006112	Idiopathic orthostatic hypotension
47965014	Orthostatic hypotension
47966010	Postural hypotension
5060961000006111	Drug-induced hypotension
5166511000006111	Induced hypotension
75071013	Hypotension
Syncope	
112741000006118	Vasovagal syncope
11811691000006118	Blackout
11828441000006110	Neurally-mediated syncope
11905391000006118	[D]Fainting
11928031000006118	Defecation syncope
11989711000006111	Defecation syncope
1222467016	Loss of consciousness
1222468014	Syncope
1235506011	Collapse - heat
1805671000006115	Feeling faint
1935991000006110	Referral for G-induced loss of consciousness
253056010	Felt faint
2533616016	Defaecation syncope
253608017	O/E - collapse - syncope
2725801000000110	Collapse with loss of consciousness
2725821000000118	Collapse without loss of consciousness
2725841000000113	Collapse with LOC (loss of consciousness)

2725851000000111	Collapse without LOC (loss of consciousness)
3006811000006111	Exertional syncope
3028501000006117	Brief loss of consciousness
303601000000116	[D]Asystolic vasovagal syncope
3158011000006115	Moderate loss of consciousness
316999012	Unconsciousness
317010018	Syncope and collapse
317011019	Blackout
317012014	Syncope
317013016	Vasovagal attack
317015011	Micturition syncope
317016012	[D]Syncope and collapse NOS
317404014	Cough syncope
3338311000006111	Carotid sinus syncope
3443351000006113	Hypotensive syncope
36036010	Syncope anginosa
370568012	Vasovagal symptom
3959691000006112	Heat collapse
3965121000006114	Tussive syncope
3965151000006117	Laryngeal syncope
402432018	O/E - unconscious
402433011	O/E - unconscious/comatose
407072012	Syncope symptom
411921018	O/E - loss of consciousness
424111000006116	[X]Psychogenic syncope
4550791000006115	O/E - syncopal collapse
5034281000006113	Syncopal vertigo
5060871000006110	Neurally-mediated syncope
5060901000006110	Vasovagal syncope due to immersion
5060911000006113	Situational syncope
5060931000006119	Defaecation syncope
5060951000006114	Deglutition syncope
514841000006111	Blackout - symptom
5466061000006117	Mechanism of syncope
5526491000006115	Syncope attack
5526501000006111	Fainting
5526511000006114	Faint
5605371000006115	Anxiety about fainting
6457481000006114	Psychogenic syncope
6609231000006110	Vaso vagal episode
6609241000006117	Vasodepressor syncope
663641000006119	Faint symptom
6916011000006119	Unconscious
6916021000006110	Mental status, unconsciousness
7074231000006114	Near syncope

7074241000006116	Presyncope
7095521000006115	No loss of consciousness
7161931000006118	Syncope due to orthostatic hypotension
7204381000006118	Convulsive syncope
7309721000006110	Witnessed syncope
8106261000006116	Traumatic subarachnoid haemorrhage with loss of consciousness
819091000006111	Heat syncope
819101000006117	Heat syncope or collapse
853671000006112	Blackout
899741000006117	Heat syncope/collapse
961911000006112	Syncopal episodes (fainting)/dizziness
983221000006113	Asystolic vasovagal syncope
Dizziness	
1759581000006110	Adverse reaction to drug desensitisation therapy - dizziness
1892951000006114	Dizziness on lying still
2159245017	Dizziness on standing up
2360901000000116	Dizziness on lying still
253031016	Dizziness present
253032011	Giddiness present
2626741000006111	Functional dizziness
317024019	[D]Dizziness and giddiness
317025018	[D]Dizziness
317026017	[D]Giddiness
317027014	Lightheadedness
317030019	[D]Dizziness and giddiness NOS
4084331000006119	Postural dizziness
4084341000006112	Postural lightheadedness
4084351000006114	Exertional dizziness
4088711000006117	Persistent postural perceptual dizziness
4088721000006113	PPPD - persistent postural perceptual dizziness
5034331000006116	Multisensory dizziness
5529421000006111	Dizziness - giddy
5529431000006114	Dizzy
6052941000006118	Dizzy spells
627241000006116	Dizziness
6459881000006118	Light-headedness
6459891000006115	Feels light headed
6459901000006116	Lightheaded
6459911000006118	Dizziness - light-headed
7104831000006114	Dizziness of unknown cause
7484131000006116	Dizziness due to drug
802161000006111	Giddiness
961911000006112	Syncopal episodes (fainting)/dizziness

Vertigo	
1778609014	Vertigo
178784013	Benign paroxysmal positional vertigo
187840011	Aural vertigo
2626731000006118	Psychogenic vertigo
2713101000006117	Auditory vertigo
2713121000006110	MÃ©niÃ¨re's vertigo
2740521000006115	Apoplectic vertigo
2824581000006111	Labyrinthine vertigo
2824601000006118	Central vestibular vertigo
287046015	Epidemic vertigo
299165019	Other and unspecified peripheral vertigo
299166018	Peripheral vertigo
	Unspecified peripheral vertigo
299167010	Benign paroxysmal positional vertigo or nystagmus
299171013	Other peripheral vertigo NOS
299173011	Malignant positional vertigo
299174017	Vertigo of central origin NOS
299544019	[X]Other peripheral vertigo
308831000033113	Vertigon
3096591000006118	Riders' vertigo
317028016	[D]Vertigo NOS
317029012	[D]Acute vertigo
3310361000006118	Objective vertigo
3316731000006112	Vestibular vertigo
3316741000006119	Peripheral vestibular vertigo
3618451000006117	Epileptic vertigo
3784401000006117	Ocular vertigo
3878711000006112	Cervical vertigo
3965131000006112	Laryngeal vertigo
3965161000006115	Charcot vertigo
4062661000006111	Central positional vertigo
4088561000006110	Essential vertigo
4088571000006115	Positional vertigo
4088591000006119	Postural vertigo
4088621000006117	Vertigo on awakening
4088671000006116	Paroxysmal vertigo
4088681000006118	Intermittent vertigo
4088741000006118	Visual vertigo
4088791000006110	Drug-induced vertigo
4088811000006114	Severe vertigo
4088841000006113	Vertigo, acute onset with vomiting and inability to stand
4197131000006118	BPPV - Benign paroxysmal positional vertigo

4742901000006110	Acute epidemic vertigo
475301015	Otogenic vertigo
4775081000006113	Disabling positional vertigo
480691012	Vertigo of central origin
5034251000006117	Migrainous vertigo
5034271000006110	Benign recurrent vertigo
5034281000006113	Syncopal vertigo
5034291000006111	Vertebrobasilar ischaemic vertigo
5600091000006114	Peripheral positional vertigo
5600101000006115	PPV - Peripheral positional vertigo
5899551000006111	Viral epidemic vertigo
5971471000006116	Benign paroxysmal positional vertigo nystagmus
5971481000006118	BPPV - Benign paroxysmal positional vertigo nystagmus
6221491000006118	Episodic recurrent vertigo
6617121000006110	Subjective vertigo
6618211000006114	Vertigo - giddiness
6618221000006118	Rotary vertigo
6618231000006115	Rotatory vertigo
6618241000006113	Vertigo (spinning sensation)
7375581000006113	Nocturnal vertigo
854511000006119	Vertigo
883801000006113	Central nystagmus/vertigo
Acute kidney injury	
1221119015	ARF - Acute renal failure
1705781000006113	Acute renal failure due to obstruction
1726511000006111	Acute-on-chronic renal failure
1847641000006114	Acute renal failure induced by non-steroidal anti-inflammatory drug
2180741000000113	Acute renal failure induced by aminoglycoside
2180861000000117	Acute renal failure induced by cisplatin
2180901000000112	Acute renal failure induced by cyclosporin A
2184271000000115	Acute renal failure due to non-traumatic rhabdomyolysis
2185551000000111	Acute renal failure induced by animal toxin
2185631000000115	Acute renal failure induced by heavy metal
2191151000000117	Acute renal failure induced by poison
2191301000000116	Acute renal failure induced by radiographic contrast media
2191381000000114	Acute renal failure induced by solvent
2198081000000118	Acute renal failure due to traumatic rhabdomyolysis
22041910000000110	Acute kidney injury
2214211000000112	Acute renal failure induced by toxin
2645796013	Acute renal failure due to ACE inhibitor
2732241000006113	Acute renal failure syndrome

2732281000006119	AKI - acute kidney injury
2878351000006115	Myoglobinuric acute renal failure
303915016	Other acute renal failure
303916015	Acute renal failure NOS
305191012	[X]Other acute renal failure
3071071000006113	Acute renal tubular necrosis
3071081000006111	Acute tubule necrosis
354413016	Acute drug-induced renal failure
354417015	Acute-on-chronic renal failure
460091000006111	Acute renal failure
460151000006118	Acute renal tubular necrosis
481692010	Acute renal failure due to rhabdomyolysis
481693017	ATN - Acute tubular necrosis
5094071000006113	Nephrotoxic acute renal failure
5094141000006118	Acute on chronic renal failure
5966771000006111	Transient acute renal failure
6992471000006118	Acute renal failure due to angiotensin-converting-enzyme inhibitor
7100101000006115	Acute renal failure due to acute cortical necrosis
7954311000006119	Acute kidney failure stage 1
7954321000006110	Acute renal failure stage 1
7954331000006113	Acute kidney failure stage 2
7954341000006115	Acute renal failure stage 2
7954351000006118	Acute kidney failure stage 3
7954361000006116	Acute renal failure stage 3
8040771000006116	Prerenal renal failure
8040781000006118	Pre-renal acute kidney injury
8040791000006115	Acute renal failure
Hypovolaemic shock	
13922631000006118	Hypovolaemia
2958681000006112	Hypovolemia
3134251000006119	Hypovolemic shock
3134261000006117	Low volume shock
317355015	[D]Hypovolaemic shock
325122017	Postoperative hypovolaemic shock
483912015	Hypovolaemia
4872531000006112	Postoperative hypovolemic shock
Stupor	
12454731000006112	[D]Coma and stupor
12716131000006119	[D]Coma and stupor NOS
2612171000006113	Spike wave stupor
292141000006118	[D] Stupor
294927012	Psychogenic stupor
295476017	Acute stupor state due to acute stress reaction
317002019	[D]Coma and stupor NOS

3245481000006112	Catatonic stupor
370461000006112	[X]Catatonic stupor
378151000006115	[X]Dissociative stupor
3954061000006111	Mental status, stupor
396761000006112	[X]Manic stupor
406059018	[D]Coma and stupor
451128012	[D]Stupor
5583321000006111	Dissociative stupor
961721000006118	Stuporous
Coma	
12454731000006112	[D]Coma and stupor
12716131000006119	[D]Coma and stupor NOS
178800012	Insulin coma
292001000006119	[D] Coma
317002019	[D]Coma and stupor NOS
406059018	[D]Coma and stupor
451127019	[D]Coma
5012691000006114	Hypothermic coma
5652471000006113	Hypoxic-ischaemic coma
5652491000006114	Drug-induced coma
6358171000006113	Comatose
959801000006110	Comatose

Death

In the UK, using the CPRD, death will be identified using a specific flag.

In Spain, using SIDIAP, date and cause of death will be identified using available information.

In Sweden, using the Swedish National Patient Register, date and cause of death will be identified using available information.

Physician's Questionnaire

Patient ID: _____

IBS-C Event Date: _____

Diarrhoea Episode Date: _____

We are conducting a post-authorisation safety study on drugs used for irritable bowel syndrome and predominantly constipation (IBS-C) in anonymised electronic database health records. For this purpose we would like to collect information strictly and only for the patient with the above mentioned ID number, who meets the study inclusion criteria. Please provide us with answers to the ten questions below reporting information from the medical history of the patient identified above:

Diagnosis Confirmation

1. The above patient has been identified as experiencing IBS-C approximately on [IBS-C event date]. Could you please either confirm or correct our information based on your most recent knowledge? Mark only one:
   ☐ Yes, I confirm the IBS-C diagnosis
   ☐ No, the IBS-C diagnosis is not confirmed, instead the gastrointestinal (GI) diagnosis is
   _____
   (If the IBS diagnosis is not confirmed please skip to question 5, otherwise continue to question 2)

2. Which drug was the main treatment used on [IBS-C event date] for managing IBS-C?:
   _____Dose:_____

3. Please confirm the earliest date of prescription for that treatment: _____

4. Which other treatments did the patient use on [IBS-C event date] or the days prior, for the management of the IBS-C? (Please provide either active substance, brand name or both, as available)
   a. _____Dose:_____
   b. _____Dose:_____
   c. _____Dose:_____

Diarrhoea Occurrence

5. Records show that this patient experienced an episode of diarrhoea on the [diarrhoea episode date].
   I confirm the diarrhoea diagnosis approximately on the above date ☐ Yes ☐ No
   If the answer is No please skip to Question 10, otherwise continue to question 6

6. If this patient was on treatment for IBS-C, were any of the treatments above discontinued due to this diarrhoea episode?
   ☐ Yes, there were treatments for IBS-C that were discontinued
   ☐ No, the patient was not on treatment for IBS-C or the treatment(s) was(were) not discontinued

7. If Yes, please specify the name of the drug(s) discontinued and the response to discontinuation
   a. _____ diarrhoea ☐ improved ☐ stayed the same ☐ worsened
   b. _____ diarrhoea ☐ improved ☐ stayed the same ☐ worsened
   c. _____ diarrhoea ☐ improved ☐ stayed the same ☐ worsened
   d. _____ diarrhoea ☐ improved ☐ stayed the same ☐ worsened

Complications of Diarrhoea

8. Did this diarrhoea episode require medical assistance or treatment other than soft diet, oral rehydration and the treatment discontinuation mentioned above, if any? ☐ Yes ☐ No

9. If you responded "Yes" to question 8, please mark all that apply from the following list, otherwise skip to Question 10.
   The patient experienced …
   ☐ dehydration that required intravenous rehydration (a)
   ☐ dehydration that required oral rehydration with solutions of electrolytes (b)
   ☐ serum potassium levels < 3.0 mEq/L (c)
   ☐ oliguria, defined a urine output < 400 mL in 24 hours (d)
   ☐ anuria, defined a urine output < 50 mL in 24 hours (e)
   ☐ serum potassium levels between 3.0 and 3.5 mEq/L (f)
   ☐ serum sodium levels > 150 mEq/L (g)
   ☐ new onset thromboembolism episodes (h)
   ☐ new onset orthostatic hypotension episodes (i)
   ☐ new onset syncope (j)
   ☐ new onset dizziness (k)
   ☐ new onset vertigo (l)
   ☐ acute renal failure (m)
   ☐ hypovolaemic shock (n)
   ☐ stupor (o)
   ☐ coma (p)
   ☐ The patient required hospitalisation because of the diarrhoea (q)
   ☐ The patient went to an emergency department or urgent care clinic due to the diarrhoea (r)
   ☐ The patient died shortly after the diarrhoea episodes (s)

☐ Patient's death was related to treatment for IBS (t)

☐ The patient restarted treatment for IBS after recovery from diarrhoea (u)

☐ Other treatment (v) (specify)

……

……....

☐ Other laboratory outcomes (w) (specify)

……

……....

Risk Factors for Complications

10. Did the patient have any of the following diagnosis on the [diarrhoea episode date]? (Please check all that apply):

☐ Hypertension (a) ☐ Diabetes (b) ☐ Cardiovascular disease (c)

☐ Crohn's disease (d) ☐ Ulcerative colitis (e) ☐ Microscopic colitis (f)

☐ Other risk factors for diarrhoea (g) (specify)

……

……....

Thank you for your cooperation. For any questions regarding this research please contact us:

Name *Organisation* *Postal address* *Email address*

Database Feasibility Assessment

This section includes a summary of the databases assessed to be used for the linaclotide studies, planned to be implemented in the UK, Spain, and Sweden. All databases identified were explored for feasibility and data content, as well as interest in conducting and availability to conduct the studies. This section contains the information provided by the candidate data sources contacted for this purpose.

Database Identification

The starting point for the feasibility assessment was the data sources previously identified in the outline protocol included in the RMP prepared in August 2012. This document included relevant information on one proposed data source per country; however, no contact with the data custodians was established at that point, and information on the availability of the key variables and an interest in collaboration in this study had not been initiated. For each of the three countries of interest, additional data sources were explored in order to select the databases that were more informative, available, and complete for the study purposes.

Data sources were identified through a targeted literature search in Embase and PubMed on the patient population of interest, with keywords to cover all IBS references. Following the search, abstracts of interest or full articles, when available, were retrieved and reviewed to identify potential data sources. Additional national and regional databases were found through a desktop search and using Evidera's prior experience in reviewing data sources. Finally, key global websites, such as those for Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT), ENCePP, and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) were accessed to identify further sources.

For all data sources identified (see Table 17), general background information was explored and some of the data sources were excluded. For those of potential interest, contact was established to further discuss content and verify the feasibility of implementing the drug use and safety study.

Database Assessment

For the four countries considered, the candidate data sources explored were the following:

Table 17. Summary of Data Sources Explored

Country	Data Source Name	Feasibility Assessment
UK	CPRD* THIN	Proposed Alternative
Spain	Aragón* SIDIAP BIFAP IASIST	Alternative Proposed Excluded Excluded
Sweden	NPR PDR	Proposed Proposed
Italy	Health Search Database Local Health Units Cegedim Longitudinal Patient Database	Proposed Alternative Alternative

Abbreviations: BIFAP Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria; CPRD Clinical Practice Research Datalink; SIDIAP Information System for the Development of Research in Primary Care; THIN The Health Improvement Network; NPR Swedish National Patient Register; PDR Swedish Prescribed Drug Register

* Included in the RMP protocol outline.

UK

In the UK, the two candidate data sources identified are very similar in content. The CPRD is the one proposed, since it has a larger population base and the possibility to link primary and secondary records for the majority of patients. CPRD also allows additional information to be requested for all of its patients through questionnaires sent to physicians.

Proposed Data Source: CPRD

CRPD, formerly known as the GPRD, contains the information recorded by GPs as part of their routine clinical practice in the UK (http://www.cprd.com). The database covers approximately 1/4 of the UK population and has approximately 16 million active users who are alive and currently contribute data to the database. Patients are representative of the whole UK population in terms of age and sex. Core data include information on sociodemographic characteristics, diagnoses, symptoms, referrals, tests ordered, some test results, prescriptions issued, and additional clinical information. These data are linkable, at least partially,—through the CPRD Division of the UK Medicines and Health Care Products Regulatory Agency (MHRA)—with other healthcare datasets (e.g., hospitalisation records, national mortality data, census data) via the patient's National Health Service (NHS) number, sex, date of birth, and postal code. The type of data collected is strictly longitudinal and from EMRs of patients attending a GP practice, with an average of 10 years of follow-up.

Medical data are coded using the Read and SNOMED systems, which is very granular and is updated regularly in response to user (physician) requests. It includes several codes for IBS and also for constipation, diarrhoea, and general gastrointestinal symptoms (e.g., bloating). Medications prescribed by the GP have fields for strength and dose. Drugs are classified following the British National Formulary. If records are linked to secondary care data using the HES, hospitalisation reasons for admission are coded by the ICD-10 and hospital tests and hospital procedures by OPCS codes.

CPRD data can be accessed by external researchers. Data are available in SAS format, and the time between the purchase and the receipt of data in 90% of studies is approximately three months. GPs can also be contacted by researchers to request details beyond what can be found in the computerised records or to confirm details of patient conditions and treatments. Additionally, CPRD has an internal research team with expertise in pharmacoepidemiology, pharmacoeconomics, and risk-benefit that can support

this type of research. Finally, it is possible to select the exact cohort of patients from CPRD's main primary care database (CPRD GOLD) and from linked databases when necessary.

The CPRD characteristics would make it suitable for the study, on linaclotide utilisation, and the second study, on linaclotide safety.

The study objectives were discussed with CPRD researchers, and it was confirmed that completion of the drug utilisation study (DUS) would be fairly straightforward. Pharmacy data, as prescribed from the GP, are readily available. The safety study will also be feasible to conduct, since severe complications are more likely to be recorded in full than milder complications, and the former are the safety outcomes of interest. Prior research on IBS has been performed based on CPRD data. This research has also been extensively published in peer-reviewed journals, with up to 11 research articles on IBS from 1999 to 2012.

The data available in the 12/14 static version of the CPRD contained 474 research-quality (acceptable) patients with at least one prescription for linaclotide.

Some limitations of the database content include lack of detailed information on secondary care (only all-cause hospitalisations can be identified) and the current unavailability of data on specialist visits and secondary care. The CPRD does not include unique codes that clearly distinguish IBS patients with constipation from those with diarrhoea, but patients can be classified based on code combinations.

Alternative Candidate Database: The Health Information Network (THIN)

THIN contains computerised and anonymised medical records from 559 PCPs covering 6% of the UK population. THIN contains information on more than 3.8 million active patients, with 11.3 million patients in total, resulting in over 77 million years of research into quality patient follow-up. Most of the contributing practices have recorded more than 15 years of data on their system and it is, therefore, representative of the non-institutionalised UK population. Core data include information on diagnoses, symptoms, referrals, tests ordered, some test results, prescriptions issued by the GP, and additional clinical information. Since the summer of 2012, it has been possible to link THIN patient longitudinal data to the HES data for England, although the number of practices with linked HES records is limited and available only for a fraction of patients.

Medical data are coded using the Read coding system and when linked to HES, hospitalisation records are coded by the ICD-10. Similarly, GP prescriptions are coded by Multilex codes following the British National Formulary.

THIN data can be accessed by external researchers and have been extensively published in peer-reviewed journals; however, no publications focused on IBS were identified. To access the data, a short version of the protocol needs to be approved by the Scientific Review Committee and by the Research Ethics Committee.

THIN could be a good alternative database for this study because it has the same characteristics and data content as the CPRD, and data extraction can be achieved with a quick turnaround of approximately one or two weeks. However, it covers a smaller number of practices and, therefore, a smaller proportion of the UK population, so recruitment of the same sample size as CPRD could take longer. The proportion of practices that can be linked to hospitalisation data from HES is smaller and around 50% of the GP practices participate in extra data collection.

Spain

Nationwide data sources for Spain could not provide the necessary information to perform this study, so the proposed data source and alternative candidate are each representative of one of its regions.

Proposed Data Source: SIDIAP

SIDIAP is a primary care database launched in 2010. It is similar to CPRD or THIN in the UK and has been collecting longitudinal data from EMRs from 274 primary care centres in Catalonia since 2006. Catalonia is a region with a total of 5.8 million patients who represent approximately 12% of the Spanish population (4% of the Spanish population in SIDIAP-Q with higher-quality indicators). Data are updated once a year, and there are several scientific publications using this data source and reporting validation study results. The date of the latest available data is December 2013, and 2014 data will be made available by May-June 2015.

Data from primary care, specialised care, hospitals, and pharmacies are available, as well as patient characteristics such as gender and date of birth, GP-diagnosed conditions, GP prescriptions, prescription dosing and size, date of prescription and dispensation, laboratory test results, other procedures, specialist referrals and diagnosis, hospital referrals, hospital procedures and discharge diagnosis, death rate, and pregnancy information. GP diagnoses are coded following the ICD-10 codes, and hospital admissions following the ICD-9.

SIDIAP does not transfer data to private entities, but it can carry out quality investigation projects (Bolivar et al., 2012) and submit results upon their completion, which will be agreed upon with the funding body in the design stage of the study. It also allows physicians to be contacted using short questionnaires (currently a group that includes 10% of the total) to extract additional information on the patient through a questionnaire. Since 2018, SIDIAP no longer allows the possibility to contact physicians for extracting extended additional information on the patient through long questionnaires. However, there is the possibility of a text review of the primary care records. This free-text review is made after an anonymisation process of the clinical records and a natural language processing of the text.

SIDIAP is considered to be an appropriate source of data for the execution of this project, as the vast majority of its patients have two or more years of follow-up and the database itself can link with the Drug Dispensation databases (and additionally with the Mortality Registry for Death Cause); both characteristics are relevant to the proposed linaclotide study. The objectives for this project were reviewed by a SIDIAP research team that was confident about the utilisation study. The team identified some challenges for the safety study, and recommended performing a preliminary descriptive and exploratory study to confirm the feasibility of conducting the study and to improve the validity of the actual study results.

Some of the challenges mentioned for the safety study were that the exact date of the prescription is only available for the first prescription. For subsequent prescriptions, only the month when it was dispensed by the pharmacy are available. Additionally, the identification of complication outcomes based on codes might be incomplete due to inconsistent recording, and it could be difficult to relate an episode of diarrhoea to potential complications. However, these challenges could be overcome by the use of free text in the medical records of patients.

Alternative Candidate: Instituto Aragonés de Ciencias de la Salud (IACS)

The Public Health and Health Services Research at the IACS in the Spanish region of Aragón has the possibility to link different electronic medical and administrative databases in the region for research purposes. With data covering 126,838 patients from six urban health centres in one Health Sector of Zaragoza, IACS covers a small percentage of the Spanish population (0.27%). When linked, these different databases provide administrative and clinical information from outpatient clinics (primary care health centres), administrative and clinical information from specialty clinics, emergency room diagnoses and care, hospital procedures and discharge diagnoses, and pharmacy prescription data.

However, the IACS does not maintain any database and, currently, each of the linkable databases belongs to two different governmental organisations that collect the data, either the Servicio Aragonés de Salud or the Departamento de Sanidad Bienestar Social y Familia. To gain access to these data, it is

required to apply to each of the data custodians by presenting a research protocol with the post-authorisation approval. Then, an extraction of data would be performed, tailored for each particular study. The participation of one of their researchers as principal investigator is required to managing a study of this kind; the investigator who will be responsible for the good use of the ad hoc database created. Information on GP-diagnosed conditions uses the International Classification of Primary Care coding. GP prescriptions use the anatomical therapeutic chemicals (ATC) classification codes.

The Aragón region database, although proposed in the study outline included in the linaclotide RMP, is not recommended as the first choice for this study since it represents a smaller proportion of the Spanish population and, at the moment, it is not maintained as an electronic database. It has also not been validated to perform these types of studies.

Data Source Excluded: BIFAP Database

The BIFAP is a population-based database in Spain containing primary care information from about 2,692 PCPs (GPs and paediatricians) from 10 different autonomous communities in Spain. It also contains 4,800,207 valid and anonymised medical charts with the following information:

- 76.561.939 records on health problems
- 414.852.056 records on pharmaceutical drugs
- 14.190.861 records on vaccinations
- 674.846.412 records with general patient data
- 24,957,871 person-years of follow-up

BIFAP is a project from the Agencia Española del Medicamento y Productos Sanitarios (AEMPS) and has been designed for use in pharmacoepidemiological studies. It is the largest and most detailed source of information in Spain, and several research articles using BIFAP data have been published, as well as validation studies for incidence and prevalence of certain disease areas, risk factors, and medication use.

BIFAP could not be included in this study since it is not accessible to researchers outside their network.

Data Source Excluded: IASIST

IASIST contains primary and secondary care clinical databases in Spain. The Inpatient Care Dataset accounts for more than 65% of real National Health System discharges and is built from real data obtained from 170 hospitals from 15 (out of a total of 17) different autonomous communities (regions) in Spain. This database is updated on a yearly basis, with one-year lag time (at the end of year 't' the complete database for year 't-1' is available). Hospitalisations are defined as those episodes with a length of stay greater than zero days (one or more days) or those with length of stay equal to zero and discharge status equal to 'death'.

Fields available within the Inpatient National Database for all hospitals are:

- Patient information, including birth date, gender, and medical record identifier
- Process information, including episode identifier, date of admission, discharge date and status
- Clinical information, including main diagnosis (ICD-9-CM), secondary diagnosis (up to 10 different diagnoses), medical/ surgical procedures (up to 10 different surgical procedures, ICD-9CM)
- Cost information, including diagnostic-related group (all patients diagnostic-related groups [AP-DRG]) and estimated inpatient cost

The primary care database accounts for at least two million people every year. This data source is built entirely from real data and covers 100% of four (out of a total of 17) different autonomous communities (regions) in Spain. Due to confidentiality reasons, IASIST cannot provide any further information on the areas that are being covered.

Major limitations for the purposes of this study data are that patients cannot be tracked across different hospitals because patient identification numbers are designated by every region and every year. For the same reason, patients cannot be tracked longitudinally over time. Additionally, primary care data cannot be linked to secondary care data, given that the information is provided to IASIST by each provider separately and patient identification is done separately by each provider. Therefore, this data source was not considered appropriate and was excluded.

Sweden

In Sweden, there exist several registries with high quality data and large coverage of the population. Given that for this study one of the main challenges were related to accrual of sufficient sample size, only national registries were considered. The two registries that have been proposed for this study include diagnosis and medications and could be linked together through a unique patient identifier:

Proposed Data Source: The National Patient Register

The Swedish National Patient Register (NPR) was initiated in 1964, initially covering inpatients in six county councils in Sweden. Since 1987, the register covers all public inpatient care and all outpatient visits since 2001. Data on primary care is not available. The information in NPR can be divided into 4 different groups covering several variables each: 1. Patient data; 2. Geographical data; 3. Administrative data from inpatient hospital admissions and outpatient visits; and 4. Medical data regarding main and up to 21 secondary diagnosis using the ICD-10 classification, external cause of injury and poisoning, and up to 30 surgical procedures from public and private service providers. A quality control check of the NPR is performed periodically, and in 2007 the main diagnosis was missing from 1.0% of records. At present, the NPR is updated once a year.

Proposed Data Source: The Prescribed Drug Registry

The Swedish Prescribed Drug Register (PDR) has been functioning since July 2005 and contains data on all prescriptions dispensed to the entire Swedish population. Data collection is administered by the National Corporation of Swedish Pharmacies, a state-owned company responsible for the provision of pharmaceutical services to the whole country. Information from all prescriptions dispensed is transferred monthly to the National Board of Health and Welfare, which is responsible for maintaining the PDR.

The register contains the following data on drugs prescribed and dispensed in ambulatory care: dispensed item (substance, brand name, formulation, and package); dispensed amount, dosage, expenditure, and reimbursement; age, sex, and unique identifier (personal registration number) of the patient; place of residence of the patient (county, municipality, and parish); date of prescribing and dispensing; the practice (primary health care centre or hospital clinic) that issued the prescription; and the prescriber's profession (e.g., general practitioner; specialist in internal medicine, psychiatry, or paediatrics). All drugs are classified according to the ATC classification system. The register does not include data on over-the-counter (OTC) medications or drugs administered in hospitals or complete data on drugs that are used in ambulatory care but are administered during day care at hospitals. The register is not complete with regard to drugs used in nursing homes.

Italy

In Italy, data sources have limited reference population size or limited availability of variables relevant for the proposed study. Additionally, linaclotide sales in Italy started in September 2014 hence the sample size contributed by Italy is relatively small.

Proposed Database: Health Search/CSD Longitudinal Patient Database

Health Search was founded in 1998 as a research unit of the Italian College of General Practitioners (SIMG). SIMG is a scientific society aimed to promote the role of General Practice within the National Health System. The main activities are focused on education and research. Research is mainly developed throughout the Health Search network, based on: (1) a school in which PCPs receive training and share

the same standards for recording electronic patients' information; (2) a database (Health Search), where PCPs collect patients' information. The group working with HSD data is a multidisciplinary team of epidemiologists, statisticians and IT experts; it provides value-added services to: (1) the PCPs who contribute to the HSD; (2) the stakeholders that are interested in using this research tool. Health Search-SIMG is currently involved in several national and multinational research projects on drug safety and drug utilization, health technology assessment (HTA) and health services research studies.

The HSD collects longitudinal data from approximately 900 active GPs across Italy, with 700 of them selected as most reliable for research purposes. The HSD contains patient demographic information, medical data (e.g., diagnoses, tests and test results, hospitalization, etc.), drug prescription, and prevention information, collected when patients visit PCPs, from approximately 2.4 million patients, and one million active patients currently assisted by the GPs selected for research project participation. The current average length of patient's electronic medical records since inception of the database is approximately 10 years. A unique identification number links all data for an individual patient in an anonymous way and no identifying details are available. The geographical distribution of patients of these PCP is from 16 Italian regions and similar to the general Italian population, without significant differences both in geographical location and age distribution (Prezioso et al., 2014; Masclee et al., 2013). The latest data currently available for research is data up to 31 December 2013.

The proposed database has been used in previous studies that also included similar European population-based primary care databases such as CPRD (Masclee et al., 2013).

Alternative Data Source: Local Health Units

A Local Health Unit (LHU) is a body assigned by the National Health System in Italy to provide healthcare to a specific geographic area, generally a province. The LHUs in Italy are responsible for assessing the medical needs and providing comprehensive care for a defined population. Each LHU is responsible for the hospital and primary care services in its area as well as for prevention and health promotion activities. LHUs have an information network that measures the expenditure for drug reimbursement for registered patients. LHUs record all claims from pharmacies concerning drugs that are fully or partially reimbursed. The data available include: demographics, hospital admission and discharge diagnoses, specialist visits, drug prescription and dispensation (primary care only), mortality and costs. A patient's personal health number can be cross-checked with the registry office and hospital database. This allows the information to be connected to the date of birth, gender and any record of previous hospitalisations. Diagnoses and procedures are recorded based on the International Classification of Diseases (ICD)-9 and ICD-9-CM codes. On average, each LHU covers a total population of 500,000 beneficiaries, and 3 to 5 LHUs have been included by Evidera in previous studies. The main limitation of this database for our current study is its lack of primary care and specialist diagnosis records.

Alternative Data Source: Cegedim Longitudinal Patient Database

The CSD Medical Research group provides access to European longitudinal patient data using data collected from the electronic medical records entered into a primary care physician's software, including 700 GPs attending over 800,000 patients from Italy. CSD includes information on the patient profile, clinical profile, prescriptions and the prescriber profile, but no information on hospital admissions (date of admission, admission diagnosis, discharge diagnosis, hospital stay duration, accident and emergency (A&E) visits or discharge status). Data characteristics are similar to those in the proposed database.

Data Source Excluded: Friuli Venezia Giulia Regional Information Health System (FVG)

FVG is in the northeastern part of Italy and has approximately 1.2 million inhabitants. In Italy, all citizens are covered by taxed-based public health insurance. The hospital discharge database of the FVG region of Italy routinely collects data from all hospitals in the region and includes information on patients' sociodemographic characteristics and treatment received during hospitalization. Given that the LHUs can capture the same data, in a larger population, this database was excluded.

Pilot Study Summary Report

Background

AbbVie is planning a nested case-control study to assess the safety of linaclotide, authorised for the symptomatic treatment of moderate-to-severe irritable bowel syndrome predominantly with constipation (IBS-C) in adults. The study goal is to assess the risk of severe complications of diarrhoea (SCD) among patients with IBS-C exposed to linaclotide or other treatments, controlling for potential risk factors. This study will be conducted in the United Kingdom (UK), amongst other countries, using data from the Clinical Practice Research Datalink (CPRD).

Information on IBS-C and SCD is not well captured in electronic data sources by standard diagnosis codes, therefore, the study plan includes additional primary data collection from general practitioners (GPs) to validate IBS-C diagnoses and potential SCD events identified through an algorithm based on electronic records. This type of additional data collection is feasible in the UK with the use of the CPRD. For cases and controls (or a sample of them, depending on the number of cases and controls), validation data will be collected though a questionnaire mailed to the attending GP with whom each identified study subject is registered.

Before using the questionnaire to collect information about IBS-C diagnoses and potential SCD events in the safety study, we conducted a pilot study to test this questionnaire with a small number of physicians in the UK.

Objective and Rationale

The objective of the pilot study was to assess the face validity of a questionnaire to collect information from PCPs to validate:

1. The correct identification of the study population (cohort of patients with IBS-C)
2. The patients experiencing the endpoints of interest

Study Design

For the execution of the pilot study, we worked in collaboration with the CPRD. GPs from practices contributing into the CPRD were randomly selected among those practices with a good track record of collaboration on prior research and were invited to participate in this pilot study.

GPs were approached and requested to participate, providing feedback through two alternative means:

- In writing (draft questionnaires were sent to GPs to be filled out and returned to the CPRD before the answers were anonymously provided to Evidera). We planned to target 12 GPs in an effort to obtain six questionnaires back.
- Orally, through a telephone interview. The CPRD was in charge of obtaining the informed consent from GPs, providing to Evidera only their first name and telephone number before they were contacted and interviewed (no further information that could identify the GP or the practice they work on was shared or sought). Telephone interviews intended to collect suggestions to any parts of the questionnaire deemed unclear, to gather feedback on coding habits, and to provide the opportunity to ask questions to the GPs about the feedback just provided, for clarification of any heterogeneous interpretations of the questionnaire. We targeted four GPs for telephone interviews.

The target number of GPs participating in this pilot study was selected to balance feedback diversity and logistical considerations, such as resources needed and time to collect responses. Reminders were sent if no response was returned after two weeks from the GPs receiving the questionnaires.

The documentation sent to GPs included questions on the GPs' coding habits for patients with IBS-C in addition to the draft questionnaires intended for case (patients with IBS-C experiencing SCD) and control validation. GPs were asked about the order and wording of the questions, whether they were

user friendly and easily understandable, and any suggestions they might have to improve the questionnaire. Questions related to the proposed Read codes to define patients with IBS-C were aimed to help understand how GPs code patients with IBS-C, since there is no single, specific code for this condition.

An optional second phase was also planned, in case significant changes to the questionnaire were necessary as a result of the collected feedback during the first phase. This second phase would assess the feasibility of using the updated questionnaire to capture the required information for validation of the safety endpoints. For this, we planned that the CPRD would target GPs who had at least one patient with IBS-C, as defined by the study-proposed combination of Read code of IBS plus a Read code for constipation or constipation-related symptoms. If this phase was necessary, we would have targeted 12 additional GPs and asked them to fill the updated questionnaire on one IBS-C patient each. The answers to the questionnaires would have provided the expected information or otherwise suggest that the questionnaire was not well understood and had to be amended consequently.

Results

The pilot study was initiated in November 2014, and closed at the end of February 2015.

We eventually targeted 19 GPs for the written questionnaire and six for the telephone interview. These numbers were larger than originally planned in an attempt to increase the chances of response in a short period of time that included the holiday season, when we anticipated a low response rate.

Two weeks after the questionnaires were first distributed, a reminder was sent to all non-responding GPs. Two GPs agreed to participate in the telephone interview and interviews were conducted. Additionally, written questionnaires were completed by five GPs and returned.

The feedback received is summarized below:

- GP coding practices of patients with IBS-C

J521 codes were the preferred codes for GPs to indicate patients with IBS-C, and the code for 'IBS' (J521.11) was selected by all GPs except one. 'History of IBS' (14CF.00) was marked by one GP but also noted by another GP as a code that would not be used to identify a patient with IBS-C. The use of free text to identify patients with IBS-C was recommended.

19C codes were the preferred codes for constipation, ahead of J520 codes. 'Constipation symptom' (19C..11) and 'Constipation' (19C..00) were the preferred codes among the former, with 'Constipation – functional' (J520.00), and 'Constipation NOS' (J520z00) among the latter. 'Psychogenic constipation' (E264500) was reported as a code that would not be used in a patient with IBS-C.

Other constipation-related symptoms frequently used in patients with IBS-C included: 'Colicky abdominal pain' (1962.00), 'Abdominal pain' (1969.00), 'Generalised abdominal pain' (197A.00), 'Abdominal distension symptom' (19A..00), 'Bloating symptom' (19B..12) and 'Nausea' (198..00). Additional codes occasionally used included: 'Central abdominal pain' (1971.00), 'Epigastric pain' (1972.00), 'Lower abdominal pain' (197C.00), 'Abdominal discomfort' (1968.00), '[D] Bloating' (R073400), '[D] Flatulence, eructation and gas pain' (R073.00) and 'Nausea symptoms' (198..12). Working diagnoses codes (including '[D]') were not likely to be preferred to code patients with IBS-C, (chosen only by one GP).

- Face-validity of the questionnaire

It was confirmed that if diarrhoea is severe, a Read code for diarrhoea should be expected in the patient's electronic medical record (EMR).

The questions to validate the SCD were all understood without difficulties and no suggestions for changes to the questions were proposed. Responses from GPs were: "Seems quite straightforward", "All questions appear clear enough", "I am content with this questionnaire, it seems straight forward to me",

"All questions seem clear and reasonable except that there is no definition of diarrhea or constipation", and [No comment].

The only suggestion provided was to review the formatting of the questionnaire because some of the answers with tick boxes were misaligned in the copy received by the GP.

One of the interviewed GPs estimated that filling out the questionnaire could take between five and 20 minutes, depending on how long the patient history is.

Given no significant changes were recommended, the second phase of the pilot study was not conducted.

Conclusions

The results of the pilot study showed that the proposed questionnaire for validation of patients with SCD appears to be user-friendly to the responding GPs and straight forward to fill out. No significant suggestions for changes to the questionnaire were proposed. The optional second phase to this pilot study was not deemed necessary.

The pilot study also showed that in terms of coding practices, most GPs mentioned the combination of codes J521.11 "IBS" and 19C.11 "Constipation Symptom" or 19C..00 "Constipation" as the preferred one used to identify IBS-C cases. Additionally, the use of free text to identify patients with IBS-C was recommended.