26/04/2024

Study protocol

Title: Association between exposure to esomeprazole/omeprazole and risk of sexual dysfunction in men

Version 3.2

Administrative details	
Substance(s)	Esomeprazole, omeprazole
Condition/ADR(s)	Sexual dysfunction
Short title of topic	Esomeprazole/omeprazole use and Sexual dysfunction
RWE study team	Andrei Barbulescu, María Clara Restrepo-Méndez, and Robert Flynn
Reviewers	Karin Hedenmalm and Daniel Morales Leaver

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1. Brief description of the study (for publication in HMA-EMA Catalogue of RWD studies)

A cohort study which will investigate a potentially increased risk of sexual dysfunction (SD) among male patients prescribed esomeprazole/omeprazole when compared to: (a) being prescribed alternative treatments from the same drug class (i.e., other proton pump inhibitors, PPIs); (b) being prescribed alternative treatments from another drug class (i.e., histamine type 2 receptor antagonists (H2RAs)); and (c) not being prescribed PPIs or H2RAs despite indications for them (non-initiators).

2. Background

Sexual dysfunction (SD) disorders are defined as disorders of sexual desire and the psychophysiological alterations of the sexual response cycle in men and women. (Shamloul & Ghanem, 2013; Valeiro et al., 2022) In men, SD can be classified as erectile dysfunction (ED), decreased libido, or abnormal ejaculation. (Hatzichristou et al., 2016; Romano et al., 2022; Shamloul & Ghanem, 2013) In women, SD includes painful intercourse and altered sexual desire, arousal and orgasm that causes distress. Normal sexual function is coordinated at different levels by multiple regulatory systems including vascular, neurological, and endocrine factors. (Calabro et al., 2019; Romano et al., 2022; Shamloul & Ghanem, 2013) Psychological and social factors may also play a role. (Calabro et al., 2019; Romano et al., 2022; Shamloul & Ghanem, 2013) Chronic disorders may impair sexual health at different levels by altering the physiological mechanisms underlying a normal sexual function or by acting at the psychological level. (Romano et al., 2022; Shamloul & Ghanem, 2013; Shen, 2019; Stringer, 2016) Moreover, medicines used in the treatment of chronic disorders may affect the functioning of the regulatory systems involved in normal sexual function, such as antihypertensive drugs, antidepressants (e.g., SSRIs) and central nervous system agents (e.g., benzodiazepines). (Rothmore, 2020; Shamloul & Ghanem, 2013; Valeiro et al., 2022)

Proton pump inhibitors (PPIs) are indicated for the management of peptic ulcer disease and gastroesophageal reflux disease. PPIs are frequently used (and often overused) medications with adverse effects including vitamin B12 deficiency, Clostridium difficile colitis, and increased risk of chronic kidney disease. (Cao et al., 2018; Laine et al., 2000; Lazarus et al., 2016) SD has been suggested as a side effect of PPIs, although the evidence is sparse, and the pathophysiology mechanism is not clear. Some evidence suggest that PPIs may contribute to impaired nitric oxide generation and endothelial dysfunction. (Nolde et al., 2021; Pinheiro et al., 2016; Yepuri et al., 2016)

During routine signal detection activities, six individual case safety reports of SD with suspected association to esomeprazole use were retrieved from EudraVigilance and an additional 18 cases were identified in the published literature. Of these, 23 comprise male individuals whose symptoms started between few days to five months after treatment initiation. In 15 of these patients, symptoms improvement was reported after treatment discontinuation. In two cases, symptoms reoccurred after restarting the treatment.

To support the evaluation of safety concerns regarding esomeprazole use, a study is proposed to provide further evidence as to whether being prescribed esomeprazole is associated with an increased risk of SD when compared to: (a) being prescribed alternative treatments from the same drug class (i.e.., other PPIs); (b) being prescribed alternative treatments from the other drug class (i.e., histamine type 2 receptor antagonists (H2RAs)); and (c) not being prescribed PPIs or H2RAs despite indications for them (non-initiators). The rationale for using multiple comparator groups is based on the fact that some of the available alternative treatments - which are preferable because of their similar indication (active comparators) - have SD listed as a possible side effect. Ideally, the active comparator should be known to have no effect on the event of interest since it is used to represent the

background risk in the disease. (Yoshida et al., 2015) However, impotence is listed as a rare side effect for lansoprazole as well as for H2RAs, and decreased libido is listed as rare side effect for famotidine. (EMC, 2024a, 2024b, 2024c) Therefore, we will opt to also include a non-user comparator (non-initiators), to gain insight into the background risk for sexual dysfunction. Of note, the safety concerns also included omeprazole (i.e. the racemate of esomeprazole and R-omeprazole) considering the partly identical structure shared by esomeprazole and omeprazole. Hence, this study will also examine whether being prescribed omeprazole is associated with an increased risk of SD when compared to the abovementioned comparators.

In view of the differences in the definition of SD and risk factors between female and male individuals, and the reported cases which occurred mostly in men and that the majority of primary care recording of SD occurs in males, this study will focus on SD in male individuals only.

3. Research question and objectives

Among male patients, is the prescription of:

1) **Esomeprazole** associated with increased risk of sexual dysfunction (SD) when compared to patients who are:
    a) prescribed other PPIs (namely omeprazole, pantoprazole and lansoprazole)?
    b) prescribed H2RAs?
    c) not prescribed either PPIs or H2RAs?
2) **Omeprazole** associated with increased risk of sexual dysfunction when compared to patients who are:
    a) prescribed other PPIs (namely esomeprazole, pantoprazole and lansoprazole)?
    b) prescribed H2RAs?
    c) not prescribed either PPIs or H2RAs?

Box 1 provides the rationale for the selection of multiple comparator groups.

Box 1. Rationale for the selection of multiple comparator groups and limitations

A. Active comparators (other PPIs, H2RA)

- Active comparators are alternatives for the target treatment within the same indication. They enable to indirectly restrict the study population to patients with a comparable indication to the target drug. If alternative treatments for the same indication can be identified and are assumed to be used interchangeably, i.e., prescribed with clinical equipoise, then confounding by indication is reduced.
- For this study, the most suitable active comparators would be either other PPIs or H2RAs which have similar indications. However, some shortcomings should be considered.
    - Lansoprazole and pantoprazole are the most common PPIs prescribed in the selected databases after esomeprazole and omeprazole. However, lansoprazole has already listed in the product information erectile dysfunction as a rare effect. Yet, the comparison with other PPIs might provide insights into whether any association observed is a class effect.

- H2RAs also have erectile dysfunction listed in the product information as a rare side effect and famotidine has also decreased libido listed. Yet, the comparison with H2RAs might provide insights into whether there is an increased risk of sexual dysfunction in esomeprazole/omeprazole users.
- The availability of over the counter (OTC) PPIs has increased over time and, subsequently their OTC use, which are not captured in electronic health records databases. Hence, exposure misclassification is expected.
- The prescribing of H2RAs has decreased over time (see Annex II, Excel file), particularly after the suspension of all ranitidine medicines in the European Union due to the presence of low levels of an impurity called N-nitrosodimethylamine (NDMA) in April, 2020.

- Other treatment alternatives which could have been considered as active comparators such as alginates - which are indicated for treatment of peptic ulcers, dyspepsia, mild forms of GERD, etc. as an adjunct to other drugs - are greatly used OTC. Thus, the potential for exposure misclassification may be greater than for H2RA considering their wide use.

B. Non-treated comparators (non-initiators of either PPIs or H2RAs treatments)

- If the indication for treatment is a risk factor for the study outcome, then treated patients are more likely than non-treated to have the indication, and therefore are at a higher risk for adverse health outcomes associated with the indication, leading to confounding by indication. In this respect, the non-treated/non-user comparator is not the preferable comparator for safety studies.
- However, to our knowledge, the main treatment indications for PPIs (e.g., GERD, duodenal and gastric ulcers) have not been associated with SD. Thus, in this study, it is not expected that the estimate of the effect will be strongly biased by confounding by indication, which makes the comparison with non-treated patients acceptable. Additionally, the comparison with a non-treated group might provide insights into the background risk for SD, which will not be gained with the comparison with the selected active comparators in view of their potential risk for erectile dysfunction as mentioned above.
- The non-initiator group in this study might be a mixed group of non-users and [PPIs, H2RAs, alginates] OTC users for which a prescribing for either PPIs or H2RAs treatment is not required probably because of the presence of milder gastroduodenal conditions potentially requiring short term, occasional treatment in low doses.

Conclusion: In view of the above-mentioned advantages and disadvantages, we choose to use multiple comparators which could aid interpretation of the findings.

4. Methods

Box 2. Summary of study methods	
Recruitment period	01/01/2005 - 31/12/2020
Data sources	IQVIA™ Disease Analyser (DA) Germany IQVIA™ Medical Research Data (IMRD) UK
Eligibility criteria	• Eligibility criteria will be applied at cohort entry (index-date, see definition below)

Box 2. Summary of study methods	
	Inclusion criteria: • Men aged 18 years or older; • With a recorded diagnosis for any of the following, prior to index date: GERD, gastric and duodenal ulcers, chronic gastroduodenitis, Zolliger-Elison syndrome, OR with a recorded recent history of comedication with any of the following: NSAIDs, acetyl salicylic and derivatives, glucocorticoids, or antithrombotic treatments; • With at least one year of recorded medical history prior index-date. *Exclusion criteria:* • Those with recorded prescription of any PPIs or H2RAs within one year before index-date; • Those with recorded history of SD OR treatment for SD at any time prior index-date; • Those with recorded history of selected severe central nervous system comorbidities (Section 4.3, Table 1) prior to index-date; • Those with history of Helicobacter pylori (H. pylori) infection or use of fixed PPI-antibiotic treatments for this indication.
Treatment protocols	Initiate any of the following substances (or none of them in the "non-initiators" cohort) at index-date (see definition below), as monotherapy (i.e., not in combination with another PPI or H2RA). *Target arms:* • esomeprazole (target arm [Cohort 1]) • omeprazole (target arm [Cohort 2]) *Comparator arms:* • pantoprazole (comparator arm [Cohort 3]) in the IQVIA™ Disease Analyser (DA) Germany database) • lansoprazole (comparator arm [Cohort 4]) in the IQVIA™ Medical Research Data (IMRD) UK database) • H2RAs, all combined (comparator arm [Cohort 5]) • non-initiators of either PPIs or H2RAs (comparator arm [Cohort 6])
Assignment procedures	We will assume treatments are randomly assigned within levels of the covariates identified as potential confounders [see Section 4.6, Potential confounding factors]
Index-date (cohort entry, beginning of follow-up)	**Active treatment arms** (including PPIs and H2RAs [Cohort 1 to 5])**:** The index date will be the date of the initiation of treatment defined as a prescription date for PPIs/H2RAs after a washout window of at least 365 days in which no previous prescription with any PPIs or H2RAs have been recorded. **Non-initiator arm** [Cohort 6]**:** Non-initiator comparators will be selected on each date of the recruitment period when esomeprazole/omeprazole initiators start treatment,

Box 2. Summary of study methods	
	matched on birth-year. This date will be the non-initiator comparators **index-date**. Thus, with regards to treatment, the active treatment arms initiate a treatment on index-date and non-initiator comparators do not.
Outcome	First recorded occurrence of SD, including the following ICD-10 codes: F52.0, F52.1, F52.2, F52.3, F52.6, F52.8, F52.9, N48.4, N94.1, N48.3 [See section 4.6, Outcome]
Follow-up	Patients will be followed-up from index-date up to maximum 1 year. Thus, patients will be followed-up from index-date to the earliest of: date of first occurrence of outcome, loss to follow-up, death (only available in IMRD UK), end of follow-up (1 year) or end of the study period [See Section 4.5, Follow-up period]
Casual contrast of interest	Intention to treat effect, i.e., patients were followed up irrespective of treatment change (main analysis).
Statistical methods	• Inverse probability of treatment weighting (IPTW) will be used to adjust for confounders measured at cohort entry. • Incidence rates (IR) and cumulative incidence proportions will be estimated for each treatment cohort. • Hazard ratios (HRs) will be estimated using a Cox proportional hazards model. • Cumulative incidence proportions will be estimated for each treatment arm using the Kaplan-Meier estimator. • Sensitivity analyses will include a **"Per-protocol"** analytical strategy and adjusting for informative censoring at treatment protocol violation. [See Section 4.7. Statistical analyses]

4.1. Study design

Comparative cohort design, including:

a) Active comparator, new user design:

- Esomeprazole initiators (target treatment [Cohort 1]) will be compared to the following comparators: pantoprazole [Cohort 3], lansoprazole [Cohort 4], and H2RAs [Cohort 5] initiators.
- Omeprazole initiators (target treatment [Cohort 2]) will be compared to the following comparators: pantoprazole [Cohort 3], lansoprazole [Cohort 4], and H2RAs [Cohort 5] initiators.

Treatment initiation will be defined as the prescription date for PPIs/H2RAs after a washout window of at least 365 days in which no previous prescription with any PPIs or H2RAs have been recorded. This date will coincide with the cohort entry or start of follow-up in the study, which we will refer to as **index-date**.

b) Non-initiator comparator

- Esomeprazole initiators (target treatment [Cohort 1]) will be compared to patients who did not have a prescription for either PPIs or H2RA despite having a recorded indication (see Section 4.3, eligibility criteria) for theses treatment (non-initiator comparator [Cohort 6]).
- Omeprazole initiators (target treatment [Cohort 2]) will be compared to patients who did not have a prescription for either PPIs or H2RA despite having a recorded indication (see Section 4.3, eligibility criteria) for theses treatment (non-initiator comparator [Cohort 6]).

As above, treatment initiation will be defined as the prescription date for esomeprazole/omeprazole after a washout window of at least 365 days in which no previous prescriptions with any PPIs or H2RAs have been recorded. This date will coincide with the start of follow-up in the study, which we will refer to as **index-date**.

Non-initiator comparators will be selected on each date of the recruitment period when esomeprazole/omeprazole initiators start treatment, matched on birth-year. This date will be the non-initiator comparators index-date. Thus, with regards to treatment, the active treatment arms initiate a treatment on index-date and non-initiator comparators do not.

A graphical representation of the study design including the assessment windows for inclusion–exclusion criteria, covariates and follow-up relative to index-date is shown in Figure 1. Further details for each component of the diagram are provided in the respective sections below.

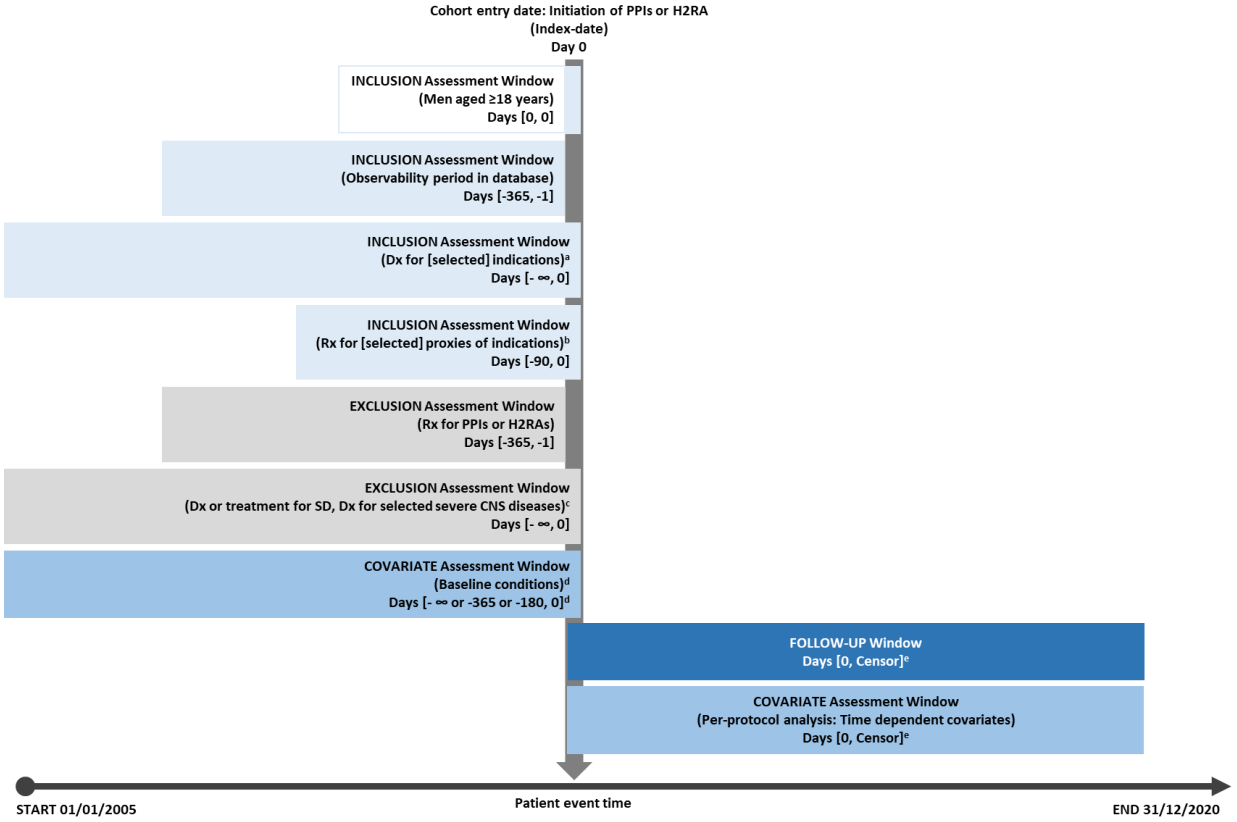

Figure 1. Study design diagram.

Dx: diagnosis; Rx: prescription; SD: sexual dysfunction

[a,b] Selected indications: GERD, gastric and duodenal ulcers, chronic forms of gastroduodenitis, and Zollinger-Ellison syndrome and recent comedication with NSAID, acetyl salicylic and derivatives, glucocorticoids, and antithrombotic treatments.

[c] Selected severe CNS diseases: Hereditary ataxia (mainly hereditary spastic paraplegia), Huntington disease, spinal muscular atrophy and related syndromes, cerebral palsy, hemiplegia, paraplegia and tetraplegia, other paralytic syndromes (monoplegia of lower limb, cauda equina syndrome, locked-in syndrome), dependence on wheelchair.

[d] Baseline conditions: See Section 4.6 on potential confounding factors.

[e] Censoring: Patients will be censored at the earliest of the following events: first occurrence of outcome, loss to follow-up (e.g., transfer out date from the general practice in IMRD or end of continuous observation of the patient by the practice in IQVIA™ DA Germany, or date of last data collection from the practice), death (only available in IMRD UK), end of follow-up (1 year) or end of the study period.

4.2. Data sources

The following databases will be used: IQVIA™ Disease Analyser (DA) Germany, and IQVIA™ Medical Research Data (IMRD) UK. Brief descriptions of these databases are provided in **Annex 1**.

4.3. Study population

The population eligible for the study will be selected based on the inclusion and exclusion criteria listed in Table 1, which will be measured at baseline (i.e., index-date). Figure 1 above provides details on the assessment windows for these eligibility criteria in relation to the index-date.

Table 1. Eligibility criteria.

Inclusion criteria	Exclusion criteria
• Patients registered with a general practice (GP) covered by IMRD or patients visiting GP in IQVIA™ DA Germany;	• Recorded prescription of any PPIs or H2RAs within one year before index-date;
• Male; AND • Aged ≥18 years;	• Recorded history of SD OR treatment for SD (e.g., Viagra) prior index-date;
• At least one year of recorded medical history prior to index-date.	• Those with recorded history of selected severe CNS diseases prior index-date, namely: Hereditary ataxia (mainly hereditary spastic paraplegia), Huntington disease, spinal muscular atrophy and related syndromes, cerebral palsy, hemiplegia, paraplegia and tetraplegia, other paralytic syndromes (monoplegia of lower limb, cauda equina syndrome, locked-in syndrome), dependence on wheelchair.
• Recorded diagnosis for GERD, gastric and duodenal ulcers, chronic gastroduodenitis, and Zollinger-Ellison syndrome[1]; OR	--

Inclusion criteria	Exclusion criteria
• History of comedication with NSAID, acetyl salicylic and derivatives, glucocorticoids, and antithrombotic treatments [1, 2]	

[1] These indications are selected indications for PPIs and H2RAs. We restricted the study population to patients with chronic indications, for which treatment is likely chronic. The rationale for this is explained in Limitations (first paragraph)

[2] These are assumed to be proxies of indications (e.g., PPIs are indicated to patients requiring continued NSAID or antithrombotic therapy).

4.4. Recruitment period

The recruitment period will start on January 1st, 2005, and will end on December 31st 2020 in both IQVIA™ DA Germany and IMRD UK.

Although the first use of esomeprazole dates to September 2000, in IMRD UK and October 2000, in IQVIA™ DA Germany, we opted to include data from 2005 the year when the distribution of male sexual dysfunction events started being consistent.

Additionally, we opted to limit the recruitment period up to 2020 because the use of H2RAs is very limited in IQVIA™ DA Germany after 2020. Of note, the suspension of all ranitidine medicines in the European Union due to the presence of low levels of an impurity called N-nitrosodimethylamine (NDMA) in April, 2020[1] led to the suspension of ranitidine, the dominant H2RA in Europe.

4.5. Follow-up period

Patients will be followed-up from index-date up to maximum one year. For instance, patients recruited in 2020 can be followed up to 2021. Thus, patients will be followed-up from index-date to the earliest of: date of first occurrence of outcome, loss to follow-up (e.g., transfer out date from the general practice in IMRD or end of continuous observation of the patient by the practice in IQVIA™ DA Germany, or date of last data collection from the practice), death (only available in IMRD UK), end of follow-up (1 year) or end of the study period.

Considering the recommended duration for these treatments (4-8 weeks for PPIs and 8-12 weeks for H2RAs), a patient may participate with several treatment episodes - and consequently index-dates - during the study period. For example, a patient may receive a prescription for 8 weeks after which the medication is discontinued to assess the need for ongoing therapy (on-demand or intermittent use). After 15 months of discontinuing this therapy, the patient may receive another prescription for the same therapy and duration. Therefore, this patient will enter the study twice and contribute with two treatment episodes. Of note, eligibility criteria will be evaluated at each index-date every time the patient contributes with a treatment episode. Figure 2 illustrates examples of patient exposure to treatments for four different patients according to calendar time (in months).

[1] Ranitidine-containing medicinal products - referral | European Medicines Agency (europa.eu)

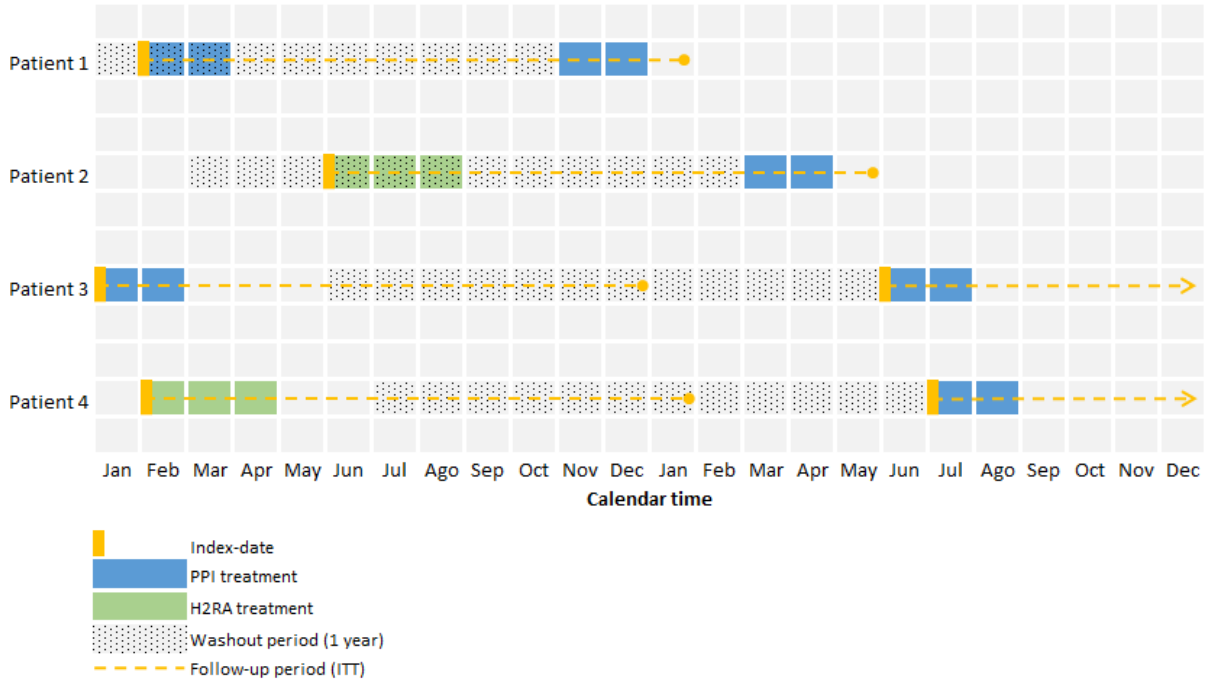

Figure 2. Patient exposure to treatments according to calendar time.

Patient 1: Patient contributes with 1 treatment episode (first episode). The second episode does not meet the criterion of 1 year washout before index date.

Patient 2: Patient contributes with 1 treatment episode (first episode). The second episode does not meet the criterion of 1 year washout before index date.

Patient 3: Patient contributes with 2 treatment episodes. The second episode meets the criterion of 1 year washout before index date.

Patient 4: Patient contributes with 2 treatment episodes. The second episode meets the criterion of 1 year washout before index date.

The follow-up period illustrated here corresponds to the 12-month follow-up for the ITT analysis.

4.6. Variables

Exposure

a) Active treatment arm (cohorts):

Patients who **initiate treatment** with either target treatments (esomeprazole or omeprazole) or active comparators (pantoprazole, lansoprazole, H2RAs) during the study period will be identified based on the dates of prescriptions in the database and considering a washout period (See Figure 2 above) of 1 year before index-date in which no previous prescription with any PPIs or H2RAs have been recorded.

Only initiation of target treatments and active comparators as **monotherapy** will be included in the study. Initiating treatment with more than one PPI or H2RA or any combination of the two on the same day will be not allowed. However, combinations with treatments other than PPIs and H2RAs are allowed (e.g., alginates and antacid basic salts). Table 2 shows the treatment assignment by target/comparator arm.

Of note, considering that these treatments have been long available on the market, their prescribing pattern (on-demand or intermittent use) and widespread over-the-counter (OTC) use, it will not be possible to identify the first prescription ever (i.e., first use or incident exposure) with any certainty. Electronic health records may not capture the entire patient history of utilisation of these treatments. In addition, these treatments are used interchangeably which would mean that a substantial number of individuals would be excluded from the study population if the study focuses only on first use ever of any of these substances. Therefore, the study will assess initiation of treatment after a washout window of at least 365 days.

Prescriptions will be identified through keyword searches using international non-proprietary names (INNs) in several prescription-related variables (e.g., "Therapy Name", "Product Name", "Molecule"). Detailed list of keywords used are provided in **Annex 2**.

PPIs will include the most prescribed substances in each database, i.e., esomeprazole, omeprazole, and pantoprazole in IQVIA™ DA Germany, and esomeprazole, omeprazole, and lansoprazole in IMRD UK. Other PPIs such as dexlansoprazole and rabeprazole are less commonly recorded in the selected databases and, therefore, will not be included in this study.

Products containing H2RAs will include the following substances (ordered by frequency of prescribing): ranitidine, famotidine, nizatidine, cimetidine in IMRD, and ranitidine, famotidine, cimetidine, nizatidine in IQVIA™ DA Germany.

Annex 2 provides details on the use of PPI and H2RA substances over time in each database.

b) Non-initiators arm (cohort)

Non-initiator comparators will be randomly sampled and selected on each date of the recruitment period when esomeprazole/omeprazole initiators start treatment, **matched on birth-year**. This date will be the non-initiator comparators index-date. Thus, with regards to treatment, the active arms initiate a treatment on index-date and non-initiator comparators do not. Matching on index-date and on year of birth is meant to ensure a similar distribution of calendar time and age at index-date, both of which are considered important potential confounders.

It should be noted that *non-initiators* refer to patients who have selected indications (see Table 1 above, inclusion criteria) recorded in the databases but who did not initiate therapy (i.e., did not have a recorded PPIs or H2RA prescription within 12 months before index-date or on index date).

Table 2 summarises the treatment assignments by cohorts.

Table 2. Treatment assignment by cohorts.

Target treatments:	Active comparators:	Non-initiator comparator:

• Treatment initiation as monotherapy* with:
  ○ Esomeprazole [Cohort 1]
	• Treatment initiation as monotherapy* with:
	  ○ Selected PPIs:
		• Prior diagnosis of indication but no treatment

Target treatments:	Active comparators:	Non-initiator comparator:
○ Omeprazole [Cohort 2]	▪ Omeprazole [Cohort 2], when esomeprazole is the target treatment; ▪ Esomeprazole [Cohort 1], when omeprazole is the target treatment; ▪ Pantoprazole in IQVIA™ DA Germany [Cohort 3], or ▪ Lansoprazole in IMRD UK [Cohort 4] ○ Selected H2RAs [Cohort 5]: ranitidine, famotidine, cimetidine, nizatidine in IQVIA™ DA Germany, and ranitidine, famotidine, nizatidine, cimetidine in IMRD UK.	initiation with either PPIs nor H2RAs within previous 12-month or on index date [Cohort 6].

* **Note:** Treatment initiation with any combination with other PPIs or H2RAs on the index-date is not part of the study.

Outcome

Sexual dysfunction (SD) will be defined as the first recorded occurrence of any of the following conditions (ICD-10 code): lack or loss of sexual desire (F52.0); sexual aversion and lack of sexual enjoyment (F52.1); failure of genital response (F52.2); orgasmic dysfunction (F52.3); nonorganic dyspareunia (F52.6); other sexual dysfunction, not caused by organic disorder or disease (F52.8); unspecified sexual dysfunction, not caused by organic disorder or disease (F52.9); impotence of organic origin (N48.4); dyspareunia (N94.1), priapism, painful erection (N48.3).

Annex 2 provides the list of WHO ICD-10 codes used to identify outcome events in IQVIA™ DA Germany. READ codes were used to identify these conditions in IMRD UK (Annex 2). Of note, SD as defined here is mostly driven by erectile dysfunction/impotence, which is the most frequent condition recorded in both databases.

Potential confounding factors:

Analyses will account for the following baseline covariates measure before index-date, which are considered risk factors for the outcome, particularly for erectile dysfunction (DynaMed, 2023; La Torre et al., 2013; Razdan et al., 2018; Shamloul & Ghanem, 2013; Trinchieri et al., 2021; Yogarajah & Mula, 2017):

(i) Main organic causes of sexual dysfunction
Neurogenic
Multiple sclerosis and other demyelinating disorders
Parkinson's disease
Alzheimer's disease and other dementias (e.g., vascular)

(i) Main organic causes of sexual dysfunction
Stroke
Autonomic neuropathies
Endocrinological
Diabetes mellitus
Hypogonadism
Hyperprolactinaemia
Hypothyroidism
Testosterone deficiency
Vasculogenic
Atherosclerosis
Systematic diseases and general ill health
Myocardial infarction
Cardiac failure
Chronic kidney disease
Severe chronic respiratory diseases: COPD, emphysema, sleep apnoea (Budweiser et al., 2009)
Major pelvic surgery: prostatectomy, urethroplasty or surgery for urethral structure, cystectomy, aorto-iliac surgery
Malignancy, and radiation in the pelvic region

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(ii) Factors related to the development of psychogenic sexual dysfunction
Depression
Anxiety
Stress disorders
Behaviour and sexuality disorders

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(iii) Drugs reported to be associated with sexual dysfunction
Cytostatic anti-androgens (prostate cancer)
Cytostatic anti-androgens (e.g., bicalutamide, cyproterone)
Cytostatic gonadotrophin-releasing hormone analogue (e.g. leuprorelin)
Antihypertensives
Diuretics
Potassium-sparing diuretics (e.g., spironolactone)
Thiazides and analogues (e.g., hydrochlorothiazide, indapamide) Loop diuretics (e.g., torasemide, furosemide) *Beta-blockers*
Beta-blockers (e.g. metoprolol, bisoprolol, carvedilol)
Anti-adrenergic agents
Alpha-adrenoreceptor blockers (doxazosin, prazosin, indoramin, trimazosin, bunazosin, urapidil) Guanidine derivatives (guanethidine, betanidine, guanoxan, debrisoquine, guanoclor, guanazodine, guanoxabenz) *Cardiovascular drugs acting on the renin-angiotensin system*
ACE inhibitors (e.g., ramipril, enalapril, lisinopril)

(iii) Drugs reported to be associated with sexual dysfunction

Angiotensin II receptor blockers (e.g., losartan, irbesartan)

Centrally Acting Anti-hypertensives

Antihypertensives centrally acting (e.g., moxonidine, clonidine, methyldopa, reserpine)

Antiarrhythmics

Digitalis glycosides

Cardiac glycosides (e.g., digoxin, digitoxin)

Other antiarrhythmics

Amiodarone, Disopyramide

Benign Prostatic Hypertrophy drugs

Alpha-adrenergic antagonists (e.g., tamsulosin, terazosin)

5-alpha testosterone reductase inhibitors (5-ARI) (e.g., finasteride, dutasteride)

Antifungal drugs

Ketoconazole, Terbinafine

Antidepressants and Mood Stabilizers

Antidepressants that negatively affect sexual function

SSRI antidepressants (e.g., citalopram, sertraline, fluoxetine)

SNRI antidepressants (e.g., venlafaxine)

Other antidepressants including tricyclics (e.g., clomipramine, amitriptyline, imipramine, doxepin) and MAOIs (e.g., phenelzine, tranylcypromine, moclobemide) and excluding bupropion, mirtazapine, agomelatine, nefazodone, trazodone and tianeptine (included below)

Antidepressants that may improve sexual function

Mirtazapine, bupropion, agomelatine, lamotrigine

Antipsychotic Drugs

Atypical antipsychotics (e.g., olanzapine, quetiapine, risperidone, aripiprazole)

Conventional antipsychotics (e.g., haloperidol, flupentixol, sulpiride)

Anxiolytic Drugs

Anxiolytics that negatively affect sexual function

e.g., benzodiazepines, hydroxyzine, meprobamate

Anxiolytics that may improve sexual function

Buspirone, Piper Methysticum (Kava)

Antiepileptic Drugs

Antiepileptics that negatively affect sexual function

Carbamazepine, phenobarbital, valproic acid and phenytoin

Antiepileptics that may improve sexual function

Lamotrigine, levetiracetam

Opioids

Lipid lowering drugs

Statins (e.g., simvastatin, atorvastatin, rosuvastatin)

Fibrates (e.g., bezafibrate, clofibrate)

Combinations of statins and fibrates with other agents (mainly ezetimibe)

Anti-Parkinsonian Drugs

Prolactin inhibitors

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(iv) Risk factors associated with sexual dysfunction

Age

(iv) Risk factors associated with sexual dysfunction
Lifestyle factors ○ Cigarette smoking ○ Substance abuse (including alcohol) **Metabolic risk factors** ○ Overweight > 25 Kg/m2 ○ BMI > 30 Kg/m2

(v) Other potential confounders
History of PPIs or H2RAs use - To account for the potential effect on past exposure (>12 months) on the likelihood of receiving subsequent PPI/H2RA therapy and the risk of outcome.
Calendar year - To account for changes in prescribing and diagnosis coding practices over time.

4.7. Statistical analysis

4.7.1. Brief summary of the analysis method (for publication HMA-EMA Catalogue of RWD studies)

In this study, the estimated treatment effect will be the comparison of the risk of sexual dysfunction, over one year, between patients who initiated (i.e., were prescribed treatment after the specified washout) esomeprazole versus patients who: a) initiated other proton pump inhibitors (PPIs, namely omeprazole, pantoprazole/lansoprazole); b) initiated histamine type 2 receptor antagonists (H2RA)) and c) patients who did not initiate treatment with either PPIs or H2RA but had received a diagnostic for a PPI or H2RA indication (i.e. non-initiators comparators). Outcome events will be attributed to the baseline treatment protocol regardless of treatment change during follow-up. (i.e., **intention-to-treat analysis** (**ITT**)).

4.7.2. Descriptive analysis

Descriptive analyses will be performed to describe the study cohorts at baseline in terms of demographic characteristics, lifestyle factors, potential indications, comorbidities, and history of treatment with drugs commonly associated with sexual dysfunction.

4.7.3. Main statistical analysis

Inverse probability of treatment weighting (IPTW)

Inverse probability of treatment weighting (IPTW) will be used to render the assignment of study treatments independent of the baseline measured covariates, thus minimising the potential confounding effect of these covariates.

Using IPTW, the average treatment effect (ATE) in the entire study population will be estimated, assuming that all important confounding variables have been accounted for. For each observation in the study population, the IPTW is the inverse of the probability of receiving the observed treatment

conditional on all variables considered sufficient for confounding adjustment. In order to stabilize the weights (i.e., less extreme weights, that are closer to the mean weight of one), the numerator of one will be replaced by the marginal probability of receiving the observed treatment in the study population (i.e., the proportion of observations in the study population with the respective treatment). (Hernan & Robins, 2006) All analyses will then be conducted in the re-weighted population without additional confounding adjustment on the assumption of no unmeasured confounding. To account for weighting the population (essentially multiplying observations by the weight coefficient) robust standard error estimators will be used (Hernan & Robins, 2020).

The distributions of baseline covariates before and after weighting was compared between esomeprazole and the other treatment arms by calculating and plotting standardized mean differences (SMD), with a SMD of <10 used to determine appropriate covariate balance. For each variable, the SMD was the difference in mean (for continuous variables) or proportion (for binary variables) between each treatment arms and the entire study population (which is the target population in the ATE to which the composition of covariates distribution in each treatment arm is standardized), divided by the study population standard deviation of the variable. (McCaffrey et al., 2013)

Intention-to-treat (ITT) analysis

The ITT approach chosen for the main analysis will involve following patients from the date of study treatment initiation (i.e., index date) until the earliest of any of the following: first outcome event date, loss to follow-up (e.g., transfer out date from the general practice in IMRD or end of continuous observation of the patient by the practice in IQVIA™ DA Germany, or date of last data collection from the practice), date of death (only available in IMRD) or the end of the study. Consequently, outcome events will be attributed to the baseline treatment regardless of treatment change during follow-up. Moreover, it will be assumed that intercurrent events that may occur during follow-up are independent of the risk of the outcome (i.e., the risk of experiencing the outcome among individuals remaining in the analysis over the course of follow-up is representative of the risk among censored individuals).

Incidence rates (IRs)

IRs will be calculated as the number of events occurring during follow-up divided by the total person-time in each treatment-arm. IRs will be presented as number of events per 100 person-years.

Cumulative incidence (Incidence proportion)

Survival (i.e., the proportion of the patients included at baseline who have not yet experienced a sexual dysfunction event) over the course of follow-up will be estimated by treatment arm using the Kaplan-Meier method. (Bland & Altman, 1998) The cumulative incidence will be calculated as the complement of survival (i.e., the proportion of the patients included at baseline who have experienced a sexual dysfunction event) at each follow-up time and will be presented as number of events per 100 patients.

Cox proportional hazards model

Hazard ratios of sexual dysfunction associated with treatment of interest (esomeprazole) versus comparators will be estimated using a Cox proportional hazards model.

4.7.4. Sensitivity analysis

The following sensitivity analyses will be performed to test the validity of the underlying assumptions and the robustness of the study findings:

Applying "per-protocol" (PP) approach: In this analysis, the follow-up of patients will be censored at the initiation of a PPI or H2RA other than the baseline treatment. Assuming that such censoring is independent of the risk of SD (i.e., non-informative censoring), this analysis will estimate the treatment effect had patients remained on the baseline treatment for the entire follow-up or discontinued the baseline treatment but without initiating an alternative PPI/H2RA.

Thus, we will consider a patient to respect the baseline treatment protocol from index-date to the date of crossing over to an alternative treatment arm. Patients will be censored at the earliest of the following events: end of index-treatment, crossing over to an alternative treatment arm, first outcome event date, loss to follow-up (e.g., transfer out date from the general practice in IMRD or end of continuous observation of the patient by the practice in IQVIA™ DA Germany, or date of last data collection from the practice), date of death or at the end of the study period.

This approach addresses the situation in which a patient initiates another PPI/H2RA after index-date, which might be problematic if the other PPI/H2RA initiated after index-date and within the 1-year follow-up might cause the outcome event instead of the baseline treatment.

It should be noted that the difference between the ITT and PP approach will lie in the follow-up period. The same baseline conditions such as eligibility criteria and washout period before index-date were applied for both analytical approaches.

Adjustment for informative censoring at treatment discontinuation in the PP analysis: In the per-protocol analysis described above, patients will be censored when they initiate another treatment. Implicit in the per-protocol analysis is an assumption that censoring is independent of the studied outcome, so that this differential treatment selection should not introduce bias.

In this analysis, we will adjust for potential selection bias via informative censoring, by reweighting patient observations using the inverse of the probability of being censored at the initiation of another treatment conditional on the same confounders selected at baseline (i.e., outcome risk factors potentially associated with treatment initiation) but updating their values during follow-up. (Hernan et al., 2000; Robins et al., 2000)

Analyses will be done using SAS Enterprise Guide 7.1 software.

4.7.5. Sample size

The sample size will be driven by the availability of individuals with exposures and outcomes within each database and no *a priori* sample size requirement will be stipulated.

4.8. Quality control

The study will be conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance will be adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents will undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis will be either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

4.9. Limitations of the research methods

Exposure misclassification may exist since neither OTC drug use nor medication use during hospitalisation are captured in the included databases. This is a particular issue because of the availability of OTC PPIs has increased over time (Johnson et al., 2017) and, probably their OTC use. Additionally, information on the actual duration of treatment corresponding to each prescription is not available and is difficult to estimate since patients may be prescribed large packs and instructed to use the drug as needed, with possible discontinuation/restart and dose-variation over time. Moreover, whether patients collected their prescriptions or consumed the prescribed medication is unknown. Due to this uncertainty and considering information from individual case reports about the latency of effect, we chose to follow patients for a maximum of one year and attribute the entire follow-up to the index treatment unless another treatment was initiated. It should be noted that, in the analysis comparing with non-initiators, we restricted the study population to patients with chronic indications, for which treatment is likely chronic.

To our knowledge, the accuracy of diagnostic coding for sexual dysfunction has not been assessed in the primary care databases available. However, the nature of the diagnosis means that its recording in primary care records could be reasonably accurate, particularly for sexual dysfunction in male individuals. Nonetheless, this assumption should be treated cautiously. In the UK, the patent for Viagra expired in June 2013, which followed a drop by 93% in the price of generic preparations of sildenafil compared to the price of branded Viagra (Connelly, 2017). Besides, Sildenafil has been available OTC without prescription from UK pharmacies since 2017 and, therefore, patients have no longer needed to see their doctor to get a diagnosis ever since. (MHRA, 2017) These events led to marked changes in diagnosis coding practices of erectile dysfunction during 2013-2014 and marked decrease of coding for impotence by GPs since 2017 which are reflected in the distribution of outcome events over calendar time. In IQVIA™ DA Germany the reporting of male sexual dysfunction appears stable after 2005. To account for uncertainties around potential misclassification due to changes in diagnostic criteria or coding practices over time, calendar period will be adjusted for in the analysis.

It also needs to be considered that patient's medical history, as captured by GP practices included in the study, may be incomplete, particularly in the IQVIA DA Germany database. In Germany, there is no mandatory GP system and patients have free doctor choice. A specialist can be consulted without referral from the GP. As a result, data are collected from visits to various medical practices which are not linked by a unique patient identifier. Therefore, the entire medical history of patients might be fragmented and for that reason there is a risk of exposure, outcome and covariates misclassification. However, this misclassification will affect both target and comparator groups.

Although confounding by indication represents a common source of bias, it is not likely that the main indications for PPIs (i.e., gastroesophageal reflux disease, esophagitis, and treatment for or prophylaxis against gastric or duodenal ulcer disease) are strongly associated with SD.

Ideally, the active comparator should be known to have no effect on the event of interest. Impotence is currently listed as a rare side effect in the UK product information for lansoprazole (EMC, 2023, 2024b), and for H2RAs. (EMC, 2024a, 2024c) Therefore, we will use multiple comparators, including non-initiators, which is meant to capture (if possible) a "background risk" among patients with the indication but not under treatment. Even though we will impose the presence of at least one chronic indication for PPIs/H2RAs to both initiators and non-initiators, it is possible that non-initiators differ from initiators in the distribution of unmeasured outcome risk factors, which would leave residual unadjusted confounding. In addition, non-initiators might include patients misclassified as untreated but who were users of OTC drugs. However, we assume that OTC use is episodic, i.e., occurring occasionally at irregular intervals and therefore, individuals might be less exposed to long-term treatments.

Finally, although more than 50 potential confounders will be adjusted for, we cannot rule out the possibility of residual confounding as not all relevant potential confounders are captured in the selected databases (e.g., other comorbid conditions or severity of comorbidities) and there might be misclassification of measured covariates due to incomplete capture of some co-morbidities or co-medication in GP data.

5. Protection of human subjects

Patient confidentiality will be protected according to the EU General Data Protection Regulation (GDPR) on the protection of individuals.

In accordance with database rules on the management of low cell counts, cells with low numbers (<6 in the IMRD database) will be removed prior to publication of the final study report. Additional cells may be redacted (events/patients typically being rounded up to the nearest 10) if needed in order to ensure that the aforementioned low cell counts cannot be re-identified. This may include both events/patients and follow-up times.

6. Management and reporting of adverse events/adverse reactions

Pursuant to the requirements for reporting of adverse events for secondary data (GVP module VI, VI.C.1.2.1.2), adverse event reporting will not be conducted as part of this study given the study objectives will be met through the use of secondary data.

7. Plans for disseminating and communicating study results

The analysis plan and study results will be published in HMA-EMA Catalogue of RWD studies upon completion.

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Annexes

Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Medical Research Data (IMRD) UK

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

Annex 2 - Codelists

EXPOSURES: PPIs AND H2RAs

- **IQVIA™ Disease Analyzer Germany**

PPIs

INN	EPHMRA ATC Code	EPHMRA ATC Text
ACETYLSALICYLIC ACID + ESOMEPRAZOLE	B01C5	Platelet aggregation inhibitors, combinations
AMOXICILLIN + OMEPRAZOLE + CLARITHROMYCIN	A02B2	Proton pump inhibitors
DICLOFENAC + OMEPRAZOLE	M01A1	Anti-rheumatics, non-steroidal plain
ESOMEPRAZOLE	A02B2	Proton pump inhibitors
LANSOPRAZOLE	A02B2	Proton pump inhibitors
NAPROXEN + ESOMEPRAZOLE	M01A1	Anti-rheumatics, non-steroidal plain
OMEPRAZOLE	A02B2	Proton pump inhibitors
PANTOPRAZOLE	A02B2	Proton pump inhibitors

H2ARs

INN	EPHMRA ATC Code	EPHMRA ATC Text
CIMETIDINE	A02B1	H2 antagonist
FAMOTIDINE	A02B1	H2 antagonist
NIZATIDINE	A02B1	H2 antagonist
RANITIDINE	A02B1	H2 antagonist

- **IQVIA™ Medical Research Data (IMRD) UK**

PPIs

Generic Drug Name
ESOMEPRAZOLE
LANSOPRAZOLE
OMEPRAZOLE
PANTOPRAZOLE
RABEPRAZOLE
KETOPROFEN/OMEPRAZOLE
NAPROXEN/ESOMEPRAZOLE
AMOXICILLIN/CLARITHROMYCIN/LANSOPRAZOLE
METRONIDAZOLE/CLARITHROMYCIN/LANSOPRAZOLE

H2ARs

Generic Drug Name
CIMETIDINE
FAMOTIDINE
NIZATIDINE
RANITIDINE
RANITIDINE BISMUTH CITRATE
CIMETIDINE/ALGINIC ACID
FAMOTIDINE/CALCIUM/MAGNESIUM

OUTCOME: SEXUAL DYSFUNCTION

- **IQVIA™ Disease Analyzer Germany**

WHO ICD10 code	WHO ICD10 Text
F52.0	Lack or loss of sexual desire
F52.1	Sexual aversion and lack of sexual enjoyment
F52.2	Failure of genital response
F52.3	Orgasmic dysfunction
F52.6	Nonorganic dyspareunia
F52.8	Other sexual dysfunction, not caused by organic disorder or disease
F52.9	Unspecified sexual dysfunction, not caused by organic disorder or disease
N48.4	Impotence of organic origin
N94.1	Dyspareunia
N48.3	Priapism -- Painful erection

- **IQVIA™ Medical Research Data (IMRD) UK**

Read code	Term
E2275	Inhibited male orgasm
67IA	Advice about impotence
7A6G0	Revascularisation for impotence
7A6G5	Ligation of penile veins for impotence
Eu521	Sexual aversion disorder
K27y1	Impotence of organic origin
1ABG	Sexual intercourse difficult
1ABB	Cannot get an erection
1ABC	Cannot sustain an erection
ZV417	Abnormal sexual function
15D	Pain on sexual intercourse
E2273	Impotence
E2273-1	Erectile dysfunction

Read code	Term
Eu520-3	[X] Lack of libido
Eu521-1	[X]Anhedonia sexual
7C25E	Management of erectile dysfunction
Eu522	Failure of genital response
Eu520-2	[X]Hypoactive sexual desire disorder
Eu523-1	[X]Inhibited orgasm
Eu520	Lack or loss of sexual desire
Eu522-2	[X]Male erectile disorder
Eu523	Orgasmic dysfunction
Eu52y	[X]Oth sex dysfunction, not caused by organic disordr/dsease
Eu523-2	Anorgasmia
Eu522-3	Psychogenic impotence
Eu52	Non-organic sexual dysfunction
Eu52z	[X]Unspec sex dysfunction not caused by organic disordr/dis
K28y7	Dyspareunia due to non psychogenic cause in the male
E2272	Frigidity
E227-99	Frigidity and impotence
K580-99	Dyspareunia - non psychogenic
K27y1-99	Erectile dysfunction organic
EMISCDY1	Dyspareunia
EMISCPA6	Pain during or after sexual intercourse
EMISCIM4	Impotency
1D1B	C/O erectile dysfunction
EMISNQRE309	Reduced libido
EMISNQPR146	Problem getting an erection
EMISICD10|F5211	Lack of sexual enjoyment
K27y7	Erectile dysfunction due to diabetes mellitus
^ESCTLO263343	Low libido
^ESCTPS316073	Psychologic dyspareunia
^ESCTPA332307	Painful ejaculation
^ESCTOR351791	Orgasm incapacity
^ESCTPO357750	Poor erection
^ESCTDY366015	Dyspareunia
^ESCTOR384422	Orgasm disorder
^ESCTDO392066	Does not enjoy having sex
^ESCTIM451123	Impotence education
^ESCTDY479108	Dyspareunia due to non-psychogenic cause in the male
^ESCTDE494548	Decreased sexual function
^ESCTDR509827	Drug-induced impotence
^ESCTEN509828	Endocrine impotence
^ESCTCO509899	Coital failure
^ESCTSU524375	Superficial pain on intercourse
^ESCTDE524377	Deep pain on intercourse

Read code	Term
^ESCTDE524378	Deep dyspareunia
^ESCTSE524379	Sexual function painful
^ESCTDE526179	Delayed erection
^ESCTER526208	Erection without orgasm
^ESCTWE526211	Weak orgasm
^ESCTHY551800	Hypoactive sexual desire disorder
^ESCTPA562100	Pain on penetration
^ESCTDY572132	Dyspareunia - non-psychogenic
^ESCTER655321	Erectile dysfunction appliance
^ESCTSE748154	Secondary erectile dysfunction
^ESCTCO748662	Complaining of erectile dysfunction
^ESCT1395247	Erectile dysfunction
^ESCT1395249	Male erectile disorder
^ESCT1395253	Erectile dysfunction due to psychophysiologic disorder
^ESCT1409249	Erectile dysfunction due to diabetes mellitus
^ESCT1450429	Non-psychogenic dyspareunia

FREQUENCY OF RECORDING OF SUBSTANCES AND CLINICAL CONDITIONS IN DATABASES

Data on frequency of recording of the abovementioned substances and diagnosis in the databases are provided upon request.