DRAFT STUDY PROTOCOL

A COHORT STUDY WITH A NESTED CASE CONTROL ANALYSIS ON THE ASSOCIATION BETWEEN ACID-SUPPRESSING DRUGS AND SEIZURES USING THIN DATABASE IN THE UK

Confidential: This study is funded with financial research support from AstraZeneca R&D.

Contents

1. PROTOCOL SYNOPSIS

Study title: A cohort study on the association between acid-suppressing drugs and seizures using THIN database in the UK.

AZ study identifier(s): D9612N00017 Acid-suppressing Drug Seizure Epidemiology Study

Principal Investigator:

Co-Investigator:

Type of study, study design: Retrospective cohort study with nested case control analysis.

Study objective(s): To estimate the incidence of seizure in the general population and stratified by epilepsy status.

To estimate the relative risk of seizure associated with use of PPI and H2RA and stratified by epilepsy status.

Setting: The Health Improvement Network (THIN) primary care database in the UK.

Study population: All individuals aged 20–84 years from 1 January 2005 to 31 December 2011 who have been enrolled with their PCP (Primary Care Physician) for at least 2 years and have a computerized prescription history of at least 1 year. Patients will have to be free of acid-suppressing drugs (PPI or H_2RAs) for at least one year, and never have a diagnosis of cancer, alcohol abuse or alcohol-related disease, or drug abuse. When an individual meet all these eligibility criteria that date will be marked as start date. Patients aged ≥ 70 years with a follow-up longer than 1 year will be excluded from the study population if they have fewer than two recorded consultations with a PCP during their entire follow-up (proxy for incomplete and invalid data recording). All remaining individuals will constitute the final study cohort.

All members of the study cohort will be followed until the earliest of: first record of seizure, a diagnosis of cancer, alcohol abuse or alcohol-related disease, or drug abuse, age of 85 years, death or end of study period (31 December 2011).

To ascertain the number of cases with a diagnosis of seizure, epidemiologists at will manually review the electronic medical records of patients, including free-text comments, with suppressed personal identifiers and information on drug use removed to

allow for a blinded revision of patient profiles. A random sample of potential cases will be further validated for accuracy of diagnosis through questionnaires to the PCP.

A nested case-control analysis will be conducted comparing incident cases with a new episode of seizure versus controls selected with incidence density sampling. The final size of the control sample will be determined by being at least four times the size of the final list of cases and be a round number.

Exposure definition: All prescriptions issued by the PCP are recorded in the database and a coded drug dictionary (Multilex) is used to record prescribed medicines. Details of every prescription issued include date, dosage, quantity dispensed, duration of therapy, and indication.

Medication will be categorized in the nested case-control analysis as follows: *current use* when the supply of the most recent prescription lasted until the index date; *recent use*, when the supply of the most recent prescription ended 1–90 days before the index date: *past use*, when the supply of the most recent prescription ended 91–365 days before the index date: and non-use, when there was no recorded use of the relevant medication in the 365 days before the index date.

In THIN, acid-suppressing drugs include PPIs: lanzoprazole, omeprazole, rabeprazol, pantoprazole, esomeprazole and H2RAs: cimetidine, famotidine, nizatidine, ranitidine

Outcome definition: A patient with an incident diagnostic code for a seizure during follow-up will be accepted as a case if the patient was referred to a consultant, and/or admitted to hospital for the event.

Statistical analysis: A nested case–control analysis will be performed to assess the effect of potential risk factors for seizure using unconditional logistic regression. In this analysis all patients ascertained with an incident episode of seizures will be used as cases. The control group will comprise a random sample of subjects frequency-matched by calendar year (described in section 4.6). Under our study design of incidence density sampling, the odds ratio (OR) is an unbiased estimator of the incidence rate ratio (RR) (Rothman 2002).

To determine the association between study outcome and current use of PPI and H_2RA, we will run unconditional logistic regression models and compute the OR and their 95% confidence intervals (95%CI). The estimates will be adjusted for the frequency-matched variable (calendar year), age, sex, time to event and other independent risk factors. Sub-analyses will be repeated in the strata of individuals with epilepsy and individuals free of epilepsy.

Study strengths: A major strength of this study is that use of THIN enables analysis of an extensive sample of PPI users that is representative of the UK primary-care population, with a similar age and sex distribution to those in the national population supporting a broad external validity of our findings and generalizability. Also, the risk in another drug class (H_2RA) that shares similar treatment indication than PPI will be analyzed to verify the specificity of the results. Validation of the outcome with the PCP

will help to reduce the extent of outcome misclassification when working with automated databases.

Study limitations: A potential limitation of the study is that use of acid suppressing drugs could be misclassified in some instances. For example, the recording of a PPI prescription in THIN does not necessarily mean that the patient actually took the medication, although it is likely that patients with repeating prescriptions do take their medication as there is a prescription almost every month. Also, lack of recording of OTC acid suppressing drugs is another source of misclassification. This misclassification of drug exposure will most likely be non-differential and thus will bias the effect estimates towards the null. Therefore, it should be noted that to the extent that misclassification due to lack of OTC acid suppressing drug recording occurs in our study population, our effect estimates will tend to underestimate the true risk.

Outcome missclassification of seizure will be substantially reduced with the two step validation process: first obtaining free text comments for the review of the patient profiles and second direct validation with the PCP. The extent of recording of comorbidity, medication use and life style habits in THIN will help to minimize as much as possible potential confounding by any of these variables.

2. INTRODUCTION

A seizure is an abnormal, unregulated electrical discharge that occurs within the brain's cortical grey matter and transiently interrupts normal brain function. Due to the numerous properties that control neuronal excitability there are many different causes of seizures and epilepsy. In principal these relate to differences between individuals in the susceptibility or threshold of seizures (e.g. genetic factors), concomitant conditions with a high likelihood of leading to seizures (e.g. traumatic brain injury) and precipitating factors, intrinsic (e.g. psychological stress, sleep deprivation) and exogenous (e.g. certain medications) (Lowenstein 1998).

Seizures may be acute symptomatic or unprovoked. Acute symptomatic seizures are seizures occurring at the time of a systemic insult or in close temporal association with a documented brain insult. (Hauser and Beghi 2008). Unprovoked seizures are seizures occurring in the absence of precipitating factors and may be caused by a static injury (remote symptomatic seizures) or a progressing injury (progressive symptomatic seizures) (Hauser and Beghi 2008). The International League Against Epilepsy (ILAE) has defined epilepsy as ''a disorder characterized by an enduring predisposition to generate epileptic seizures and by neurobiologic, cognitive, psychological and social consequences of this condition. This definition requires the occurrence of at least one epileptic seizure'' (Fisher et al. 2005). The Commission on Epidemiology and Prognosis (1993) has recommended the use of the term acute symptomatic seizures as separate from the unprovoked seizures that define epilepsy in epidemiology studies (Beghi et al 2010).

The incidence of acute symptomatic seizures has been estimated to be 29–39 per 100,000 per year across several studies, regions and time periods. These predominate in men, in the youngest age class, and in the elderly (Hauser and Beghi 2008). Traumatic brain injury, cerebrovascular disease, drug withdrawal, and metabolic insults are the most common causes. In recent studies, the incidence of unprovoked seizures has been estimated to be 46-57 per 100,000 person-years. As with epilepsy, single unprovoked seizures predominate in men and in patients less than 12 months and older than 65 years (Hauser and Beghi 2008). Seizure etiology is the single most important risk factor for the increased mortality in patients with a first seizure (Hauser and Beghi 2008).

Drugs associated with the development of convulsion/seizure include cocaine, other CNS stimulants, cyclosporine, tacrolimus, pentylenetetrazole, picrotoxin, strychnine. There are also drugs, described to lower seizure threshold such as aminophylline, antidepressants, sedating antihistamines, antimalarial drugs, some antipsychotics (eg, clozapine), buspirone, fluoroquinolones, theophylline (Ruffman et al 2006).
In a study from 1977, seizures were recorded in less than 1% of 32 812 consecutive patients prospectively monitored for drug toxicity in selected medical wards (Porter et Jick 1977).

Antiepileptic medications are a heterogeneous pharmacologic class characterized by various chemical structures and postulated mechanisms of actions (Patorno et al, 2010). The main therapeutic applications of antiepileptics include epilepsy, bipolar disorder, depression, neuralgia, and migraine (Ettinger et al, 2007). Antiepileptic drugs (AEDs) are among the most commonly prescribed centrally active agents. In a survey, carried out in a Danish County, 1.1% of the studied people received AEDs. The use of these drugs increased with increasing age (Rochat et al 2001).

Proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs) are widely prescribed acid-suppressive medications that in general have good safety profiles (Yang and Metz, 2010). AstraZeneca has received spontaneous reports of convulsion/seizure reported in patients taking esomeprazole and omeprazole. As commonly observed in postmarketing reports, information with regard to possible underlying cause, concomitant medication and potentially contributing factors were limited. In AstraZeneca placebo-controlled studies comprising esomeprazole or omeprazole no reports of convulsion/ seizure in patients given PPIs were found.

There are 3 articles based on Prescription Event Monitoring (PEM) addressing the association between proton pump inhibitors (PPI) and the occurrence of adverse events. The first report included patients (n=16,204) who had been treated with omeprazole by general practitioners in England between June 1989 and June 1990 (Wilton et al 1993). Among the events recorded during a six months period there were 17 records of convulsions. The authors stated that “in five cases the possibility of a link with omeprazole cannot be excluded”. In another PEM report assessing the safety profile of esomeprazole that included 11,595 patients, there is no mention of seizures/convulsions recorded as adverse events (Davies et al 2008), and in another PEM report with 11,541 patients treated with pantoprazole one case of epilepsy (new event) was reported (Wilton et al 2003).

Case reports of neurotoxicity including seizures in relation to histamine 2 receptor antagonists have been reported (Edmonds et al 1979). In a post-marketing surveillance report of the safety of cimetidine including 9928 patients taking cimetidine and 9351 controls there was no association reported between cimetidine and epilepsy. Major convulsions recorded for the first time as a primary diagnosis were reported in five users of cimetidine and three controls (Colin Jones et al 1985).

This observational study will further investigate the potential association between seizures and acid suppressing drugs in clinical practice and contribute to quantify the potential risk of seizures associated with the use of acid-suppressing drugs (PPI and H_2RA).

3. STUDY OBJECTIVES

- To estimate the incidence of seizure in the general population and stratified by epilepsy status

- To estimate the relative risk of seizure associated with use of PPI and H_2RA and stratified by epilepsy status.

4. METHODS

4.1 Study design

A nested case-control analysis in a retrospective cohort study will be performed using The Health Improvement Network (THIN) database in the UK. Data is prospectively recorded by participating primary care physicians as part of their routine patient care (see 4.2).

A nested case-control analysis will be conducted comparing incident cases of seizure versus controls selected with incidence density sampling. A graphical presentation of the study design is provided in Figure 1.

The rationale of our study design is:

1) to enhance the internal validity of users of acid-suppressing drugs by ascertaining individuals newly prescribed acid-suppressing drugs.

2) to maximize the power to quantify the risk of seizure associated with current use of acid-suppressing drugs by including all the experience available of acid-suppressing users.

4.2 Source population

THIN is a computerized medical research database that contains systematically recorded data on more than 3 million UK primary care patients. It is representative of this population with regard to age, sex, and geographic distribution, and has been validated for use in pharmacoepidemiological research in multiple studies (Lewis et al 2007). Participating primary care practitioners (PCPs) record data as part of their routine patient

care, including demographics and life style factors (e.g. alcohol use, body mass index (BMI) and smoking status), consultation rates, referrals, hospital admissions, laboratory test results, diagnoses, prescriptions ordered by the PCPs, and a free text section, and send their data anonymously to THIN for use in research projects. Prescriptions issued by PCPs are recorded automatically in the database. The Read classification is used to code specific diagnoses (Stuart-Buttle et al 1996), and a drug dictionary based on data from the MULTILEX classification is used to code drug prescriptions (First Data Bank 2010).

The rationale for selection of THIN is the unique attributes of primary care databases in the UK (e.g. GPRD, Qresearch) for pharmacoepidemiological research. As GPRD and THIN are basically equivalent, we chose the database our research group has greater experience.

4.3 Study population

THIN will be used to identify all individuals aged 20–84 years from 1 January 2005 to 31 December 2011, who have been enrolled with their PCP for at least 2 years and have a computerized prescription history of at least 1 year. Patients will have to be free of acid-suppressing drugs (PPI or H_2RAs) for at least one year, and never have a diagnosis of cancer, alcohol abuse or alcohol-related disease, or drug abuse. When an individual meet all these eligibility criteria that date will be marked as start date. Patients aged ≥ 70 years with a follow-up longer than 1 year will be excluded from the study population if they have fewer than two recorded consultations with a PCP during their entire follow-up (proxy for incomplete and invalid data recording). All remaining individuals will constitute the final study population.

4.3.1 Eligibility criteria

To be included in the study, patients must meet all of the following criteria at start date:

- At least 2 years of registration with the PCP
- At least 1 year of computerized prescription history
- Age 20-84 years

4.3.2 Exclusion criteria

All patients fulfilling one of the following criteria will be excluded:

- Patients with at least 1 prescription of PPI or H_2RA in the year prior to start date
- Cancer before start date
- Alcohol abuse or alcohol-related disease before start date
- Drug abuse before start date
- Patients aged ≥ 70 years with a follow-up after start date longer than 1 year and fewer than 2 recorded consultations with a PCP during their entire follow-up

4.4 Follow-up

All members of the study cohort will be followed up from the day after start date until the first occurrence of the following endpoints:

- First recorded entry of seizure (Table 2)
- Age = 85 years
- Cancer
- Alcohol abuse or alcohol-related disease
- Drug abuse
- End of the study period

4.5 Outcome definition and ascertainment

Free text comments will be requested before reviewing patient profiles. Information will include demographic data and all clinical information. The profiles of computer detected patients with seizure/convulsion (Table 2) identified with the initial computer search and including free-text comments, will be reviewed manually to ascertain the number of potential cases with an incident episode of seizure. All patient personal identifiers will be suppressed and information on drug use removed to allow for a blinded revision of patient profiles. The date of onset of study outcome will be used as index date. Doubtful cases will be reviewed by two MD researchers and agreement will be reached. Patients will not be retained as seizure cases if they were admitted to hospital in the month before the index date; in-patient drug exposure is not available and therefore recent exposure in these patients would be unknown All patients meeting our operational definition of seizure (see below) will be considered potential cases.

4.5.1 Operational definition of incident case of seizure

A patient with an incident diagnosis of seizure during follow-up will be accepted as a case if the patient was referred to a consultant, and/or admitted to hospital for the event.

For the sub-analyses among patients with a diagnosis of epilepsy we will, however, also accept a broader case definition, i.e. an incident diagnostic code for a seizure during follow-up regardless of referral to specialist, or admission to hospital. The broader definition of seizure will be employed because we suspect that the threshold for seeking hospitalisation may differ between patients with epilepsy and non-epilepsy patients experiencing a seizure. Also, patients with epilepsy may already have attended specialist care when recruited into the cohort and will therefore not necessarily be referred to renewed specialist evaluation due to a further seizure in the follow-up period.

We will attempt to classify seizures into three categories:

i. Acute symptomatic seizures:

Seizures occurring in close temporal relationship to one or more of the following:

CVD, traumatic brain injury, CNS-infection, severe systemic illness with fever, presenting symptom of multiple sclerosis (or within 7 days of relapse of this disorder), autoimmune diseases with signs of activation, metabolic causes (including hypoglycemia and low serum sodium), and cerebral hypoxia.

Close temporal relationship to the seizure is defined as 1 week for the majority of events listed, with certain exceptions. Longer intervals will be accepted in certain cases (e.g. subdural hematoma with no known trauma, cases of CNS-infection with signs of

persistent infection). Conversely, a shorter time-limit will be requested for hypoglycemia (24 hours). We will generally follow the recommendations of Beghi et al (2010) for the classification of acute symptomatic seizures.

ii. Unprovoked seizures:

Seizures not fulfilling the criteria for acute symptomatic seizures will be considered unprovoked seizures, if sufficiently documented with regard to the aforementioned possible causes of seizures listed under (i).

iii. Unclassifiable seizures:

Seizures with insufficient documentation to rule out acute symptomatic seizures.

Alcohol-related seizures or seizure in cancer patients will lead to exclusion.

4.5.2 Case validation with PCPs

We will send for a random sample of 300 potential cases a questionnaire to PCPs requesting them to send copies of all related paper-based information in order to confirm our operational definition of incident seizure. If the information from the questionnaire and medical records confirms our case definition of incident seizure in 85% of instances or greater, we will not request additional records for the remaining potential cases.

4.6 Selection of Controls

A random series of controls, calendar-year-frequency matched to seizure cases will be sampled from the pooled study cohorts. This will be done by generating a random date within the study period for each study member. If the random date for a study member is included in the follow-up period, that person will be marked as an eligible control and the random date will be used as their index date. This method of selection of controls in nested case-control studies is known as "incidence density" sampling. The final size of the control sample will be determined by being at least four times the size of the final list of cases and be a round number.

4.7 Characterization and assessment of risk factors

The following potential confounders and/or effect modifiers will be ascertained:

Demographics; Age at index date (20-39, 40-49, 50-64, 65-74 and 75-84 years), sex and calendar year of index date (2005-2006, 2007-2008 and 2009-2011). We will also calculate the time interval between start date and index date and subsequently categorize it into 5 time periods: first month; 2 to 6 months; 7 to 12 months; 1 to 2 years and longer than 2 years. This variable can be considered as adjustment/proxy for time to event. Socioeconomic status will be computed with the Townsend score.

Life style factors; Body mass index (calculated from recorded height and weight; weight in kg / (height in metres2) will be ascertained prior to index date. Standard cut points used to classify subjects are: underweight (BMI less than 20), normal weight (BMI 20-25), overweight (BMI 25 to 29) and obese (BMI ≥30 kg/m2). Smoking status will be categorized into current smoker, past smoker, never smoker. Missing data will be assessed as a separate category. Most recent value before index date will be ascertained.

Comorbidity; Diabetes, coronary heart disease (MI, unstable angina or angina), cerebrovascular disease (ischaemic or haemorrhagic), epilepsy, seizure, COPD, GERD, and peptic ulcer antecedents (which includes dyspepsia, gastritis, uncomplicated peptic ulcer and complicated peptic ulcer), bipolar disorder, anxiety, depression, neuralgia/neuralgic pain, polyneuropathy/peripheral neuropathy, migraine, autoimmune disorders, CNS infections, cerebral trauma, hypertensive encephalopathy, eclampsia, mental retardation, cerebral palsy, dementia. Comorbidity will be ascertained prior to index date.

Comedication; Antiepileptic drugs, anxiolytics, hypnotics, antibiotics, antihypertensives (e.g. diuretics, beta-blockers…), antihistamines, antidepressants, statins, antidiabetics, nitrates, clopidogrel, low-dose ASA, NSAIDs, oral corticosteroids, oral anticoagulants. We will also collect information on polypharmacy: number of prescribed different drugs in the 30 days prior to the index date (0, 1-2, 3-5, 6-9, 10 or more). Comedication will be ascertained prior to index date.

Health care utilization: Number of GP visits, referrals and hospitalizations the year prior to index date.

4.8 Exposure definition

We will categorize medication use in the nested case-control analysis as follows: *current use* when the supply of the most recent prescription lasted until the index date; *recent use*, when the supply of the most recent prescription ended 1–90 days before the index date: *past use*, when the supply of the most recent prescription ended 91–365 days before the index date: and non-use, when there was no recorded use of the relevant medication in the 365 days before the index date.

Current users of PPI at index date will be further analyzed according to duration of treatment (continuous use on PPI therapy will be defined as the sequence of consecutive PPI Rx without presenting at least one break (gap of 30 days or greater between the end of supply and the start of supply of two consecutive Rx). Dose-response among current users of PPI will also be analyzed. Similar classification scheme will be applied to users of H_2RA.

4.9 Statistical analysis

Incidence rate of seizure overall as well as age and sex-specific will be computed in the study cohort.

A nested case–control analysis will be performed to assess the effect of acid-suppressing drugs and potential risk factors for seizure using unconditional logistic regression. In this analysis all patients ascertained with an incident episode of seizures will be used as

cases. The control group will comprise a random sample of study cohort members, frequency-matched by calendar year (described in section 4.6). Under our study design of incidence density sampling, the odds ratio (OR) is an unbiased estimator of the incidence rate ratio (RR) (Rothman 2002).

To determine the association between study outcome and current use of PPI and H_2RA, we will run unconditional logistic regression models and compute the OR and their 95% confidence intervals (95%CI). The estimates will be adjusted for the frequency-matched variable (calendar year), age, sex, time to event and other independent risk factors described in section 4.7.

Sub-analyses will be repeated in the strata of individuals with epilepsy and individuals free of epilepsy for descriptive purposes.

Statistical analyses will be performed using Stata package version 11.0 (StataCorp LP, College Station, TX, USA).

4.9.1 Sample size

Assuming an experience of 100,000 person-years among PPI current users, 100,000 person-years among non users of PPI and an incidence rate of seizures of 50 per 100,000 person-years among non users of PPI and a true relative risk of one, a 95% CI would extend to 1.48 if the estimated ratio is 1. We expect to accumulate larger person-time experience than mentioned above both among current users of PPI and non users.

5. STUDY STRENGTHS AND LIMITATIONS

Strengths

A major strength of this study is that use of THIN enables analysis of an extensive sample of PPI users that is representative of the UK primary-care population, with a similar age and sex distribution to those in the national population supporting a broad external validity of our findings and generalizability. Also, we will analyze the risk in another drug class (H_2RA) that share similar treatment indication than PPI to verify the specificity of the results. Validation of the outcome with the PCP will help to reduce the extent of outcome misclassification when working with automated databases.

Limitations

A potential limitation of the study is that acid suppressing drug use could be misclassified in some instances. For example, the recording of a PPI prescription in THIN does not necessarily mean that the patient actually took the medication, although it is likely that patients with repeating prescriptions do take their medication as there is a prescription almost every month. Also, lack of recording of OTC acid suppressing drugs is another source of misclassification (PPI available as OTC June 2009 on UK market). This misclassification of drug exposure will most likely be non-differential and thus will bias the effect estimates towards the null. Therefore, it should be noted that to the extent

such misclassification occurs in our study population, our effect estimates will tend to underestimate the true risk. As with any medication, PPI users might differ from non-users in a number of characteristics, such as treatment indication, severity of the treatment indication, co-morbidity, etc. Like in all observational studies, there is always the possibility for some remaining confounding not amenable to adjust after all our efforts in the design and analyses.

Outcome missclassification of seizure will be substantially reduced with our two step valdidation process: first obtaining free text comments for the review of the patient profiles and second the direct validation with the PCP. The extent of recording of comorbidity, medication use and life style habits in THIN will help to minimize as much as possible potential confounding by any these varaibles.

6. PROJECT FORMALITIES AND TIMELINES

6.1 Privacy and confidentiality

Privacy issues will be addressed and respected at each stage of the study. All analyses and reporting will be done on appropriately de-identified data and only in aggregate form. AstraZeneca will not receive any patient or provider identifiable information from at any time. We will abide by the Guidelines for Good Pharmacoepidemiology Practices (GPP, 2007). The study protocol is dependent on approval by the ethical review board Multicenter Research Ethics Committee (MREC) for studies performed in THIN.

6.2 Project management

Principal Investigator:

Co-investigator:

6.3 Study reporting

The final analyses and study report is estimated to be delivered within 20 months of external approval from ethic committee assuming 3 months for anonymization of free text comments by the external provider of THIN data (AIS) and 3-4 months for obtaining questionnaires from PCPs, aiming at high response rate (around 80-90%) with anonymization of all information. At least one manuscript based on the findings of this project will be submitted for publication to a peer-reviewed journal.

6.4 Data management

will comply with all applicable data protection, security and privacy laws, rules and regulations with respect to the collection, production, use, processing, storage, transfer, modification, deletion, and/or disclosure of any information related to this study

under this Agreement. will ensure that information is not disclosed or transferred to any third party not mentioned in this protocol. will ensure that appropriate technical and organizational measures are taken to protect information against accidental or unlawful destruction or accidental loss or alteration, or unauthorized disclosure or access and against all other unlawful forms of processing. will store the Database used to perform this study at the premises of

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Table 1 List of acid-suppressing drugs

PPIs
Lansoprazole
Omeprazole
Rabeprazole
Pantoprazole
Esomeprazole
H_2RAs
Cimetidine
Famotidine
Nizatidine
Ranitidine

Table 2 List of seizure codes

1478.00	H/O: febrile convulsions
1B27.00	Seizures in response to acute event
1B64.00	Had a convulsion
1B64.11	Convulsion - symptom
1B6B.00	Febrile convulsion
282..11	O/E - a convulsion
282..13	O/E - a seizure
2827.00	O/E - febrile convulsion
2828.00	Absence seizure
667R.00	2 to 4 seizures a month
667S.00	1 to 7 seizures a week
667T.00	Daily seizures
667V.00	Many seizures a day
667W.00	Emergency epilepsy treatment since last appointment
F132z12	Myoclonic seizure
F250200	Epileptic seizures - atonic
F250300	Epileptic seizures - akinetic
F251200	Epileptic seizures - clonic
F251300	Epileptic seizures - myoclonic
F251400	Epileptic seizures - tonic
F251600	Grand mal seizure
F253.11	Status epilepticus
F254500	Complex partial epileptic seizure
F255600	Simple partial epileptic seizure
F25X.00	Status epilepticus, unspecified

F25y300	Complex partial status epilepticus
F25z.11	Fit (in known epileptic) NOS
Fyu5200	[X]Other status epilepticus
Fyu5900	[X]Status epilepticus, unspecified
R003.00	[D]Convulsions
R003000	[D]Convulsions, febrile
R003011	[D]Pyrexial convulsion
R003200	[D]Fit
R003211	[D]Fit (in non epileptic) NOS
R003300	[D]Reflex anoxic seizure
R003400	[D]Nocturnal seizure
R003y00	[D]Other specified convulsion
R003z00	[D]Convulsion NOS
R003z11	[D]Seizure NOS
Ryu7100	[X]Other and unspecified convulsions

Table 3 Logistical steps of study conduct and estimated time for each step to study completion

Provided estimated timelines for the conduct of the observational study on the association between acid-suppressing drugs and seizures are based on the Principal Investigators (PI´s) experience in performing similar pharmacoepidemiology studies with the THIN database.

The timeline of submission of the final report is estimated to be delivered within 20 months after protocol approval and include the following main steps:

Cumulative time period (mths)	Activity	Time AIS * (external provider) of THIN data, mths)	Time PI (mths)
	Ethical approval for studies performed in THIN; MREC (Multicenter Research Ethics Committee)		
	Quality checking of information in database		
	Searches in database to identify potential cases and request for free text comments of the identified potential cases		
	Anonymization of free text comments		

	Manual review of computerized records and free text comments (blinded to all exposure information) to identify remaining potential cases for which requests are made to send questionnaires to the general practitioner (GP)		
	AIS to send questionnaire to GP, aiming at a high response rate (around 80-90 %) . Anonymization of data.		
	PI to review all anonymized information from questionnaires, copies of additional information the GP deemed to be related to the outcome of interest (hospital summaries, consultant referral letters and results of laboratory test) and the computerized profiles to assign case status (blinded for exposure information)		
	Analyses and draft report provided to AZ		
	Final report to be delivered to AZ and AZ to submit to MHRA		

Figure 1. Study design