Bayer HealthCare

<Observational> / <Post Authorization> Study Information

Title	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Protocol version identifier	V5 IMPACT 18116
Date of last version of protocol	10 August 2015
EU PAS register number *(row can be deleted for non-PASS Studies or marked as NA)*	Study not yet registered
Active substance	Acetylsalicylic acid (ASA)
Medicinal product *(if a device, please adapt accordingly)*	ASPIRIN
Product reference *(row may be deleted for non-PASS Studies or marked as NA)*	Low dose Acetylsalicylic acid (ASA)
Procedure number *(row may be deleted for non-PASS Studies or marked as NA)*	NA
Marketing authorization holder(s)	Bayer Healthcare AG, 51368 Leverkusen, Germany
Joint PASS *(row may be deleted for non-PASS Studies or marked as NA)*	NO
Research question and objectives	The proposed pharmacoepidemiological comparative cohort study using an existing secondary data source and with prospective data collection will investigate the risk of major bleeding (including gastrointestinal and

	intracranial bleeding episodes) among new users of low-dose acetylsalicylic acid (ASA) in clinical practice using The Health Improvement Network (THIN) database, UK. The study population largely overlaps with the population targeted for secondary CVD prevention and CRC prevention, for which we have recently completed a study assessing its chemopreventative effect (current users of low-dose ASA had a significantly reduced risk of CRC, OR: 0.66 (95% CI: 0.60–0.74)), as well as evaluated the preventative effect on CVD outcomes associated with the continuous use of low dose ASA in a similar population. This new evidence will provide new insights on the evaluation of the benefit–risk profile of low-dose ASA and will support an upcoming regulatory submission package. Primary study objectives are: - To estimate the incidence and time to event of intracraneal bleeding (IB), upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB) among new users of low-dose ASA in a UK general population. - To estimate the relative risk of IB, UGIB and LGIB associated with use of low-dose ASA overall and in age and sex-specific strata compared to non-use. - To analyze the duration and dose response of low-dose ASA on the risk of IB, UGIB and LGIB. Secondary study objectives are: - To estimate the relative risk of IB, UGIB, and LGIB associated with use of other medications such as clopidogrel, oral anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs), independently from use of low-dose ASA and concomitantly.

Country(-ies) of study	United Kingdom (UK)
Author	Montse Soriano-Gabarro, MD, MSc, Global Epidemiology, Bayer Luis A Garcia Rodriguez, MD, CEIFE

Marketing authorization holder *(table below mandatory for PASS studies)*

Marketing authorization holder(s)	Bayer Healthcare AG, 51368 Leverkusen, Germany >
MAH contact person	Artur Lutfullin, Global Regulatory Affairs, Aspirin

The study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of Contents

2. List of abbreviations

ASA	Acetylsalicylic acid
BMI	Body mass index
CEIFE	Centro Español de Investigación Farmacoepidemiológica
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
EMA	European Medicines Agency
EPISAT	EPIdemiological Study on the Safety of Aspirin in THIN
GI	Gastroinestinal
GERD	Gastroesophageal reflux disease
GP	General Practitioner
H_2RAs	H_2-receptor antagonists
HES	Hospital Episodes Statistics
HRT	Hormone replacement therapy
HS	Haemorrhagic stroke
IHD	Ischaemic heart diseases
IB	Intracranial bleeding
IS	Ischaemic stroke
ITT	Intention to treat
LGIB	Lower gastroinestinal bleeding
MAH	Marketing Authorization Holder
MI	Myocardial infarction
MREC	Multicenter Research Ethics Committee
NSAIDs	Non-steroidal anti-inflammatory drugs
OTC	Over the counter
OR	Odds Ratio
PAD	Peripheral artery diseases
PASS	Post-Authorization Safety Study
PCP	Primary care physician
PPIs	Proton Pump inhibitors
REC	Research Ethics Committee
RCT	Randomized clinical trials
RR	Relative risk
SRC	Scientific Research Committee
SSRIs	Selective serotonin reuptake inhibitors

TX	Texas
TIA	Transient ischaemic accident
THIN	The Health Improvement Network
UA	Unstable angina
UGIB	Upper gastrointestinal bleeding
UK	United Kingdom
US	United States

3. Responsible parties

Dr Luis A Garcia Rodriguez
Spanish Centre for Pharmacoepidemiologic Research (CEIFE)
Almirante, 28, 2
28004
Madrid, Spain
Phone: +34-91-531 3404
Email:lagarcia@ceife.es

4. Abstract

Title: A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK

Short title: EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT

Rationale and background: Low-dose acetylsalicylic acid (ASA) is effective in the prevention of cardiovascular events owing to their antiplatelet properties; guidelines recommend the long-term use of low-dose ASA for secondary prevention of cardiovascular events and for primary prevention, although with less body of evidence for the latter. For any drug therapy, it is important that an accurate benefit–risk assessment is made. As an example with this drug, prevention strategies to minimize gastrointestinal (GI) problems are conferring an acceptable safety profile in the general population. However, further evaluations on GI safety profile and other major bleeding for aspirin is still warranted to establish its role as safety for long term use in general population, specially when target population encompass the elderly group (70 years).

Research question and objectives: This report describes a pharmacoepidemiological research proposal carried out to investigate the risk of major bleeding (including gastrointestinal and intracranial bleeding episodes) among new users of low-dose acetylsalicylic acid (ASA) in clinical practice.

Study design: We will identify two population-based prospective cohorts using The Health Improvement Network (THIN) database in the UK. A cohort of firstly users of low dose ASA and an unexposed cohort. Follow-up will be performed to ascertain incident cases of major bleeding outcomes and nested case-control analyses will be performed.

Population: The study period for enrollment of the two study cohorts (e.g. ascertaining ASA and non-ASA cohort at start date) will start in January 2000 and end in December 2012. Individuals will be required to be aged between 40-84 years, to be enrolled with the PCP for at least 2 years, to have a history of computerized prescriptions for at least 1 year prior, to have at least one encounter/visit recorded in the last three years and to be free of ASA, cancer, alcohol abuse, coagulopathies, esophageal varices and chronic liver disease to become a member of the study population. The date an individual meet all these criteria will be considered the entry date for enrollment. To identify the two cohorts, individuals will be followed up from entry date up to one of the following criteria endpoints, whichever came first: first prescription of low-dose ASA, diagnosis of cancer, alcohol abuse, coagulopathies, oesophageal varices, chronic liver disease, aged 85 years, death or end of the study period. Every day a new user of ASA is ascertained, one non-user of ASA (up to that date) will be sampled.

Variables: The following characteristics will be assessed in the study population

-Exposure to low dose ASA includes

Use of low-dose ASA will be classified into recency (i.e. non users, current users, daily dose, duration and indication of low dose ASA (primary or secondary prevention).

-Covariates

- **Demographic and life style factors:** Age, body mass index (calculated from recorded height and weight; weight in kg / [height in metres], smoking (past smoker, never smoker and current smoking), alcohol comspumiton, Alcohol consumption was categorized into units per week (u/w): 1–4, 5–9, 10–14, 15–20, and ≥20.
- **Other comorbidities**: Will include the following variables: Comorbidities evaluated will include: hypertension, diabetes (type I and II, separately), hyperlipidemia, IHD, atrial fibrillation, chronic obstructive pulmonary diseases (COPD), asthma, anemia, depression, osteoarthritis, gastroesophageal reflux disease (GERD), peptic ulcer antecendents.
- **Concomitant medication**: The following medications will be ascertained; antihypertensive medications, statins, antidiabetics, NSAIDs (traditional NSAIDs

(tNSAIDs), COXIBs), paracetamol, oral and inhaled steroids (separately), clopidogrel, warfarin, other oral anticoagulants, nitrates, dipyridamole, selective serotonine reuptake inhibitors (SSRIs), other antidepressants, hypnotics/anxiolytics, antipsychotics, tramadol, digoxin, proton pump inhibitors (PPIs) and H_2-receptor antagonists (H_2RAs) and hormonal replacement therapy (HRT).

- **Health care utilization**: As a proxy for overall health status, we will consider the number of visits to the PCP, number of referrals to specialists, and number of hospitalizations.

-**Outcomes:** Intracraneal bleeding (IB), upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB)

Data sources: The study will be conducted in the following database:

- The Health Improvement Network (THIN) – United Kingdom (UK)

Study size: Based on our recent study on ASA and colorectal cancer, we expect a sample size of the ASA cohort close to 200,000 (individuals firstly exposed to low dose ASA). A comparison cohort (sampled 1:1) will be subsequently selected.

Data analysis: The following analyses will be performed:

Cohort analysis (ITT analysis): Kaplan-Meier survival curves for low-dose ASA cohort and comparison-unexposed cohort will be performed. Cox proportional hazard models will be used to estimate the relative risk (hazard rate ratio) and 95% CI of incident major bleeding episodes associated with low-dose ASA cohort adjusted for matching variables and independent risk factors (ascertained before start date), Cox regression models take into account time to event. We will censor the Cox analysis to the first year of follow-up to reduce the misclassification of low-dose ASA that inevitably will occur. Incidence rates of each major bleeding outcome overall as well as age- and sex-specific will be computed in the two cohorts with Poisson regression, separately.

Nested case-control analysis (As treated analysis): Three separate nested case–control analyses will be performed to assess the effect of potential risk factors for each bleeding outcome of interest using unconditional logistic regression. All patients confirmed as incident case in the cohort analysis will also be used as cases in nested case-control analysis. Under

our study design of incidence density sampling, the odds ratio (OR) is an unbiased estimator of the incidence rate ratio (RR) [1]. Statistical analyses will be performed using Stata package version 12.0 (StataCorp LP, College Station, TX, US).

Milestones*:* See below.

5. Amendments and updates

None

6. Milestones

Table 1 Milestones

Milestone	Planned date
Start of data collection	01/09/2015
End of data collection	01/06/2016
<Study progress report 1>*	Update study report,coinciding with PBRER February 2016
<Study progress report n>*	NA
<Interim report 1>*	NA
<Interim report n>*	NA
<Registration in the EU PAS register>	Not yet done. Planned 01/09/2015
<Other important timeline 1>	NA
<Other important timeline n>	NA
Final report of study results	01/08/2016

*only if agreed with authorities

7. Rationale and background

Cardiovascular disease is the leading cause of death, accounting for approximately 30% of all deaths worldwide [2]. Low-dose acetylsalicylic acid (ASA) is effective in the prevention of cardiovascular events owing to their antiplatelet properties; guidelines

recommend the long-term use of low-dose ASA for secondary prevention of cardiovascular events[3]. More controversy is around the benefit of prescribing low dose ASA as a primary prevention. While some authors found a litte benefit concluding the uncertain net value [4], a recent metanalysis performed by *Xie M and colleagues* evaluated the benefit and harms of low dose ASA indicated for primary prevention[5]. Authors included a total of forteen trials, reporting reduction in major cardiovascular events (RR 0.90 (95% CI: 0.85-.95), myocardial infarction (0.86 (95%CI: 0.75-0.93), ischemic stroke (0.86 (95%CI: 0.75-0.98), and all cause mortality (0.94 (95%CI: 0.89-0.99); as a counterpart the risk of haemorrhagic stroke was 1.34 (95%CI: 1.01-1.79) and 1.55 (95% CI:1.35-1.78) for major bleeding episodes.

For any drug therapy, it is important that an accurate benefit–risk assessment is made. Although relative risks are useful in estimating the relative effects of drug therapies, attributable risks are considered to have greater public health relevance as they take into account the baseline incidence of the event of interest. Thus, a rare adverse outcome with a high relative risk may be of less clinical importance than a frequent event with a low relative risk. Our group, carried out a series of studies of nearly 40 000 patients with ischaemic heart disease or cerebrovascular disease who were newly prescribed ASA treatment for secondary prevention, finding that approximately 30% of them discontinue ASA therapy. The results of the present analysis suggest that a reduction of 0.4 cases of upper gastrointestinal bleeding (UGIB) and an increase of 8 ischaemic events (5 non-fatal MIs and 3 IS/TIA) among every 1000 patients could be attributed to the discontinuation of ASA during the first year of treatment[6]. Thus, on the risk management decisions not only the risk and benefit should be evaluated but the consequences of both harms and benefits on quality of life. As an example with this drug, prevention strategies to minimize GI problems are conferring an acceptable safety profile in the general population. However, further evaluations on GI safety profile and other major bleeding for aspirin in the target population is still warranted to establish its role as safety for long term use in general population.

8. Research questions and objectives

This report describes a pharmacoepidemiological research proposal carried out to investigate the risk of major bleeding (including gastrointestinal and intracranial bleeding

episodes) among new users of low-dose acetylsalicylic acid (ASA) in clinical practice. These will be based on population-based cohorts using data from a primary care database in the UK: The Health Improvement Network (THIN) and will serve to make a clinically meaningful benefit–risk assessment regarding major bleeding consequences of ASA exposure in general population. Finding from this effort will serve to evaluate the risk benefit of low dose ASA in clinical practice

8.1 Primary objective

The primary objectives in this study are:

- To estimate the incidence and time to event of intracraneal bleeding (IB), upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB) among new users of low-dose ASA in a UK general population
- To estimate the relative risk of IB, UGIB and LGIB associated with use of low-dose ASA overall and in age and sex-specific strata compared to non-use
- To analyze the duration and dose response of low-dose ASA on the risk of IB, UGIB and (LGIB

8.2 Secondary objective(s)

The secondary objective in this study is:

- To estimate the relative risk of IB, UGIB, and LGIB associated with use of other medications such as clopidogrel, oral anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs), independently from use of low-dose ASA and concomitantly

9. Research methods

9.1 Study design

We will identify two population-based cohorts using The Health Improvement Network (THIN) database in the UK. Follow-up will be performed to ascertain incident cases of major bleeding outcomes and nested case-control analyses will be performed to estimate the association between new users of low-dose ASA and bleeding outcomes.

9.1.1 Follow-up analysis

We will follow-up our two study cohorts from start date (first ASA Rx among low-dose cohort and matching date among the unexposed comparison cohort) until the occurrence of major bleeding outcomes or any other criteria or end of follow-up.

9.1.2. Nested case-control analysis

Three separate nested case-control analyses (one for each outcome of interest) will be conducted among these two study cohorts comparing incident cases of each major bleeding outcomes versus controls identified with incidence density sampling.

Rationale of the proposed study design includes:

1) The cohort design will allow estimation of incidence rates. Kaplan-Meier survival curves will be estimated to describe the time to occurrence of each bleeding outcome of interest, and cumulative risks will be produced.

2) Ascertaining users newly prescribed low-dose ASA will enhance the internal validity of users of low-dose ASA, removing the possibility of "survivors" among prevalent users.

3) For both cohorts, ascertaining all information available on new users of low-dose ASA and a random sample of the comparison "unexposed" cohort will maximize the efficiency of our sample size. Moreover, matching the comparison cohort for time since date of eligibility will 1) control for potential temporal trends in both ASA use and outcome incidence, therefore reducing confounding, and 2) allowing the same reference period before start of follow-up to collect baseline information in both cohorts increasing the internal validity of measurement of associations.

4) The nested case-control is an efficient analysis that may also enhance the internal validity, as it will permit to ascertain information on potential confounders on all cases and only a sample of the pooled study cohort members (e.g. controls). This is particularly efficient when manual review is needed to complement information for

some variables (e.g., daily dose). It also permits a direct analysis of time-dependent use of medications. In addition, density sampling for controls in a nested case-control is not biased by competing risks[7]

9.2 Setting

To emulate the enrollment design from clinical trials we will carry out the ascertainment of the exposed and unexposed cohorts concurrently. Each day there is a person qualifying as low-dose ASA new user (first time ever recorded prescription), we will assign that person as a member of the ASA cohort and will enroll on the same day a person free of ASA who meets all other eligibility criteria implemented in the selection of the ASA new user cohort. Of note, we will randomly select one individual among the pool of eligible individuals meeting the matching criteria (age, sex and PCP visits) on that day.

Once an individual from the study population becomes member of one of the two cohorts, she/he will not be eligible to be selected again as member of any of the two cohorts at any time after that date. Then, based on their exposure status at enrollment date (low-dose ASA cohort or comparison unexposed cohort) an intention-to-treat (ITT) analysis will be carried out initially. Briefly, the ITT is based on the initial treatment randomly assigned and does not take into account changes in treatment occurring over the duration of the randomized clinical trials (RCT) (in this case, during the follow-up used to ascertain outcomes of interest). It compares the risk of the outcome in the treated cohort with the risk in non-treated cohort irrespective from the exposure status over the entire follow-up. Following an ITT philosophy, one would not change the exposure classification of an individual even if the subject switches treatment arm over time. The rationale is that factors affecting adherence or treatment discontinuation may be harder to identify and adjust. In the present study, we will limit the ITT analysis (Cox regression) to the first year of follow-up to reduce misclassification of low-dose ASA exposure that inevitably will occur. Finally, we will perform As-Treated analysis using a nested case-control design.

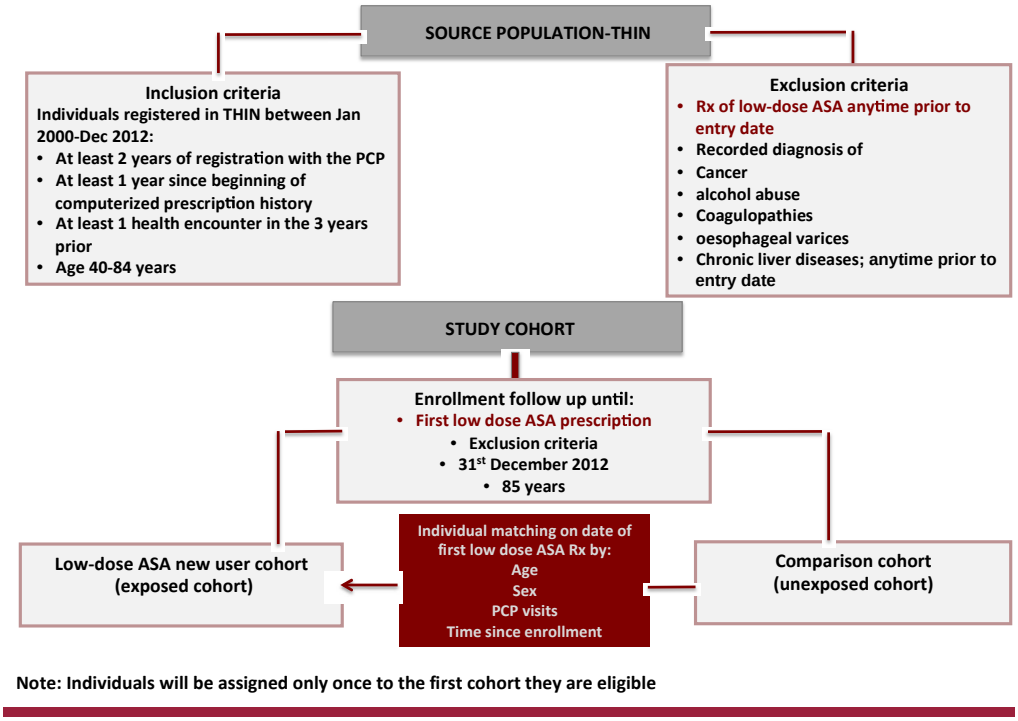
Study cohorts enrollment

The study period for enrollment of the two study cohorts (e.g. ASA and non-ASA cohort at start date) will start in January 2000 and end in December 2012. Individuals will be

required to be aged between 40-84 years, to be enrolled with the PCP for at least 2 years, to have a history of computerized prescriptions for at least 1 year prior, to have at least one encounter/visit recorded in the last three years and to be free of ASA, cancer, alcohol abuse, coagulopathies, esophageal varices and chronic liver disease to become a member of the study population. The date an individual met all these criteria will mark that individaal as eligible member of the study population (e.g. source population) and that date will be considered the entry date. To identify both study cohorts, individuals will be followed up from entry date up to one of the following endpoints, whichever came first: first prescription of low-dose ASA, diagnosis of cancer, alcohol abuse, coagulopathies, oesophageal varices, chronic liver disease, aged 85 years, death or end of the study period.

Every day one person is ascertained as newly exposed to low-dose ASA (start date for outcome follow-up) during enrollment follow-up, we will look for one member of the study population not yet censored and with the same distribution of matching factors (age, sex, time since entry date and number of GP visits in the year prior to start date) than its low-dose ASA pair with the only difference of being free of ASA on that day (start date). With this design, an individual selected as a non-exposed pair during the enrollment follow-up cannot become member of the low-dose ASA cohort at a later date, if she/he receives a prescription of low-dose ASA after being selected as member of the non-exposed cohort. Likewise, an individual selected as member of low-dose ASA cohort pair during the initial follow-up will not have the opportunity to become member of unexposed cohort if after being selected as member of the exposed cohort he stops low-dose ASA treatment. (**Figure 1**). Unlike RCTs with their baseline randomization, our non-experimental study design will still entail unbalanced characteristics despite the matching involved in the ascertainment of the two cohorts. Additional adjustements will be performed in the analysis stage.

Figure 1. Study population



9.2.1 Study time frame

As indicated, the study period to ascertain both cohorts, exposed and unexposed cohort at start date, will cover from January 2000 and end in December 2012, (e.g. enrolment period). Afterwards, a follow up will be performed to ascertained major bleeding episodes adding one extra year (up to 31/12/2013) as well as the upper bound age limit extended up to 89 years

9.2.2 Selection criteria

- ***Inclusion criteria to qualify as member of the study population***

- Aged 40-84 years
- Enrolled with the PCP for at least 2 years,
- To have a history of computerized prescriptions for at least 1 year prior
- To have at least one encounter/visit recorded in the last three years

- ***Exclusion criteria to qualify as member of the study population***

- To be exposed to low dose ASA before entering in the study

- Having a diagnosis of cancer before entering in the study
- Having a diagnosis of alcohol abuse before entering in the study
- Having a diagnosis of coagulopathies before entering in the study
- Having a diagnosis of esophageal varices before entering in the study
- Having a diagnosis of chronic liver disease before entering in the study

9.2.3 Study population

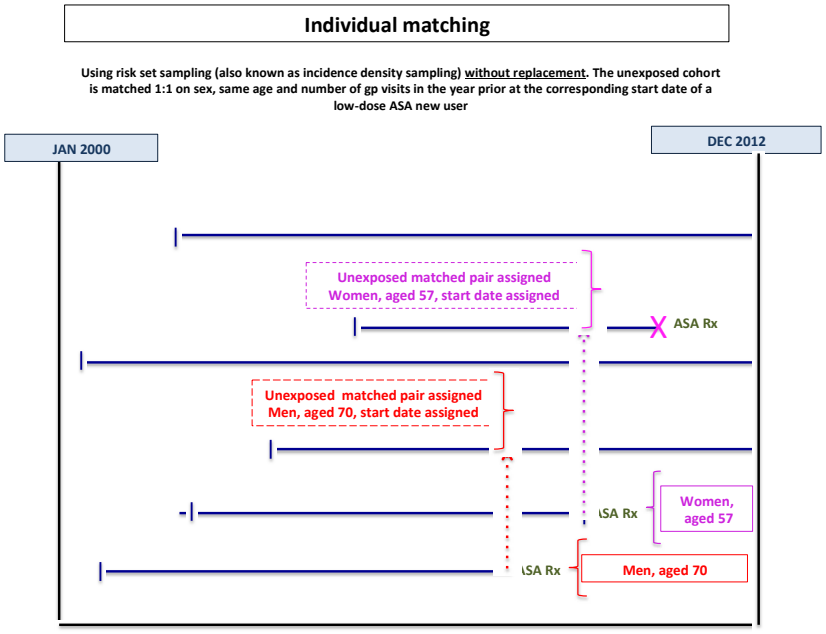
The study period for enrollment of the two study cohorts will start in January 2000 and end in December 2012. Individuals will be required to be aged between 40-84 years, to be enrolled with the PCP for at least 2 years, to have a history of computerized prescriptions for at least 1 year prior, to have at least one encounter/visit recorded in the last three years and to be free of ASA, cancer, alcohol abuse, coagulopathies, esophageal varices and chronic liver disease to become a member of the study population. The date an individual met all these criteria will be considered as entry date. Individuals will be followed up from entry date up to one of the following endpoints, whichever came first: first prescription of low-dose ASA, diagnosis of cancer, alcohol abuse, coagulopathies, oesophageal varices, chronic liver disease, aged 85 years, death or end of the study period

Sampling strategy

To emulate the design from clinical trials we will carry out the ascertainment of the exposed and unexposed cohort concurrently. Each day there is a person qualifying as low-dose ASA new user, we will assign that person as a member of the ASA cohort and will enroll on the same day a person free of ASA who meets all other eligibility criteria implemented in the selection of the ASA new user cohort. Cohorts will matched with the following factors: age at first ASA date/, sex and number of PCP visits in the year prior. (Figure 2) Once an individual from the study population becomes member of one of the two cohorts, she/he will not be eligible to be selected again as member of any of the two cohorts at any time after that date. Then, based on their exposure status at start date (low-dose ASA cohort or comparison unexposed cohort) an intention-to-treat (ITT) analysis will be carried out during the first year of follow-up (secondary analysis). Briefly, the ITT, mainly used in RCTs designed to test efficacy/effectiveness, is based on the initial treatment randomly assigned and does not take into account changes in treatment occurring over the duration of

the RCT (in this case, during the follow-up used to ascertain outcomes of interest). It compares the risk of the outcome in the treated cohort with the risk in non-treated cohort irrespective from the exposure status over the entire follow-up. Following an ITT philosophy, one would not change the exposure classification of an individual even if the subject switches treatment arm over time. The rationale is that factors affecting adherence or treatment discontinuation may be harder to identify and adjust. In the present study, we will limit the ITT analysis (Cox regression) to the first year of follow-up to reduce misclassification of low-dose ASA that inevitably will occur over time. (**Figure 2**). Contrary to randomized clinical trial, observational studies lack of a randomization process. However, the current cohort sampling mimicks the enrollment of clinical trials in that on the same day the “treated” and “non-treated” study members are selected applying a number of matching criteria. Nevertheless, residual confounding or unmeasured confounding will still remain with this sampling strategy, as there is no randomization to low-dose ASA use.

Figure 2. Sampling method to ascertain the unexposed cohort



Representativeness

THIN is a primary care database representative of the UK population with regards to age, sex and geographic distribution, and has been validated for use in pharmacoepidemiological research (Blak et al., 2011; Lewis et al., 2007). Since this study is intended to be done into a clinical practice setting findings from this effort will be generalizable to all individuals who are exposed to low dose ASA for the first time either for primary or secondary prevention.

9.3 Variables

9.3.1 Baseline characteristics

Information on age (50–64, 65–74, 75–89 years), sex and lifestyle factors will be ascertained using two time frames: anytime before the start date (date of low dose ASA exposure; random date for unexposed cohort) and anytime before the index date (stop date of outcomes follow up among cases and random date in controls), with the most recent value used in both time frames. Lifestyle factors ascertained included: body mass index (BMI),

smoking and alcohol intake. BMI will be calculated as weight in kg divided by height in metres squared. Standard cut-offs will be used to classify subjects as underweight (BMI <20), normal weight (BMI 20–24.99), overweight (BMI 25– 29.99) or obese (BMI ≥30 kg/m^2). Smoking status will be categorized into current smoker, past smoker, and never smoker. Alcohol consumption was categorized into units per week (u/w): 1–4, 5–9, 10–14, 15–20, and ≥20. Information on healthcare utilization (number of PCP visits, referrals, and hospitalizations) will be ascertained in the year before the index date. In addition, we will also collect the number of different drug treatments (using the BCD dictionary) in the month before the start date and categorized this comedication variable into the following groups: use between 0–1 drugs, 2–4 drugs and >5 drugs

Information on comorbidities will be extracted from the database anytime before the start date, anytime before the index date and between both dates. Comorbidities evaluated will include: hypertension, diabetes (type I and II, separately), hyperlipidemia, ischaemic heart diseases (IHD), atrial fibrillation, chronic obstructive pulmonary diseases (COPD), asthma, anemia, depression, osteoarthritis, gastroesophageal reflux disease (GERD), peptic ulcer antecendents. In addition, we will collect the following variables related with upper gastrointestinal disorders: dyspepsia, uncomplicated peptic ulcer and complicated peptic ulcer. These variables were collected using two different time windows: anytime up to the start date and from day one after start date up to 30 days before the index date. We will also create an aggregate variable that includes any combination of the three variables.

9.3.2 Exposure

9.3.2.1 Low-dose ASA exposure: categories and duration of use

Use of low-dose ASA will be classified into four categories; *current use*, when supply of the most recent prescription lasted until the index date or ended 0-30 days before the index date; *recent use* when supply of the most recent prescription ended 31-365 days before the index date; *past use* when supply of the most recent prescription ended ≥365 days before the index date and *non-use* when there was no recorded use at any time prior the index date. Duration of treatment was calculated by summing the individual duration of all consecutive prescriptions; gaps in treatment >60 days were considered to be genuine breaks in treatment

and duration was computed using the consecutive period of uninterrupted ASA treatment closest to the index date (e.g. gaps in treatment ≤60 days are included in the computation of duration). Cumulative duration (total use) was also computed summing all the days of low-dose ASA supply irrespective of gaps between prescriptions.

9.3.2.2 Low-dose ASA exposure: ascertainment of daily dose

We will use the following doses for daily dose: 75 mg, 150 mg and 300 mg. We will evaluate separately the dose at the start date and the index date using the information recorded in the database and classified current users into one of these three dose categories. Sometimes, the instructions inserted by primary care providers were possibly erroneous or unspecific i.e. take twice per day (when they mean once per day), written instructions for administration inhalers, or take as required. This would result in a misclassification of the daily dose in both directions (over and underestimation of the true dose). To address this, we will carry out an additional analysis measuring the dose already applied in prior projetcs on the topic. Among current users, we will firstly ascertain the date of the last low-dose ASA prescription immediately before the index date. Secondly, we will ascertain the date of the most distant low-dose ASA prescription within the year before the date of last ASA prescription prior to the index date. Thirdly, we will compute the interval between the two low-dose ASA prescriptions described above. Then, we will add up the total number of low-dose ASA tablets prescribed during that interval and computed a ratio dividing it by the time interval (in days). It should be noted that in the UK only presentations of 75 mg and 300 mg are available, thus daily doses of 150 mg are derived from instructions (posology) written by the PCP. Among patients with presentation of 75 mg before index date, we will change it to a daily dose of 150 mg if the ratio was greater than 1.7, otherwise we kept it as 75 mg. Among patients with presentation of 300 mg before index date, we will change it to daily dose of 150 mg if the ratio was smaller than 0.7, otherwise we kept it as 300 mg. For patients with only one low-dose ASA prescription, we will assume the dose based on the instructions. We will also assess the formulation of low-dose ASA subdividing current users into either plain tablet users and enteric coated users.

9.3.2.3 Low-dose ASA indication

To ascertain the indication for low-dose ASA among patients in the low-dose ASA cohort, we used a computer algorithm that searched THIN for any recorded Read codes suggestive of cardiovascular diseases (CVD) **(Appendix 1)** from anytime before the first low-dose ASA prescription up to 30 days after. We prioritized the information closest to the date of the first low-dose ASA prescription. Using both a hierarchy of the Read codes and the date the Read code was recorded, we classified patients into the following indication categories: myocardial infarction (MI), stroke (including ischaemic stroke (IS) and transient ischaemic accident (TIA)), unstable angina (UA), angina, peripheral artery diseases (PAD) and IHD.

9.3.2.4 Cocomitant medication

The following medications will be ascertained; antihypertensive medications, statins, antidiabetics, NSAIDs (traditional NSAIDs (tNSAIDs), COXIBs), paracetamol, oral and inhaled steroids (separately), clopidogrel, warfarin, other oral anticoagulants, nitrates, dipyridamole, SSRIs, other antidepressants, hypnotics/anxiolytics, antipsychotics, tramadol, digoxin, HRT, proton pump inhibitors (PPIs) and H_2-receptor antagonists (H_2RAs). Medication use will be classified into four categories: *current use*, when the supply of the most recent prescription lasted until the index date or ended in the 30 days before the index date; *recent use*, when supply of the most recent prescription ended 31–90 days before the index date; *past use* when supply of the most recent prescription ended 91-365 days before the index date and *non-use* when supply of the most recent prescription ended more than 365 days before the index date or there was no recorded use at any time prior to index date.

For NSAIDs we will classify current users into three separate categories (tNSAIDs or COXIBs): current users of both drugs, current users of only tNSAIDs and current users of only COXIBs. We will estimate the cumulative duration as described above in low-dose ASA section excluding at this stage current users of both drugs who represented a minor proportion. In addition, we will evaluate the effect of daily dose among current users of only tNSAIDs and only COXIBs. Cut-off values for dose (in mg) will be as follows: aceclofenac 200, acemetacin 120, azapropazone 600, celecoxib 200, diclofenac 100, diflunisal 1500, etodolac 400, etoricoxib 90, fenbufen 900, fenoprofen 1200, flurbiprofen 150, ibuprofen

1200, indomethacin 75, ketoprofen 150, ketorolac 30, lumiracoxib 200, mefenamic acid 1000, meloxicam 7.5, nabumetone 1000, naproxen 750, piroxicam 10, rofecoxib 25, sulindac 200, tenoxicam 10, tiaprofenic 600, and valdecoxib 20. Doses less than or equal to the cut-off value will be grouped into low–medium doses, and doses greater than the cut-off value will be grouped into high doses. In addition, among current users excluding concomitant use of tNSAIDs and Coxibs, we will estimated the relative risk of upper and lower gastrointestinal bleeding episode associated to the most the most widely used tNSAIDs (Diclofenac, Ibuprofen, Meloxicam, Naproxen) and Coxibs (Celecoxib, Eterocoxib and Rofecoxib).

Additionally current users of proton pump inhibitors (PPIs) and H_2-receptor antagonists (H_2RAs) will be subdivided into two mutually exclusive categories: *single*, when there is use of only one PPI or H_2RA respectively in the 30 days before the index date, and *multiple*, when the patient uses more than one PPI or H_2RA in the 30 days before the index date.

To evaluate the interaction between the drugs of interest A + B (e.g., low-dose ASA & clopidogrel; low-dose ASA and warfarin, etc) we will follow the same definition for every combination of drugs. For that, we will create one variable with five mutually exclusive levels of exposure: *non use of either agent (No A No B)* (within the year prior to index date); current *use of both agents (A+B)*; *current use of only A (non use of B within the year prior)*; *current use of only B (non use of A within the year prior)*; and *remaining* (other combinations of recency of both agents).

Finally, we will also collect in the month prior to the index date the number of different drug treatments (using Gemscript dictionary) and categorized this co-medication variable called polytherapy, into the following groups: use up to 2 drugs, use between 3 to 5 drugs, use between 6 to 9 drugs, use between 10 to 14 drugs and use of 15 and more drugs.

9.3.3 Outcome measures

Intracraneal Bleeding

All members from low-dose ASA cohort and comparison cohort will be followed from start date (date of enrolment) until the occurrence of one of the following endpoints, whichever comes first.

- Case detection: Intracraneal bleeding (**See Appendix 2 for specific intracranial bleeding Read codes**)
- Cancer
- Coagulopathies
- Alcohol abuse
- Oesophageal varices
- Chronic liver disease
- Age of 90 years
- Death
- End of the study period (31 December 2013)

A recent study performed by our group on intracranial bleeding showed an overall confirmation of 82% after validation with questionnaires sent to PCP [8] compared to the information based on free text comments. Accordingly, we will request free text comments for all computer-detected potential cases ascertained with the automatic search. All patient personal identifiers will be suppressed and information on drug use will be removed to allow for a blinded review of patient profiles. Cases will be discarded during this review in the following instances: the initial diagnostic code is not confirmed, the cerebrovascular event is ischemic and not hemorrhagic, the case is prevalent rather than incident (i.e., not a primary event). Cases will be classified into trauma and non-trauma related.

Upper gastrointestinal bleeding

All members from low-dose ASA cohort and comparison cohort will be followed from start date) until the earliest occurrence of one of the following endpoints:

- Case detection: Upper gastrointestinal bleeding (**See Appendix 3 for Read codes**)
- Cancer
- Coagulopathies
- Alcohol abuse

- Oesophageal varices
- Chronic liver disease
- Age of 90 years
- Death
- End of the study period (31 December 2013)

We (CEIFE) have previous experience with UGIB as reflected on a number of publications that included validation exercises. For example, a positive predictive value close to 95% was observed using PCPs' questionnaires as gold standard [9,10]. Accordingly, we will request free text comments for all computer-detected potential cases ascertained with the automatic search. All patient personal identifiers will be suppressed and information on drug use will be removed to allow for a blinded review of patient profiles. Confirmed cases of UGIB will be all those who had been referred to a consultant or admitted to hospital, for whom the site of bleeding or perforation was the stomach or duodenum. Patients whose site of bleeding or perforation is the esophagus will be excluded

Lower gastrointestinal bleeding

All members from low-dose ASA cohort and comparison cohort will be followed from start date (date of enrolment) until the occurrence of one of the following endpoints, whichever comes first.

- Case detection: Lower gastrointestinal bleeding (**See Appendix 4 for Read codes**)
- Cancer
- Coagulopathies
- Alcohol abuse
- Oesophageal varices
- Chronic liver disease
- Age of 90 years
- Death
- End of the study period (31 December 2013)

In a recent study performed by our group using a cohort of patients followed after an episode of acute coronary syndrome [11], we found a confirmation rate of 82% when comparing

the case ascertainment status based on review of patient profiles with free text comments to the information in PCPs' questionnaires [12]. Accordingly, we will request free text comments for all computer-detected potential cases ascertained with the automatic search. All patient personal identifiers will be suppressed and information on drug use will be removed to allow for a blinded review of patient profiles. Confirmed cases of LGIB will be all those who had been referred to a consultant or admitted to hospital and the site of bleeding located in jejunum, ileum, colon or rectum.We will classify cases according to the clinical diagnosis of the bleed into diverticulosis/diverticulitis, polyposis, inflammatory bowel disease, ischemic colitis, angiodysplasia and other cause of bleeding. Cases of bleeding due to hemorrhoids will be discarded.

In addition, we will identify in the subset ot patients whose practices are linked to Hospital Episode Statistics (HES) those with ICD discharge codes related to all 3 study outcomes. Briefly, HES are data collected from National Health Service (NHS) hospitals in England by the Secondary Uses Services (SUS), a programme that supports secondary care in the NHS. HES data include details of all hospital care funded by the NHS in England. It contains: admitted patient care data from 1997 onwards, outpatient attendance data from 2003 onwards and accident and Emergency (A&E) data from 2007 onwards.It should be noted that available HES files extend until to March 2012 and include 158 practices (approximately one third of all THIN practices). The full HES dataset contains more than 400 fields, although in most cases many of these are not completed by the hospital, either because they are not applicable or recording is not mandatory. Each HES record may contain a wide range of information about an individual patient admitted to an NHS hospital, including:

- Clinical information about diagnoses, procedures and operations.
- Information about the patient, such as age, gender and ethnic category.
- Administrative information, such as dates of admission and discharge dates.

Using information available from HES and information in THIN incorporating free text comments, we will cross-validate the diagnoses of bleeding in both directions and ascertain the agreement/disagreement in both directions (THIN versus HES and HES versus THIN). Outpatient records in HES are complete as far as the recording of visits but rarely have

diagnoses listed: in addition to the date, the service where the outpatient visit was booked is also recorded.

9.4 Selection of controls in the two cohorts

For each outcome of interest, a random date within the study period will be generated among all study members without the event of interest of the two study cohorts (low-dose ASA and unexposed cohorts). If the random date for a study member is included in her/his follow-up period, that person will be marked as an eligible control and the random date will be used as index date in the nested case-control analysis. This method of selection of controls in nested case-control studies is known as incidence density sampling. Controls will be frequency-matched to the set of cases by calendar year. The final size of the control sample will be determined by being approximately four times the size of the set of cases and rounded to the closest one thousand unit.

9.5 Data sources

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 and epidemiological research in multiple studies [13]. Participating primary care practitioners (PCPs) record prospectively 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 [14], and a drug dictionary based on data from the Gemstrip, a set of data based on the NHS dictionary of medicine and device. It describes the clinical, commercial and physical attributes of the medicines, medical devices and appliances used in the healthcare industry (http://www.resip.co.uk/gemscript)

9.6 Study Size

Based on our recent study on ASA and colorectal cancer, we expect a sample size of the ASA cohort close to 200,000 (individuals firstly exposed to low dose ASA).A comparison cohort (sampled 1:1) will be subsequently selected.

Considering the incidence of the three outcomes of interest in a relatively similar age and sex distribution (12/10,000/year for UGIB, 26 for LGIB and 5 for haemorrhagic stroke-(*AHA 2014 abstract; Risk of Hemorrhagic Stroke and Gastrointestinal Bleeding After Hospitalization for a Serious Acute Coronary Event*), we estimated the sample size needed for each outcome, using a power of 0.80 with a two tailed level of significance of 0.05, and we will have enough sample size to run all analyses proposed.

Estimated HR	Sample per outcome IC	Sample per outcome UGIB	Sample per outcome LGIB
2.50	5,045	1,974	1,017
2.00	9,444	3,695	1,902
1.80	13,619	5,328	2,741
1.70	17,062	6,674	3,434
1.50	30,661	11,992	6,169

Note: Follow-up time was estimated for each outcome based on a pilot exploration in this population. Corresponding estimated follow-up time for each outcome were as follows: 5.2 years for IC, 5.6 years for UGIB and 5.1 years for LGIB. Source: http://www.clinsearch.net/tools/SampleSizeSurvival

9.7 Data management

CEIFE 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. CEIFE will ensure that information is not disclosed or transferred to any third party not mentioned in this protocol. CEIFE 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. CEIFE will store the Database used to perform this study at the premises of CEIFE. For each study project, all material including: study protocol, copy

of Scientific Review Committee approval, algorithms and data collections, datasets, STATA programs, results from validation exercises and questionnaires, final STATA programs, and final report and publications are kept in one folder cross-shared by the CEIFE team. Monthly back-ups are performed and kept in a secure location, and all material is kept for 10 years.

9.8 Data analysis

The design of the current study is a comparative cohort using an existing secondary data source with prospective data collection. The primary statistical analysis will be a nested case-control analysis for each outcome of interest however we will perfom a descriptive analysis as well as we will measure the outcome rates of each outcome per cohort. A secondary COX regression analysis will be perfomed over the first year of follow-up with fixed asssigment of exposure at start date (e.g. ITT)

Descriptive Analysis

We will describe the population of new users of low dose ASA and the unexposed cohort estimating the frequency of demographic and life style factors, health care utilization, comorbidities and comedication at start date. Appropriate comparison tests including Chi-square test and Student's t-test will be used for comparison between groups for categorical variables and continuous variables,respectively. Same descriptive analysis will be performed within the three independent nested case control studies, between cases and controls. Missing data will be treated as other category within the variable.

Cohort analysis

Kaplan-Meier survival curves for low-dose ASA cohort and comparison-unexposed cohort will be performed. As a secondary analysis, Cox proportional hazard models will be used to estimate the relative risk (hazard rate ratio) and 95% CI of incident major bleeding episodes associated with low-dose ASA cohort adjusted for matching variables and independent risk factors (ascertained before start date) censoring follow-up at the first year. Cox regression models take into account time to event. We will perfom this secondary analysis to compare with other studies who assign exposure satus as fixed variable at start

date. We will censor the Cox analysis to the first year of follow-up to reduce the misclassification of low-dose ASA that inevitably will occur over time.

Incidence rates of each major bleeding outcome overall as well as age- and sex-specific will be computed in the two cohorts with Poisson regression, separately.

Nested case-control analysis

Three separate nested case–control analyses will be performed to assess the effect of potential risk factors for each bleeding outcome of interest using unconditional logistic regression. All patients confirmed as incident case in the cohort analysis will also be used as cases in nested case-control analysis. Under our study design of incidence density sampling, the odds ratio (OR) is an unbiased estimator of the incidence rate ratio (RR) [1]. Statistical analyses will be performed using Stata package version 12.0 (StataCorp LP, College Station, TX, US).

9.9 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.

All programming written by the executing researcher will be reviewed independently by a senior researcher. All key study documents, such as the statistical analysis plan and study reports, will undergo quality control and senior scientific review.

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. The Company will not receive any patient or provider identifiable information from CEIFE at any time. We will abide by the Guidelines for Good Pharmacoepidemiology Practices (GPP, 2007). The study protocol is

dependent on approval by a Scientific Research Committee (SRC) that review studies performed in THIN.

9.10 Limitations of the research methods

Our study will take advantage of one of the largest electronical medical record databases in primary care setting worldwide. The validity of this database has been demonstrated in previous studies [15]. Patients included in THIN are representative of the entire UK population with respect to age, sex and geographical region [16]. Therefore, results may be extrapolated to the general UK population.

To identify our cohort of new users of low dose ASA, we will apply an intention to treat design with nested case–control analyses to control for confounders during the follow up.

Regarding the outcomes of interes it should be noted that this group has previous experience with this outcome of interest as reflected on the list of publications showing validation exercises performed. For example, a positive predictive value of >95% was estimated for the upper gastrointestinal bleeding (UGIB) definition compared with PCPs' records in a random sample [10 9]. For intracranial bleeding a recent study performed by this group, showed a confirmation of 82% when validating through sending questionnaires to PCP[8]. Although this is a secondary objective and those episodes are highly specific, we will request free text comments of patient profiles for all potential cases detected in the automatic search. Thus, the positivie predictive value of our methodological approach and thus the fiability of our case definition is expected to be >80% for our study outcomes

Although there is a lack of systematic recording of OTC ASA use, cross-sectional studies have shown that ASA for secondary prevention is predominantly prescription-based in the age range of our study population, in the UK [17-19]. Based on analysis of free-text comments in a sample of records in the THIN database, we estimated that approximately 10% of individuals aged between 40 and 89 years with cardiovascular antecedents were likely using OTC ASA, which should not have greatly affected our study results. In addition,

patients aged over 65 years in the UK receive free prescriptions, and primary healthcare is easily accessed. THIN is therefore likely to be a representative source of data on ASA use in this age group in the UK. Although all prescriptions issued from the PCP are recorded in THIN, it cannot be known whether these prescriptions are subsequently dispensed from pharmacies or whether patients actually take the medicine. However, for most patients, review of medical records have shown that there was a prescription for ASA almost every month suggesting they were likely to be taking their medication. In addition, our group aimed to quantify the extent of OTC low-dose ASA use among patients in The Health Improvement Network (THIN) primary care database in the UK by means of a novel validation exercise. Our findings showed a small impact of misclassification of low-dose ASA use in THIN due to unrecorded OTC use ranging between 3-4%. Based on the very small proportion of false negatives (individuals with no recorded ASA Rx but are taking OTC low-dose ASA) supports the usefulness of THIN for drug utilization and safety studies of low-dose ASA.

We will have limited information on some potential confounders such as Helicobacter pylori infection that is not recorded systematically in THIN. Furthermore, although we will endeavour to control confounding as much as possible, residual confounding is always a possibility in observational studies and can not be ruled out.

9.11 Other aspects

None

10. Protection of human subjects

This study protocol will be approved by a Research Ethics Committee (REC), and the study will be conducted in accordance with Good Pharmacoepidemiology Practices.We will send the study protocol to the Multicenter Research Ethics Committee (MREC). In this investigation we will use a medical record linkage database where the information of patients is anonymized and there is no need to obtain informed consent from patients.

Centro Español de Investigación Farmacoepidemiológica (CEIFE) 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. CEIFE will ensure that information is not disclosed or transferred to any third party not mentioned in this protocol. CEIFE 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. CEIFE will store the Database used to perform this study at the premises of CEIFE. 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. We will abide by the Guidelines for Good Pharmacoepidemiology Practices [20]. The study protocol is dependent on approval by a Scientific Research Committee (SRC) for studies performed in THIN.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI– Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required.

12. Plans for disseminating and communicating study results

At least one manuscript based on the findings from this project will be submitted for publication to a peer-review journal.

13. List of references

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17. Bedson, J., Whitehurst, T., Lewis, M. & Croft, P. Factors affecting over-the-counter use of aspirin in the secondary prophylaxis of cardiovascular disease. *Br J Gen Pract* **51**, 1001-1003 (2001).

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Annex 1. List of stand-alone documents <<*On hold*>>

None applicable.

Annex 2. ENCePP checklist for study protocols *(mandatory for PASS studies)* <<*on hold*>>

The ENCePP checklist for study protocols should be completed and signed by the main author of the study protocol and should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Please check for the current version of the ENCePP checklist for study protocols at http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml.

The checklist will facilitate the review of the protocol and evaluation of whether companies considered important methodological aspects. For each of the questions of the checklist, the company should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009

Study title:
A pharmacoepidemiological study on the risk of bleeding in new users of low dose aspirin in THIN

Study reference number:
BAYER IMPACT 18116, EU PAS register number not yet assigned

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	11
1.1.2 End of data collection[2]	☒	☐	☐	11
1.1.3 Study progress report(s)	☒	☐	☐	11
1.1.4 Interim progress report(s)	☐	☐	☒	11
1.1.5 Registration in the EU PAS register	☒	☐	☐	11
1.1.6 Final report of study results.	☒	☐	☐	11

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	11
2.1.2 The objective(s) of the study?	☒	☐	☐	12-13
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	15-18
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☒	☐	☐	12-13
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	13
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	12-13

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	29-30

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15-16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	15-19
4.2.2 Age and sex?	☒	☐	☐	15-19
4.2.3 Country of origin?	☒	☐	☐	15-19
4.2.4 Disease/indication?	☒	☐	☐	15-19
4.2.5 Co-morbidity?	☒	☐	☐	15-19
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	18-19

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	21-22
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	21-22; 32
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	21-22
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
product?				
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	21-22

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	24-27
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	24-27; 31-32

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	20,23,29-30
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	20,23,29-30

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	28
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital	☒	☐	☐	28
	☒	☐	☐	28

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
statistics, etc.) 8.1.3 Covariates?				
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, product quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	28
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	28
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	28
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	28
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	28
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	28
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	29

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	26-28
10.3 Are descriptive analyses included?	☒	☐	☐	26-28

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.4 Are stratified analyses included?	☒	☐	☐	29-30
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	29-30
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	29-30

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29-31
11.3 Are methods of quality assurance described?	☒	☐	☐	29
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☐	29
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	31-32
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	31-32
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	31-32
12.3 Does the protocol address other limitations?	☒	☐	☐	31-32

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	33
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	33

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☐	☒	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	34

Comments:

Name of the main author of the protocol: _Luis A Garcia Rodriguez_____

Date: / /

Signature: _____

Annex 3. Additional information

Appendix 1a. Read codes for MI.

Read	Descriptor
G30..00	Acute myocardial infarction
G30..13	Cardiac rupture following myocardial infarction (MI)
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G30..11	Attack - heart
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G311500	Acute coronary syndrome
G310.00	Postmyocardial infarction syndrome
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
3232.00	ECG: old myocardial infarction
3235.00	ECG: subendocardial infarct
323Z.00	ECG: myocardial infarct NOS
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
G307100	Acute non-ST segment elevation myocardial infarction
G312.00	Coronary thrombosis not resulting in myocardial infarction
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct

Read	Descriptor
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G384.00	Postoperative subendocardial myocardial infarction
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site

Appendix 1b. Read code for unstable angina.

Read code	Descriptor
G311.11	Crescendo angina
G311.13	Unstable angina
G311.14	Angina at rest
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G330.00	Angina decubitus
G330000	Nocturnal angina
G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris

Appendix 1c. Read codes for revascularization.

Read code	Descriptor
ZV45700	[V]Presence of aortocoronary bypass graft
7920000	Saphenous vein graft replacement of one coronary artery
7920.00	Saphenous vein graft replacement of coronary artery
792..00	Coronary artery operations
7920100	Saphenous vein graft replacement of two coronary arteries
7920.11	Saphenous vein graft bypass of coronary artery
7920200	Saphenous vein graft replacement of three coronary arteries
7920300	Saphenous vein graft replacement of four+ coronary arteries
7920y00	Saphenous vein graft replacement of coronary artery OS
7920z00	Saphenous vein graft replacement coronary artery NOS
7921000	Autograft replacement of one coronary artery NEC
7921.00	Other autograft replacement of coronary artery
7921100	Autograft replacement of two coronary arteries NEC
7921.11	Other autograft bypass of coronary artery
792..11	Coronary artery bypass graft operations
7921200	Autograft replacement of three coronary arteries NEC
7921300	Autograft replacement of four of more coronary arteries NEC
7921y00	Other autograft replacement of coronary artery OS
7921z00	Other autograft replacement of coronary artery NOS
7922000	Allograft replacement of one coronary artery
7922.00	Allograft replacement of coronary artery
7922100	Allograft replacement of two coronary arteries
7922.11	Allograft bypass of coronary artery
7922200	Allograft replacement of three coronary arteries
7922300	Allograft replacement of four or more coronary arteries
7922y00	Other specified allograft replacement of coronary artery
7922z00	Allograft replacement of coronary artery NOS
7923000	Prosthetic replacement of one coronary artery
7923.00	Prosthetic replacement of coronary artery
7923100	Prosthetic replacement of two coronary arteries
7923.11	Prosthetic bypass of coronary artery
7923200	Prosthetic replacement of three coronary arteries
7923300	Prosthetic replacement of four or more coronary arteries
7923y00	Other specified prosthetic replacement of coronary artery
7923z00	Prosthetic replacement of coronary artery NOS
7924000	Revision of bypass for one coronary artery
7924.00	Revision of bypass for coronary artery
7924100	Revision of bypass for two coronary arteries

Read code	Descriptor
7924200	Revision of bypass for three coronary arteries
7924300	Revision of bypass for four or more coronary arteries
7924400	Revision of connection of thoracic artery to coronary artery
7924y00	Other specified revision of bypass for coronary artery
7924z00	Revision of bypass for coronary artery NOS
7925000	Double anastomosis of mammary arteries to coronary arteries
7925.00	Connection of mammary artery to coronary artery
7925100	Double implant of mammary arteries into coronary arteries
7925.11	Creation of bypass from mammary artery to coronary artery
7925200	Single anast mammary art to left ant descend coronary art
7925300	Single anastomosis of mammary artery to coronary artery NEC
7925400	Single implantation of mammary artery into coronary artery
7925y00	Connection of mammary artery to coronary artery OS
7925z00	Connection of mammary artery to coronary artery NOS
7926000	Double anastom thoracic arteries to coronary arteries NEC
7926.00	Connection of other thoracic artery to coronary artery
7926100	Double implant thoracic arteries into coronary arteries NEC
7926200	Single anastomosis of thoracic artery to coronary artery NEC
7926300	Single implantation thoracic artery into coronary artery NEC
7926y00	Connection of other thoracic artery to coronary artery OS
7926z00	Connection of other thoracic artery to coronary artery NOS
7927000	Repair of arteriovenous fistula of coronary artery
7927.00	Other open operations on coronary artery
7927100	Repair of aneurysm of coronary artery
7927200	Transection of muscle bridge of coronary artery
7927300	Transposition of coronary artery NEC
7927400	Exploration of coronary artery
7927500	Open angioplasty of coronary artery
7927y00	Other specified other open operation on coronary artery
7927z00	Other open operation on coronary artery NOS
7928000	Percut transluminal balloon angioplasty one coronary artery
7928.00	Transluminal balloon angioplasty of coronary artery
7928100	Percut translum balloon angioplasty mult coronary arteries
7928.11	Percutaneous balloon coronary angioplasty
7928200	Percut translum balloon angioplasty bypass graft coronary a
7928y00	Transluminal balloon angioplasty of coronary artery OS
7928z00	Transluminal balloon angioplasty of coronary artery NOS
7929000	Percutaneous transluminal laser coronary angioplasty
7929.00	Other therapeutic transluminal operations on coronary artery
7929100	Percut transluminal coronary thrombolysis with streptokinase

Read code	Descriptor
7929111	Percut translum coronary thrombolytic therapy- streptokinase
7929200	Percut translum inject therap subst to coronary artery NEC
7929300	Rotary blade coronary angioplasty
7929400	Insertion of coronary artery stent
7929y00	Other therapeutic transluminal op on coronary artery OS
7929z00	Other therapeutic transluminal op on coronary artery NOS
792B000	Endarterectomy of coronary artery NEC
792B.00	Repair of coronary artery NEC
792By00	Other specified repair of coronary artery
792Bz00	Repair of coronary artery NOS
792C000	Replacement of coronary arteries using multiple methods
792C.00	Other replacement of coronary artery
792Cy00	Other specified replacement of coronary artery
792Cz00	Replacement of coronary artery NOS
792D.00	Other bypass of coronary artery
792Dy00	Other specified other bypass of coronary artery
792Dz00	Other bypass of coronary artery NOS
792y.00	Other specified operations on coronary artery
792z.00	Coronary artery operations NOS
ZV45800	[V]Presence of coronary angioplasty implant and graft
ZV45K00	[V]Presence of coronary artery bypass graft
ZV45K11	[V]Presence of coronary artery bypass graft - CABG
ZV45L00	[V]Status following coronary angioplasty NOS
790H300	Revascularisation of wall of heart
88A8.00	Thrombolytic therapy
SP00300	Mechanical complication of coronary bypass

Appendix 1d. Read codes for ischaemic stroke.

Read code	Descriptor
G6...00	Cerebrovascular disease
G68..00	Late effects of cerebrovascular disease
G683.00	Sequelae of cerebral infarction
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
G6y..00	Other specified cerebrovascular disease
G6z..00	Cerebrovascular disease NOS
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
14A7.00	H/O: CVA/stroke
14A7.11	H/O: CVA
14A7.12	H/O: stroke
1477.00	H/O: cerebrovascular disease
Gyu6.00	[X]Cerebrovascular diseases
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6700	[X]Other specified cerebrovascular diseases
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
14AK.00	H/O: Stroke in last year
662e.00	Stroke/CVA annual review
662e.11	Stroke annual review
662M.00	Stroke monitoring
662M100	Stroke 6 month review
662M200	Stroke initial post discharge review
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
L440.12	Stroke in the puerperium
ZV12511	[V]Personal history of stroke
ZV12512	[V]Personal history of cerebrovascular accident (CVA)
7A24400	Open embolectomy of cerebral artery
7A24500	Open embolectomy of circle of Willis
7A24600	Open embolisation of cerebral artery
7A24700	Open embolisation of circle of Willis
7A25000	Percutaneous transluminal embolisation of cerebral artery
7A25100	Percutaneous transluminal embolisation of circle of Willis

Read code	Descriptor
7A25200	Embolisation of cerebral artery NEC
7A25300	Embolisation of circle of Willis NEC
8HBJ.00	Stroke / transient ischaemic attack referral
8HTQ.00	Referral to stroke clinic
ZLEP.00	Discharge from stroke serv
9Om..00	Stroke/transient ischaemic attack monitoring administration
9Om0.00	Stroke/transient ischaemic attack monitoring first letter
9Om1.00	Stroke/transient ischaemic attack monitoring second letter
9Om2.00	Stroke/transient ischaemic attack monitoring third letter
9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati
9Om4.00	Stroke/transient ischaemic attack monitoring telephone invte
G63..00	Precerebral arterial occlusion
G63..11	Infarction - precerebral
G63..12	Stenosis of precerebral arteries
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion
G633.00	Multiple and bilateral precerebral arterial occlusion
G634.00	Carotid artery stenosis
G63y.00	Other precerebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome

Read code	Descriptor
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G669.00	Cerebral palsy, not congenital or infantile, acute
G67..00	Other cerebrovascular disease
G670.00	Cerebral atherosclerosis
G670.11	Precerebral atherosclerosis
G671.00	Generalised ischaemic cerebrovascular disease NOS
G671000	Acute cerebrovascular insufficiency NOS
G671100	Chronic cerebral ischaemia
G671z00	Generalised ischaemic cerebrovascular disease NOS
G676.00	Nonpyogenic venous sinus thrombosis
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
G678.00	Cereb autosom dominant arteriop subcort infarcts leukoenceph
G679.00	Small vessel cerebrovascular disease
G67A.00	Cerebral vein thrombosis
G67y.00	Other cerebrovascular disease OS
G67z.00	Other cerebrovascular disease NOS
G68..00	Late effects of cerebrovascular disease

Appendix 1e. Read codes for TIA.

Read code	Descriptor
8HBJ.00	Stroke / transient ischaemic attack referral
9Om..00	Stroke/transient ischaemic attack monitoring administration
9Om0.00	Stroke/transient ischaemic attack monitoring first letter
9Om1.00	Stroke/transient ischaemic attack monitoring second letter
9Om2.00	Stroke/transient ischaemic attack monitoring third letter
9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati
9Om4.00	Stroke/transient ischaemic attack monitoring telephone invte
Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G655.00	Transient global amnesia
G656.00	Vertebrobasilar insufficiency
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS

Appendix 1f. Read codes for PAD.

Read codes	Descriptor
14AE.00	H/O: aortic aneurysm
14NB.00	H/O: Peripheral vascular disease procedure
2456.00	O/E - arterial wall - aneurysm
2I16.00	O/E - gangrene
33C5.00	Peripheral vasc. resistance
A3A0F00	Gas gangrene-foot
A930.00	Syphilitic aortic aneurysm
C107.00	Diabetes mellitus with peripheral circulatory disorder
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107300	IDDM with peripheral circulatory disorder
C107400	NIDDM with peripheral circulatory disorder
C107y00	Other specified diabetes mellitus with periph circ comps
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
C108G00	Insulin dependent diab mell with peripheral angiopathy
C108G11	Type I diabetes mellitus with peripheral angiopathy
C109F00	Non-insulin-dependent d m with peripheral angiopath
C109F11	Type II diabetes mellitus with peripheral angiopathy
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
F161100	Myelopathy due to arterial thrombosis of spinal cord
F371100	Polyneuropathy in polyarteritis nodosa
F396300	Myopathy due to polyarteritis nodosa
F423200	Retinal arterial branch occlusion
F423500	Retinal partial arterial occlusion NOS
F423700	Retinal transient arterial occlusion NOS
G420.00	Arteriovenous fistula of pulmonary vessels
G7...00	Arterial, arteriole and capillary disease
G7...11	Capillary disease
G70..00	Atherosclerosis
G70..11	Arteriosclerosis
G700.00	Aortic atherosclerosis
G700.11	Aorto-iliac disease
G701.00	Renal artery atherosclerosis
G701000	Atherosclerotic renal artery stenosis
G701011	ARAS - Atherosclerotic renal artery stenosis
G702.00	Extremity artery atheroma
G702000	Monckeberg's medial sclerosis
G702z00	Extremity artery atheroma NOS
G703.00	Acquired renal artery stenosis

Read codes	Descriptor
G70y.00	Other specified artery atheroma
G70y000	Carotid artery atherosclerosis
G70y011	Carotid artery disease
G70z.00	Arteriosclerotic vascular disease NOS
G71..00	Aortic aneurysm
G710.00	Dissecting aortic aneurysm
G711.00	Thoracic aortic aneurysm which has ruptured
G711.11	Ruptured thoracic aortic aneurysm
G712.00	Thoracic aortic aneurysm without mention of rupture
G713.00	Abdominal aortic aneurysm which has ruptured
G713.11	Ruptured abdominal aortic aneurysm
G713000	Ruptured suprarenal aortic aneurysm
G714.00	Abdominal aortic aneurysm without mention of rupture
G714.11	AAA - Abdominal aortic aneurysm without mention of rupture
G714000	Juxtarenal aortic aneurysm
G714100	Inflammatory abdominal aortic aneurysm
G714200	Infrarenal abdominal aortic aneurysm
G714300	Aneurysm of suprarenal aorta
G715.00	Ruptured aortic aneurysm NOS
G715000	Thoracoabdominal aortic aneurysm, ruptured
G716.00	Aortic aneurysm without mention of rupture NOS
G716000	Thoracoabdominal aortic aneurysm, without mention of rupture
G717.00	Aortic aneurysm - syphilitic
G718.00	Leaking abdominal aortic aneurysm
G719.00	Abscess of aortic root
G71A.00	Aortic root dilatation
G71z.00	Aortic aneurysm NOS
G72..00	Other aneurysm
G720.00	Aneurysm of artery of arm
G720000	Aneurysm of brachial artery
G720100	Aneurysm of radial artery
G720200	Aneurysm of ulnar artery
G720z00	Aneurysm of arm artery NOS
G721.00	Aneurysm of renal artery
G721000	Acquired renal artery aneurysm
G722.00	Aneurysm of iliac artery
G722000	Aneurysm of common iliac artery
G722100	Aneurysm of external iliac artery
G722200	Aneurysm of internal iliac artery
G722z00	Aneurysm of iliac artery NOS

Read codes	Descriptor
G723.00	Aneurysm of leg artery
G723000	Aneurysm of femoral artery
G723100	Aneurysm of popliteal artery
G723200	Aneurysm of anterior tibial artery
G723300	Aneurysm of dorsalis pedis artery
G723400	Aneurysm of posterior tibial artery
G723500	Ruptured popliteal artery aneurysm
G723600	Post radiological femoral false aneurysm
G723z00	Aneurysm of leg artery NOS
G724.00	Arterial false aneurysm
G724.11	False aneurysm
G725.00	Dissection of artery of upper extremity
G725.11	Dissection of artery of arm
G726.00	Dissection of renal artery
G727.00	Dissection of iliac artery
G728.00	Dissection of artery of lower extremity
G728.11	Dissection of artery of leg
G729.00	Aneurysm and dissection of precerebral artery
G72A.00	Dissection of other specified arteries
G72B.00	Dissection of artery
G72C.00	Ruptured aneurysm of dialysis vascular access
G72D.00	Aneurysm of dialysis arteriovenous fistula
G72D000	Aneurysm of superficialised artery of dialysis AV fistula
G72D100	Aneurysm of needle site of dialysis arteriovenous fistula
G72D200	Aneurysm of anastomotic site of dialysis AV fistula
G72E.00	Aneurysm of dialysis vascular access
G72y.00	Aneurysm of other artery
G72y000	Aneurysm of common carotid art
G72y100	Aneurysm of external carotid artery
G72y200	Aneurysm of internal carotid artery
G72y300	Aneurysm of neck artery NOS
G72y400	Aneurysm of subclavian artery
G72y500	Aneurysm of splenic artery
G72y600	Aneurysm of axillary artery
G72y700	Aneurysm of coeliac artery
G72y800	Aneurysm of superior mesenteric artery
G72y900	Aneurysm of inferior mesenteric artery
G72yA00	Aneurysm of hepatic artery
G72yB00	Aneurysm of other visceral artery
G72yz00	Other aneurysm NOS

Read codes	Descriptor
G72z.00	Aneurysm NOS
G73..00	Other peripheral vascular disease
G73..11	Peripheral ischaemic vascular disease
G73..12	Ischaemia of legs
G73..13	Peripheral ischaemia
G730.00	Raynaud's syndrome
G730000	Raynaud's disease
G730100	Raynaud's phenomenon
G730111	Vibratory white finger
G730z00	Raynaud's syndrome NOS
G731.00	Thromboangiitis obliterans
G731000	Buerger's disease
G731100	Presenile gangrene
G731z00	Thromboangiitis obliterans NOS
G732.00	Peripheral gangrene
G732000	Gangrene of toe
G732100	Gangrene of foot
G732200	Gangrene of finger
G732300	Gangrene of thumb
G732400	Gangrene of hand
G733.00	Ischaemic foot
G734.00	Peripheral arterial disease
G73y.00	Other specified peripheral vascular disease
G73y000	Diabetic peripheral angiopathy
G73y100	Peripheral angiopathic disease EC NOS
G73y200	Acrocyanosis
G73y400	Acroparaesthesia - Schultze's type
G73y411	Schultze's simple acroparaesthesia
G73y500	Acroparaesthesia - Nothnagel's type
G73y511	Nothnagel's vasomotor acroparaesthesia
G73y600	Acroparaesthesia - unspecified
G73y700	Erythrocyanosis
G73y800	Erythromelalgia
G73y811	Erythralgia
G73yz00	Other specified peripheral vascular disease NOS
G73z.00	Peripheral vascular disease NOS
G73z000	Intermittent claudication
G73z011	Claudication
G73z012	Vascular claudication
G73z100	Spasm of peripheral artery

Read codes	Descriptor
G73zz00	Peripheral vascular disease NOS
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
G740.11	Aortic bifurcation syndrome
G740.12	Aortoiliac obstruction
G740.13	Leriche's syndrome
G740.14	Saddle embolus
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
G742A00	Post radiological embolism of upper limb artery
G742B00	Post radiological embolism of lower limb artery
G742z00	Peripheral arterial embolism and thrombosis NOS
G743.00	Embolism and thrombosis of other and unspec parts aorta
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
G75..00	Polyarteritis nodosa and allied conditions
G750.00	Polyarteritis nodosa

Read codes	Descriptor
G750.11	Necrotising angiitis
G751.00	Acute febrile mucocutaneous lymph node syndrome
G751000	Kawasaki disease
G751z00	Acute febrile mucocutaneous lymph node syndrome NOS
G752.00	Hypersensitivity angiitis
G752.11	Hypersensitivity arteritis
G752000	Goodpasture's syndrome
G752100	Goodpasture's disease
G752111	Antiglomerular basement membrane disease
G752112	Anti GBM disease - Antiglomerular basement membrane disease
G752z00	Hypersensitivity angiitis NOS
G753.00	Lethal midline granuloma
G754.00	Wegener's granulomatosis
G755.00	Giant cell arteritis
G755000	Cranial arteritis
G755100	Temporal arteritis
G755200	Horton's disease
G755z00	Giant cell arteritis NOS
G756.00	Thrombotic microangiopathy
G756000	Moschcowitz syndrome
G756100	Thrombotic thrombocytopenic purpura
G756z00	Thrombotic microangiopathy NOS
G757.00	Takayasu's disease
G757.11	Aortic arch arteritis
G757.12	Pulseless disease
G758.00	Churg-Strauss vasculitis
G759.00	Juvenile polyarteritis
G75A.00	Microscopic polyangiitis
G75X.00	Necrotising vasculopathy, unspecified
G75z.00	Polyarteritis nodosa and allied conditions NOS
G76..00	Other disorders of arteries and arterioles
G760.00	Acquired arteriovenous fistula
G761.00	Stricture of artery
G762.00	Rupture of artery
G762000	Aorto-duodenal fistula
G763.00	Hyperplasia of renal artery
G764.00	Coeliac artery compression syndrome
G764.11	Marable's syndrome
G765.00	Necrosis of artery
G766.00	Arteritis unspecified

Read codes	Descriptor
G766.11	Aortitis
G767.00	Aortitis - syphilitic
G768.00	Other disorders of arteries and arterioles
G768000	Fibromuscular hyperplasia of arteries NOS
G768100	Arterial fibromuscular dysplasia
G768z00	Other disorders of arteries and arterioles NOS
G769.00	Anterior spinal and vertebral artery compression syndromes
G76A.00	Arterial insufficiency
G76B.00	Vasculitis
G76z.00	Disorders of arteries and arterioles NOS
G76z000	Iliac artery occlusion
G76z100	Femoral artery occlusion
G76z200	Popliteal artery occlusion
G77..00	Diseases of capillaries
G770.00	Hereditary haemorrhagic telangiectasia
G770.11	Rendu - Osler - Weber disease
G7y..00	Other specified arterial, arteriole or capillary disease
G7z..00	Arterial, arteriole and capillary diseases NOS
Gyu7100	[X]Aortic aneurysm of unspecified site, ruptured
Gyu7200	[X]Aortic aneurysm of unspecified site, nonruptured
Gyu7400	[X]Other specified peripheral vascular diseases
Gyu7A00	[X]Peripheral angiopathy in diseases classified elsewhere
J420.18	Mesenteric thrombosis
K138000	Renal artery embolism
N200.00	Giant cell arteritis with polymyalgia rheumatica
Nyu4100	[X]Other giant cell arteritis
P76..00	Other peripheral vascular system anomalies
P76..11	Other congenital anomalies of peripheral arteries
P76..12	Other congenital anomalies of peripheral veins
P76y.00	Congenital anomaly of peripheral vascular system OS
P76yz00	Other congenital anomaly of peripheral vascular system NOS
P76z.00	Peripheral vascular system anomaly NOS
Pyu2B00	[X]Oth specified cong malform of peripheral vascular system
R054.00	[D]Gangrene
R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
R055000	[D]Failure of peripheral circulation
R055011	[D]Peripheral circulatory failure
SP12.00	Peripheral vascular complications of care
SP12z00	Peripheral vascular complications of care NOS

Appendix 1g. Read codes for IHD.

Read code	Descriptor
G3...00	Ischaemic heart disease
G3...11	Arteriosclerotic heart disease
G3...12	Atherosclerotic heart disease
G3...13	IHD - Ischaemic heart disease
G30..00	Acute myocardial infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30A.00	Mural thrombosis
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction

Read code	Descriptor
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome
G310.11	Dressler's syndrome
G311.00	Preinfarction syndrome
G311.11	Crescendo angina
G311.12	Impending infarction
G311.13	Unstable angina
G311.14	Angina at rest
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G311500	Acute coronary syndrome
G311z00	Preinfarction syndrome NOS
G312.00	Coronary thrombosis not resulting in myocardial infarction
G31y.00	Other acute and subacute ischaemic heart disease
G31y000	Acute coronary insufficiency
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G33..00	Angina pectoris
G330.00	Angina decubitus
G330000	Nocturnal angina
G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina

Read code	Descriptor
G331.11	Variant angina pectoris
G332.00	Coronary artery spasm
G33z.00	Angina pectoris NOS
G33z000	Status anginosus
G33z100	Stenocardia
G33z200	Syncope anginosa
G33z300	Angina on effort
G33z400	Ischaemic chest pain
G33z500	Post infarct angina
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
G34..00	Other chronic ischaemic heart disease
G340.00	Coronary atherosclerosis
G340.11	Triple vessel disease of the heart
G340.12	Coronary artery disease
G340000	Single coronary vessel disease
G340100	Double coronary vessel disease
G341.00	Aneurysm of heart
G341.11	Cardiac aneurysm
G341000	Ventricular cardiac aneurysm
G341100	Other cardiac wall aneurysm
G341111	Mural cardiac aneurysm
G341200	Aneurysm of coronary vessels
G341300	Acquired atrioventricular fistula of heart
G341z00	Aneurysm of heart NOS
G342.00	Atherosclerotic cardiovascular disease
G343.00	Ischaemic cardiomyopathy
G344.00	Silent myocardial ischaemia
G34y.00	Other specified chronic ischaemic heart disease
G34y000	Chronic coronary insufficiency
G34y100	Chronic myocardial ischaemia
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS

Read code	Descriptor
G34z000	Asymptomatic coronary heart disease
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G37..00	Cardiac syndrome X
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G382.00	Postoperative transmural myocardial infarction other sites
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G39..00	Coronary microvascular disease
G3y..00	Other specified ischaemic heart disease
G3z..00	Ischaemic heart disease NOS
14A3.00	H/O: myocardial infarct
14A4.00	H/O: myocardial infarct >60
14A5.00	H/O: angina pectoris
14AJ.00	H/O: Angina in last year
14AL.00	H/O: Treatment for ischaemic heart disease
322..00	ECG: myocardial ischaemia
3222.00	ECG:shows myocardial ischaemia
322Z.00	ECG: myocardial ischaemia NOS
3232.00	ECG: old myocardial infarction

Read code	Descriptor
3235.00	ECG: subendocardial infarct
323Z.00	ECG: myocardial infarct NOS
3889.00	Euroscore for angina
388E.00	Canadian Cardiovascular Society classification of angina
388F.00	Cardiovascular Limitations and Symptoms Profile angina score
662K.00	Angina control
662K000	Angina control - good
662K100	Angina control - poor
662K200	Angina control - improving
662K300	Angina control - worsening
662Kz00	Angina control NOS
68B2.00	Ischaemic heart disease screen
790H300	Revascularisation of wall of heart
792..00	Coronary artery operations
792..11	Coronary artery bypass graft operations
7920.00	Saphenous vein graft replacement of coronary artery
7920.11	Saphenous vein graft bypass of coronary artery
7920000	Saphenous vein graft replacement of one coronary artery
7920100	Saphenous vein graft replacement of two coronary arteries
7920200	Saphenous vein graft replacement of three coronary arteries
7920300	Saphenous vein graft replacement of four+ coronary arteries
7920y00	Saphenous vein graft replacement of coronary artery OS
7920z00	Saphenous vein graft replacement coronary artery NOS
7921.00	Other autograft replacement of coronary artery
7921.11	Other autograft bypass of coronary artery
7921000	Autograft replacement of one coronary artery NEC
7921100	Autograft replacement of two coronary arteries NEC
7921200	Autograft replacement of three coronary arteries NEC
7921300	Autograft replacement of four of more coronary arteries NEC
7921y00	Other autograft replacement of coronary artery OS
7921z00	Other autograft replacement of coronary artery NOS
7922.00	Allograft replacement of coronary artery
7922.11	Allograft bypass of coronary artery
7922000	Allograft replacement of one coronary artery

Read code	Descriptor
7922100	Allograft replacement of two coronary arteries
7922200	Allograft replacement of three coronary arteries
7922300	Allograft replacement of four or more coronary arteries
7922y00	Other specified allograft replacement of coronary artery
7922z00	Allograft replacement of coronary artery NOS
7923.00	Prosthetic replacement of coronary artery
7923.11	Prosthetic bypass of coronary artery
7923000	Prosthetic replacement of one coronary artery
7923100	Prosthetic replacement of two coronary arteries
7923200	Prosthetic replacement of three coronary arteries
7923300	Prosthetic replacement of four or more coronary arteries
7923y00	Other specified prosthetic replacement of coronary artery
7923z00	Prosthetic replacement of coronary artery NOS
7924.00	Revision of bypass for coronary artery
7924000	Revision of bypass for one coronary artery
7924100	Revision of bypass for two coronary arteries
7924200	Revision of bypass for three coronary arteries
7924300	Revision of bypass for four or more coronary arteries
7924400	Revision of connection of thoracic artery to coronary artery
7924y00	Other specified revision of bypass for coronary artery
7924z00	Revision of bypass for coronary artery NOS
7925.00	Connection of mammary artery to coronary artery
7925.11	Creation of bypass from mammary artery to coronary artery
7925000	Double anastomosis of mammary arteries to coronary arteries
7925100	Double implant of mammary arteries into coronary arteries
7925200	Single anast mammary art to left ant descend coronary art
7925300	Single anastomosis of mammary artery to coronary artery NEC
7925400	Single implantation of mammary artery into coronary artery
7925y00	Connection of mammary artery to coronary artery OS
7925z00	Connection of mammary artery to coronary artery NOS
7926.00	Connection of other thoracic artery to coronary artery
7926000	Double anastom thoracic arteries to coronary arteries NEC
7926100	Double implant thoracic arteries into coronary arteries NEC
7926200	Single anastomosis of thoracic artery to coronary artery NEC

Read code	Descriptor
7926300	Single implantation thoracic artery into coronary artery NEC
7926y00	Connection of other thoracic artery to coronary artery OS
7926z00	Connection of other thoracic artery to coronary artery NOS
7927.00	Other open operations on coronary artery
7927000	Repair of arteriovenous fistula of coronary artery
7927100	Repair of aneurysm of coronary artery
7927200	Transection of muscle bridge of coronary artery
7927300	Transposition of coronary artery NEC
7927400	Exploration of coronary artery
7927500	Open angioplasty of coronary artery
7927y00	Other specified other open operation on coronary artery
7927z00	Other open operation on coronary artery NOS
7928.00	Transluminal balloon angioplasty of coronary artery
7928.11	Percutaneous balloon coronary angioplasty
7928000	Percut transluminal balloon angioplasty one coronary artery
7928100	Percut translum balloon angioplasty mult coronary arteries
7928200	Percut translum balloon angioplasty bypass graft coronary a
7928y00	Transluminal balloon angioplasty of coronary artery OS
7928z00	Transluminal balloon angioplasty of coronary artery NOS
7929.00	Other therapeutic transluminal operations on coronary artery
7929000	Percutaneous transluminal laser coronary angioplasty
7929100	Percut transluminal coronary thrombolysis with streptokinase
7929111	Percut translum coronary thrombolytic therapy- streptokinase
7929200	Percut translum inject therap subst to coronary artery NEC
7929300	Rotary blade coronary angioplasty
7929400	Insertion of coronary artery stent
7929y00	Other therapeutic transluminal op on coronary artery OS
7929z00	Other therapeutic transluminal op on coronary artery NOS
792B.00	Repair of coronary artery NEC
792B000	Endarterectomy of coronary artery NEC
792By00	Other specified repair of coronary artery
792Bz00	Repair of coronary artery NOS
792C.00	Other replacement of coronary artery
792C000	Replacement of coronary arteries using multiple methods

Read code	Descriptor
792Cy00	Other specified replacement of coronary artery
792Cz00	Replacement of coronary artery NOS
792D.00	Other bypass of coronary artery
792Dy00	Other specified other bypass of coronary artery
792Dz00	Other bypass of coronary artery NOS
792y.00	Other specified operations on coronary artery
792z.00	Coronary artery operations NOS
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
88A8.00	Thrombolytic therapy
8B27.00	Antianginal therapy
G5y2.00	Cardiovascular arteriosclerosis unspecified
Gyu3000	[X]Other forms of angina pectoris
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3200	[X]Other forms of acute ischaemic heart disease
Gyu3300	[X]Other forms of chronic ischaemic heart disease
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Q494.00	Transient myocardial ischaemia of newborn
SP00300	Mechanical complication of coronary bypass
ZR37.00	Canadian Cardiovascular Society classification of angina
ZR3P.00	CLASP angina score
ZR3P.11	CLASP angina score
ZRB1.00	Euroscore for angina
ZV45700	[V]Presence of aortocoronary bypass graft
ZV45800	[V]Presence of coronary angioplasty implant and graft
ZV45K00	[V]Presence of coronary artery bypass graft
ZV45K11	[V]Presence of coronary artery bypass graft - CABG
ZV45L00	[V]Status following coronary angioplasty NOS

Appendix 1h. Read codes for stable angina.

Read code	Descriptor
14A5.00	H/O: angina pectoris
14AJ.00	H/O: Angina in last year
3889.00	Euroscore for angina
388E.00	Canadian Cardiovascular Society classification of angina
388F.00	Cardiovascular Limitations and Symptoms Profile angina score
662K000	Angina control - good
662K.00	Angina control
662K100	Angina control - poor
662K200	Angina control - improving
662K300	Angina control - worsening
662Kz00	Angina control NOS
8B27.00	Antianginal therapy
G33..00	Angina pectoris
G33z.00	Angina pectoris NOS
G33z300	Angina on effort
G33z500	Post infarct angina
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
Gyu3000	[X]Other forms of angina pectoris
ZR37.00	Canadian Cardiovascular Society classification of angina
ZR3P.00	CLASP angina score
ZR3P.11	CLASP angina score
ZRB1.00	Euroscore for angina

Appendix 2. Read codes for intracranial bleeding

Read	Descriptor
7004100	Evacuation of haematoma from temporal lobe of brain
7004200	Evacuation of haematoma from cerebellum
7004300	Evacuation of intracerebral haematoma NEC
7008200	Aspiration of haematoma of brain tissue
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G619.00	Lobar cerebral haemorrhage
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G681.00	Sequelae of intracerebral haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
7017000	Evacuation of subdural haematoma
7034.00	Drainage of subdural space
7034y00	Other specified drainage of subdural space
7034z00	Drainage of subdural space NOS
G621.00	Subdural haemorrhage - nontraumatic
G622.00	Subdural haematoma - nontraumatic
G623.00	Subdural haemorrhage NOS
S62..13	Subdural haemorrhage following injury
S622.00	Closed traumatic subdural haemorrhage
S622000	Subdural h'ge inj no open intracranial wnd + unspec consc
S622100	Subdural h'ge inj no open intracranial wound+no loss consc
S622200	Subdural h'ge inj no open intracranial wound+<1hr loss consc
S622300	Subdural h'ge inj no open intracran wnd+1-24hr loss consc
S622400	Subdural h'ge inj no open intracranial wnd+>24 LOC +recovery
S622500	Subdural h'ge inj no open intracran wnd+>24hr LOC -restored

S622600	Subdural h'ge inj no open intracran wnd+LOC unspec duration
S622z00	Subdural h'ge inj no open intracran wound+concussion unspec
S623.00	Open traumatic subdural haemorrhage
S623000	Subdural h'ge inj + open intracranial wound + unspec consc
S623100	Subdural h'ge inj + open intracranial wound+no loss consc
S623200	Subdural h'ge inj + open intracranial wound+<1hr loss consc
S623300	Subdural h'ge inj + open intracranial wnd+1-24hr loss consc
S623400	Subdural h'ge inj + open intracran wound+>24hr LOC +recovery
S623500	Subdural h'ge inj + open intracran wnd+>24hr LOC -restored
S623600	Subdural h'ge inj + open intracran wnd+LOC unspec duration
S623z00	Subdural h'ge inj + open intracranial wnd+concussion unspec
S628.00	Traumatic subdural haemorrhage
S629.00	Traumatic subdural haematoma
S629000	Traumatic subdural haematoma without open intracranial wound
S629100	Traumatic subdural haematoma with open intracranial wound
G60..00	Subarachnoid haemorrhage
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
G60z.00	Subarachnoid haemorrhage NOS
G680.00	Sequelae of subarachnoid haemorrhage
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
S62..12	Subarachnoid haemorrhage following injury
S620.00	Closed traumatic subarachnoid haemorrhage
S620000	Subarachnoid h'ge inj no open intracran wound + unspec consc
S620100	Subarachnoid h'ge inj no open intracran wnd+no loss consc
S620200	Subarachnoid h'ge inj no open intracran wnd+<1hr loss consc
S620300	Subarachnoid h'ge inj no open intracran wound + 1-24hr LOC
S620400	Subarachnoid h'ge inj no open intracran wnd+>24 LOC+recovery
S620500	Subarach h'ge inj no open intracran wnd+>24hrs LOC-restored
S620600	Subarach h'ge inj no open intracran wnd+LOC unspec duration
S620z00	Subarach h'ge inj no open intracran wnd + concussion unspec
S621.00	Open traumatic subarachnoid haemorrhage
S621000	Subarachnoid h'ge inj + open intracran wound + unspec consc
S621100	Subarachnoid h'ge inj + open intracranial wound + no LOC
S621200	Subarachnoid h'ge inj + open intracran wound+<1hr loss consc

S621300	Subarachnoid h'ge inj + open intracran wnd+1-24hr loss consc
S621400	Subarach h'ge inj + open intracran wnd +>24hr LOC + recovery
S621500	Subarach h'ge inj + open intracran wnd+>24hr LOC -restored
S621600	Subarach h'ge inj + open intracran wnd+LOC unspec duration
S621z00	Subarachnoid h'ge inj + open intracran wnd+concussion unspec
S627.00	Traumatic subarachnoid haemorrhage
7032000	Evacuation of extradural haematoma
G600.00	Ruptured berry aneurysm
G62..00	Other and unspecified intracranial haemorrhage
G620.00	Extradural haemorrhage - nontraumatic
G62z.00	Intracranial haemorrhage NOS
G682.00	Sequelae of other nontraumatic intracranial haemorrhage
Gyu6B00	[X]Sequelae of other nontraumatic intracranial haemorrhage
S62..00	Cerebral haemorrhage following injury
S62..11	Extradural haemorrhage following injury
S62..14	Traumatic cerebral haemorrhage
S620.11	Middle meningeal haemmorhage following injury
S624.00	Closed traumatic extradural haemorrhage
S624.11	Epidural haematoma following injury
S624000	Extradural h'ge inj no open intracranial wnd + unspec consc
S624100	Extradural h'ge inj no open intracranial wnd + no loss consc
S624200	Extradural h'ge inj no open intracranial wnd+<1hr loss consc
S624300	Extradural h'ge inj no open intracran wnd+1-24hr loss consc
S624400	Extradural h'ge inj no open intracran wnd+>24hr LOC+recovery
S624500	Extradural h'ge inj no open intracran wnd+>24hr LOC-restored
S624600	Extradural h'ge inj no open intracra wnd+LOC unspec duration
S624z00	Extradural h'ge inj no open intracran wnd+concussion unspec
S625.00	Open traumatic extradural haemorrhage
S625000	Extradural h'ge inj + open intracranial wnd + unspec consc
S625100	Extradural h'ge inj + open intracranial wound+no loss consc
S625200	Extradural h'ge inj + open intracranial wnd+<1hr loss consc
S625300	Extradural h'ge inj + open intracran wnd+1-24hr loss consc
S625400	Extradural h'ge inj + open intracran wnd+>24hr LOC+recovery
S625500	Extradural h'ge inj + open intracran wnd+>24hr LOC -restored
S625600	Extradural h'ge inj + open intracran wnd+LOC unspec duration
S625z00	Extradural h'ge inj + open intracran wnd+concussion unspec
S626.00	Epidural haemorrhage
S62A.00	Traumatic extradural haematoma
S62A000	Traumatic extradural haemat without open intracranial wound
S62A100	Traumatic extradural haematoma with open intracranial wound
S62z.00	Cerebral haemorrhage following injury NOS
S63..00	Other cerebral haemorrhage following injury

S630.00	Other cerebral h'ge after injury no open intracranial wound
S630.11	Cerebral compression due to injury
S630.12	Intracranial haematoma following injury
S630000	Oth cerebral h'ge inj no open intracran wnd+unspec consc
S630100	Oth cerebral h'ge inj no open intracranial wnd+no loss consc
S630200	Oth cerebral h'ge inj no open intracran wnd+<1hr loss consc
S630300	Oth cerebral h'ge inj no open intracran wnd+1-24hr LOC
S630400	Oth cereb h'ge inj no open intracran wnd+>24hr LOC +recovery
S630500	Oth cereb h'ge inj no open intracran wnd+>24hr LOC -restored
S630600	Oth cereb h'ge inj no open intracran wnd+LOC unspec duration
S630z00	Oth cereb h'ge inj no open intracran wnd+concussion unspec
S631.00	Other cerebral h'ge after injury + open intracranial wound
S631000	Oth cerebral h'ge inj + open intracran wnd + unspec consc
S631100	Oth cerebral h'ge inj + open intracranial wnd+no loss consc
S631200	Oth cerebral h'ge inj + open intracran wnd+<1hr loss consc
S631300	Oth cerebral h'ge inj + open intracran wnd+1-24hr loss consc
S631400	Oth cereb h'ge inj + open intracran wnd+>24hr LOC + recovery
S631500	Oth cereb h'ge inj + open intracran wnd+>24hr LOC -restored
S631600	Oth cereb h'ge inj + open intracran wnd+LOC unspec duration
S631z00	Oth cereb h'ge inj + open intracran wnd+concussion unspec
S63z.00	Other cerebral haemorrhage following injury NOS

Appendix 3. Read codes for upper gastrointestinal bleeding

Read	Descriptor
14C8.00	H/O: haematemesis
14C9.00	H/O: melaena
1994.11	Blood in vomit - symptom
19E4.12	C/O - melaena
4737.11	Melaena - O/E of faeces
4A23.00	Vomit: frank blood present
4A23.11	Blood in vomit O/E
4A24.00	Vomit: coffee ground
4A24.11	Coffee ground vomit
4A5..00	Vomit occult blood
4A5..11	Occult blood in vomit
4A51.00	Vomit occult blood positive
4A5Z.00	Vomit occult blood NOS
J110100	Acute gastric ulcer with haemorrhage
J110111	Bleeding acute gastric ulcer
J110300	Acute gastric ulcer with haemorrhage and perforation
J110400	Acute gastric ulcer with obstruction
J111100	Chronic gastric ulcer with haemorrhage
J111111	Bleeding chronic gastric ulcer
J111300	Chronic gastric ulcer with haemorrhage and perforation
J111400	Chronic gastric ulcer with obstruction
J11y100	Unspecified gastric ulcer with haemorrhage
J11y300	Unspecified gastric ulcer with haemorrhage and perforation
J11y400	Unspecified gastric ulcer with obstruction
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
J120100	Acute duodenal ulcer with haemorrhage
J120300	Acute duodenal ulcer with haemorrhage and perforation
J120400	Acute duodenal ulcer with obstruction
J121100	Chronic duodenal ulcer with haemorrhage
J121111	Bleeding chronic duodenal ulcer
J121300	Chronic duodenal ulcer with haemorrhage and perforation
J121400	Chronic duodenal ulcer with obstruction
J12y100	Unspecified duodenal ulcer with haemorrhage
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
J12y400	Unspecified duodenal ulcer with obstruction
J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
J130100	Acute peptic ulcer with haemorrhage
J130300	Acute peptic ulcer with haemorrhage and perforation
J130400	Acute peptic ulcer with obstruction
J131100	Chronic peptic ulcer with haemorrhage
J131300	Chronic peptic ulcer with haemorrhage and perforation
J131400	Chronic peptic ulcer with obstruction
J13y100	Unspecified peptic ulcer with haemorrhage
J13y300	Unspecified peptic ulcer with haemorrhage and perforation
J13y400	Unspecified peptic ulcer with obstruction
J13yy00	Unspec peptic ulcer; unspec haemorrhage and/or perforation
J140100	Acute gastrojejunal ulcer with haemorrhage

J140300	Acute gastrojejunal ulcer with haemorrhage and perforation
J140400	Acute gastrojejunal ulcer with obstruction
J141100	Chronic gastrojejunal ulcer with haemorrhage
J141300	Chronic gastrojejunal ulcer with haemorrhage and perforation
J141400	Chronic gastrojejunal ulcer with obstruction
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J14y300	Unspec gastrojejunal ulcer with haemorrhage and perforation
J14y400	Unspecified gastrojejunal ulcer with obstruction
J14yy00	Unspec gastrojejunal ulcer; unspec haemorrhage/perforation
J150000	Acute haemorrhagic gastritis
J68..00	Gastrointestinal haemorrhage
J680.00	Haematemesis
J680.11	Vomiting of blood
J681.00	Melaena
J681.11	Blood in stool
J681.12	Altered blood in stools
J681.13	Blood in stools altered
J68z.00	Gastrointestinal haemorrhage unspecified
J68z.11	GIB - Gastrointestinal bleeding
J68z000	Gastric haemorrhage NOS
J68z100	Intestinal haemorrhage NOS
J68z200	Upper gastrointestinal haemorrhage
J68zz00	Gastrointestinal tract haemorrhage NOS
1994.00	Vomiting blood - fresh
1995.00	Vomiting blood - coffee ground
J110200	Acute gastric ulcer with perforation
J111200	Chronic gastric ulcer with perforation
J111211	Perforated chronic gastric ulcer
J11y200	Unspecified gastric ulcer with perforation
J120200	Acute duodenal ulcer with perforation
J121200	Chronic duodenal ulcer with perforation
J121211	Perforated chronic duodenal ulcer
J12y200	Unspecified duodenal ulcer with perforation
J130200	Acute peptic ulcer with perforation
J131200	Chronic peptic ulcer with perforation
J13y200	Unspecified peptic ulcer with perforation
J13yy00	Unspec peptic ulcer; unspec haemorrhage and/or perforation
J140200	Acute gastrojejunal ulcer with perforation
J141200	Chronic gastrojejunal ulcer with perforation
J14y200	Unspecified gastrojejunal ulcer with perforation

Appendix 4. Read codes for lower gastrointestinal bleeding

Read	Descriptor
4737.11	Melaena - O/E of faeces
14C9.00	H/O: melaena
19E4.12	C/O - melaena
J140100	Acute gastrojejunal ulcer with haemorrhage
J140400	Acute gastrojejunal ulcer with obstruction
J141100	Chronic gastrojejunal ulcer with haemorrhage
J141400	Chronic gastrojejunal ulcer with obstruction
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J14y400	Unspecified gastrojejunal ulcer with obstruction
J510900	Bleeding diverticulosis
J573.00	Haemorrhage of rectum and anus
J573.11	Bleeding PR
J573000	Rectal haemorrhage
J573011	Rectal bleeding
J573012	PRB - Rectal bleeding
J573100	Anal haemorrhage
J573z00	Haemorrhage of rectum and anus NOS
J68..00	Gastrointestinal haemorrhage
J681.00	Melaena
J681.11	Blood in stool
J681.12	Altered blood in stools
J681.13	Blood in stools altered
J68z.00	Gastrointestinal haemorrhage unspecified
J68z.11	GIB - Gastrointestinal bleeding
J68z100	Intestinal haemorrhage NOS
J68zz00	Gastrointestinal tract haemorrhage NOS

Annex 4. Signature pages

Bayer HealthCare

Signature Page – Study conduct responsible - CEIFE

Title	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Protocol version identifier	V3
Date of last version of protocol	30 June 2015
IMPACT study number	18116
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product) *(if a device, please adapt accordingly)*	Acetylsalicylic acid
Marketing authorization holder(s)	Bayer Healthcare AG

Function	Spanish Centre for Pharmacoepidemiologic Research CEIFE
Name	Luis A Garcia Rodriguez
Title	Epidemiologist, Director CEIFE
Address	Almirante, 28, 2, 28004 Madrid, Spain

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Bayer HealthCare

Signature Page – Study conduct responsible/study epidemiologist - Global Epidemiology

Title	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Protocol version identifier	V3
Date of last version of protocol	30 June 2015
IMPACT study number	18116
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product) *(if a device, please adapt accordingly)*	Acetylsalicylic acid
Marketing authorization holder(s)	Bayer Healthcare AG

Function	Global Epidemiology
Name	Montse Soriano Gabarro
Title	Epidemiologist
Address	Bayer Pharma AG, Muellerstr. 178, 13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Bayer HealthCare

Signature Page – Medical Expert - Global Medial Affairs

Title	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Protocol version identifier	V3
Date of last version of protocol	30 June 2015
IMPACT study number	18116
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product) *(if a device, please adapt accordingly)*	Acetylsalicylic acid
Marketing authorization holder(s)	Bayer Healthcare AG

Function	Global Medical Affairs
Name	Elmar Detering
Title	Global Medical Affairs Physician
Address	Bayer Pharma AG, Muellerstr. 178, 13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Bayer HealthCare

Signature Page – Study Safety Leader – Global Pharmacovigilance

Title	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Protocol version identifier	V3
Date of last version of protocol	30 June 2015
IMPACT study number	18116
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product) *(if a device, please adapt accordingly)*	Acetylsalicylic acid
Marketing authorization holder(s)	Bayer Healthcare AG

Function	Global Pharmacovigilance
Name	Eddy Nkwepo
Title	Global Safety Leader
Address	Bayer HealthCare Pharmaceuticals Inc, 100 Bayer Boulevard, P.O. Box 915 Whippany, NJ 07981-0915, USA

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Bayer HealthCare

Signature Page – Study statistician- Clinical Statistics

Title	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Protocol version identifier	V3
Date of last version of protocol	30 June 2015
IMPACT study number	18116
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product) *(if a device, please adapt accordingly)*	Acetylsalicylic acid
Marketing authorization holder(s)	Bayer Healthcare AG

Function	Clinical Statistics
Name	Akos Ferenc Pap
Title	Statistician
Address	Bayer Pharma AG, Muellerstr. 178, 13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Bayer HealthCare

Signature Page – Regulatory strategist - Global Regulatory Affairs

Title	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Protocol version identifier	V3
Date of last version of protocol	30 June 2015
IMPACT study number	18116
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product) *(if a device, please adapt accordingly)*	Acetylsalicylic acid
Marketing authorization holder(s)	Bayer Healthcare AG

Function	Global Regulatory Affairs
Name	Artur Lutfullin
Title	Global Regulatory Strategist
Address	Bayer Pharma AG, Muellerstr. 178, 13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Bayer HealthCare

Signature Page – Clinical Development - Global Clinical Development

Title	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Protocol version identifier	V3
Date of last version of protocol	30 June 2015
IMPACT study number	18116
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product) *(if a device, please adapt accordingly)*	Acetylsalicylic acid
Marketing authorization holder(s)	Bayer Healthcare AG

Function	Global Clinical Development
Name	Ru Fong Cheng
Title	Global Clinical Lead
Address	Bayer HealthCare Pharmaceuticals Inc, 100 Bayer Boulevard, P.O. Box 915 Whippany, NJ 07981-0915, USA

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Bayer HealthCare

Signature Page – Qualified Person responsible for Pharmacovigilance (QPPV) - QPPV office

Title	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Protocol version identifier	V3
Date of last version of protocol	30 June 2015
IMPACT study number	18116
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product) *(if a device, please adapt accordingly)*	Acetylsalicylic acid
Marketing authorization holder(s)	Bayer Healthcare AG

Function	QPPV office
Name	Michael Kayser
Title	Qualified Person responsible for Pharmacovigilance (QPPV)
Address	Bayer Pharma AG, Muellerstr. 178, 13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____