NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY PROTOCOL
PASS information

Title	Incidence and pattern description of gastrointestinal, skin, genital, corneal, and mucosal erosions, ulcerations , perforations, haemorrhages, fistulas, abscesses, delayed wound healing and death among patients treated with nicorandil with and without diverticular disease
Study protocol number	EMR200101_502
Protocol version identifier	Rev 4.3
Date of last version of protocol	20/04/2015
EU PAS register number	n/a
Active substance	Nicorandil (ATC: C01DX16)
Medicinal product	Ikorel, Dancor, Adancor, Nicorandil Zentiva, Angicor
Product reference	C01DX16
Procedure number	UK/H/xxxx/WS/100
Marketing authorisation holder(s) in EU	Merck KGaA PPD
License holder outside EU	PPD
Joint PASS	Yes
Research question and objectives	To quantify the time-related risk (ie the incidence) and patterns of erosions, ulcerations, perforations, haemorrhages, abscesses, fistulae, delayed wound healing in patients treated with nicorandil (including but not restricted to gastrointestinal, skin, ocular, mucosal, anal; alone or in multiple locations), and death in a real world setting; together with the exploration of high risk subgroups (including patients with diverticular disease), other risk factors, and a dose & time effect assessment.
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2 List of Abbreviations

ATC– Anatomical Therapeutic Classification

CI – Confidence Intervals

CPRD – Clinical Practice Research Datalink

DAYSUPP: Days Supplied For. The time a patient receives a drug following a prescription, 1 DAYSUPP=30 days for Nicorandil in this study.

EU PSUR - European Periodic Safety Update Report

GI – Gastrointestinal

MAH: Marketing Authorization Holder

PUFAEDG – Perforation, Ulcer, Fistula, Abscess, Erosion, Diverticulosis, Diverticulitis, Death, Delayed wound healing, Gastrointestinal haemorrhage

RMP – Risk management Plan

UK – United Kingdom

3 Responsible Parties

PPD Merck KGaA, Darmstadt (design, protocol, statistical analysis plan, data collection and analysis, report, funding)

PPD PPD PPD (protocol, statistical analysis plan, report, funding)

PPD PPD PPD (protocol, statistical analysis plan, report, funding)

PPD , PPD (statistical analysis plan, analytics and quality check)

4 Abstract

Incidence of gastrointestinal, skin, genital, corneal, and mucosal ulcerations and related erosions, perforations, haemorrhages, fistulas and abscesses among patients treated with nicorandil

Rationale and background
Nicorandil is a treatment approved for the prevention and management of angina pectoris. Important identified risks of nicorandil are ulcerations at different locations of the body (including GI, skin, genital, mucosal, conjunctival and corneal ulcerations) and related events (including perforations, fistula, abscess and GI haemorrhage). The current SMPC states: "Gastrointestinal ulcerations, skin and mucosal ulcerations have been reported with Nicorandil use". One of the recommendations from the EU PSUR Work Sharing (Procedure No AT/H/PSUR /0023/002) for nicorandil concerned the introduction of a risk management plan including an outline of a post-authorization safety study as a pharmacovigilance measure in order to quantify the risk of ulceration (including all sites of occurrence), and related events (including perforations, fistula,

abscess and GI haemorrhage) and identify any high risk subgroups. For this purpose, the MAHs designed a retrospective cohort study to be conducted using the UK Clinical Practice Research Datalink (CPRD) database.

Research question and objectives
The purpose of this study is to quantify the time-related risk (ie the incidence) and patterns of erosions, ulcerations, perforations, haemorrhages, abscesses, fistulae, delayed wound healing in patients treated with nicorandil (including but not restricted to gastrointestinal, skin, ocular, mucosal, anal; alone or in multiple locations), and death in a real world setting; together with the exploration of high risk subgroups (including patients with diverticular disease), other risk factors, and a dose & time effect assessment.

Study design
This is a retrospective cohort study using secondary data. The design of the study is purely descriptive, making use of electronic medical records data from the UK longitudinal general practitioner database CPRD. A comparison group is not included. The inclusion criteria will be: patients aged 18 and older, with a diagnosis of angina pectoris between Jan 1995 and Dec 2014, and an initial prescription for Nicorandil. They will be longitudinally followed-up until end of observation period or death (whichever occurs first). Exposure will be determined individually for each patient as the number of days between first Nicorandil prescription and discontinuation, death or end of observation period. Outcomes of interest will include Perforation, Ulcer, Fistula, Abscess, Erosion, Diverticulosis, Diverticulitis, Death, Delayed wound healing, gastrointestinal haemorrhage (PUFAEDG). Standard descriptive statistics and Kaplan-Meier time to event assessment will be used. The main outcomes will be the incidence rates and 95% confidence intervals for the outcomes of interest, as stratified by variables (see below). For continuous variables, the sample size, mean, median, Q1, Q3, standard deviation and range (minimum, maximum) will be provided. Frequency distributions will be provided for categorical variables.

Population and Study size
According to preliminary counts, the study will include around 40,000 female and male subjects aged 18 years and more, who had preliminary diagnosis of angina pectoris originating from a representative setting for the UK primary health care setting. Given its observational nature, no a priori sample-size calculation will be performed.

Variables
Variables will include gender, age, nicorandil dose and exposure, compliance to nicorandil, comorbidities and Charlson´s comorbidities index, prevalent diverticular disease, concomitant medications, previous history of any outcome of interest, smoking status, alcohol consumption, body mass index, calendar year as well as an exhaustive list of potential risk factors for the outcomes of interest.

Planned Analyses
Descriptive analytics will be provided for baseline (3 months before first nicorandil prescription), the exposure to Nicorandil (from first prescription treatment discontinuation, database censoring or death), the total database exposure (From first prescription to death or database or censoring) periods on all considered variables.
The primary data analysis will consist of calculating incidence rates and their 95% CI per 100,000 person-years for unique or multiple PUFAEDG in patients with Nicorandil during the exposure period. A top-down approach will be used in terms of grouping for each subcategory of events, ie all perforation events grouped together followed by organ-level estimates, followed by specific coding terms. Outcome calculation will also be grouped by anatomical location and multiplicity of events. Kaplan-Meier curves will be generated for each outcome.
The secondary analytic phase will concentrate on patients who had a first PUFAEDG within the 3 months before first Nicorandil prescription (prevalent condition during the baseline period) versus those who did not. Incidence rates for further unique or multiple PUFAEDG and their 95% CI per 100,000 person-years, in patients using Nicorandil will be calculated following a similar top-down approach and grouping of outcomes. The identified sequences of outcomes will be assessed as the incidences of each specific pattern of events found in the analysis patterns of events. A dedicated subanalysis will be performed on patients presenting pre-existing or incidental diverticulosis or diverticulitis. Kaplan-Meier curves will be generated for each outcome.
The third analytic phase will focus on the variables associated with events and events sequences (as independent variable) against all the dependent variables cited above. A dedicated subanalysis will be

performed on patients presenting prevalent or incidental diverticulosis or diverticulitis. Cox proportional hazards models will be fitted to estimate the differential impact of these variables in the risk of developing each outcome of interest grouped as PUFAEDG.

5 Amendments and Updates

Version	Date	Section of study protocol	Amendment or update	Reason

6 Milestones

Milestone	Planned date*
Protocol submission	End of April 2015
Start of data collection	Upon authorities approval; Q3 2015
End of data collection	8 weeks after authorities approval; Q4 2015
Final Report of Study Results	Within 20 weeks of finalising analysis of study data Anticipated for Q1 2016

* * These are anticipated timelines, which depend on the approval date of the study protocol by competent authorities. If protocol approval is later than the beginning of Q3 2015, the timelines for study start, final analysis of study data and submission of study report will be shifted accordingly.
Q = quarter (Q1 first quarter; Q2 second quarter; Q3 third quarter; Q4 fourth quarter)

7 Rationale and Background

Myocardial ischemia is one of the common causes of disability, reduced quality of life and death in adults. Angina pectoris, or angina for short, is the term used when chest pain is thought to be attributable to myocardial ischemia. In patients with myocardial ischemia, chest pain is often but not always present, although other associated symptoms with ischemia may be present (such as exertional shortness of breath, nausea, diaphoresis, fatigue). This has been termed "silent ischemia," although it may be more accurately termed "painless ischemia."

Angina can be subdivided further into two categories: angina of effort (stable angina) and variant angina (unstable angina). Stable angina is a common disorder caused by the narrowing of the arteries (atherosclerosis) that supply oxygen-rich blood to the heart muscle. In the case of angina of effort, the heart (coronary) arteries can provide the heart muscle (myocardium) adequate blood during rest but not during periods of exercise, stress, or excitement—any of which may precipitate pain. Patients with angina of effort have an increased risk of myocardial infarction. Unstable angina is less common and may occurs even independently of atherosclerosis. Unstable angina occurs at rest, and may be sometimes caused by coronary artery muscle spasm of variable duration or intensity. Unstable angina can have a variety of different presentations which may correlate with prognosis in the absence of intervention. Regardless of type, the risk is greatest with angina that is refractory to or occurs despite maximal medical therapy and with an

accelerating tempo of ischemic symptoms in the preceding 48 hours (crescendo angina). Unstable angina can be classified in several categories: new onset angina, rest angina, early post-myocardial infarction angina, postrevascularization angina, periprocedural angina and late angina [1].

Nicorandil (2-[(pyridin-3-ylcarbonyl)amino]ethyl nitrate) is a treatment approved for the prevention and management of angina pectoris. It is marketed under the trade names Dancor, Adancor, Angicor, Ikorel and Nicorandil Zentiva in the European Economic Area. Nicorandil is a nicotinamide ester with a dual mechanism of action. Its distinctive pharmacological effect is to open ATP-sensitive potassium channels (KATP), thereby dilating peripheral and coronary resistance arterioles; but it also possesses a nitrate moiety which dilates systemic veins and epicardial coronary arteries. Thus, nicorandil increases coronary blood flow, reduces preload and after-load, and has an antianginal efficacy and safety profile similar to that of oral nitrates, β-blockers, and calcium antagonists [2].

The efficacy of Nicorandil has been evaluated in multiple randomized controlled trials, a recent meta-analysis [3], and a large-scale observational study conducted in Japan in 2010 [4]. Case reports of ulcerations and related perforations, fistula, abscess have been reported at various mucocutaneous localizations [5-22]. Campolmi et al. initially reported a case of corneal perforation associated with mucocutaneous ulcer during treatment course [12]. In addition to ulcerations and perforations, several cases of fistula into adjacent organs, for example, orocutaneous and rectovaginal fistula, have also been described [17, 18]. It has been reported that the ulcerations develop several days to years during the treatment course with nicorandil and that treatment discontinuation allowed for case resolution. For example, in three case studies apthous ulcers developed following a median duration of 12 months, ranging from 2-36 months whereas corneal ulcers developed following a mean duration of only 30 days, after initiation of nicorandil treatment [9,10,11]. Using the central hospital and community pharmacy database in UK for years 2004-10, Colvin et al. estimated the mean annual incidence of anal ulcers among nicorandil users as 0.37% [6]. With an exception to this, no large-scale observational study has been performed to examine the incidence of these specific outcomes.

8 Research Question and Objectives

Primary:

- The primary purpose of this study is to determine the time-related frequency (i.e. the incidence) and patterns of Perforation, Ulcer, Fistula, Abscess, Erosion, Diverticulosis, Diverticulitis, Death, Delayed wound healing, Gastrointestinal hemorrhage (PUFAEDG) in patients with angina who are receiving Nicorandil treatment.

Secondary:

- To describe the patterns of PUFAEDG as unique or multiple events in patients with angina who are receiving Nicorandil (including recurrence, progression and reversibility of events).

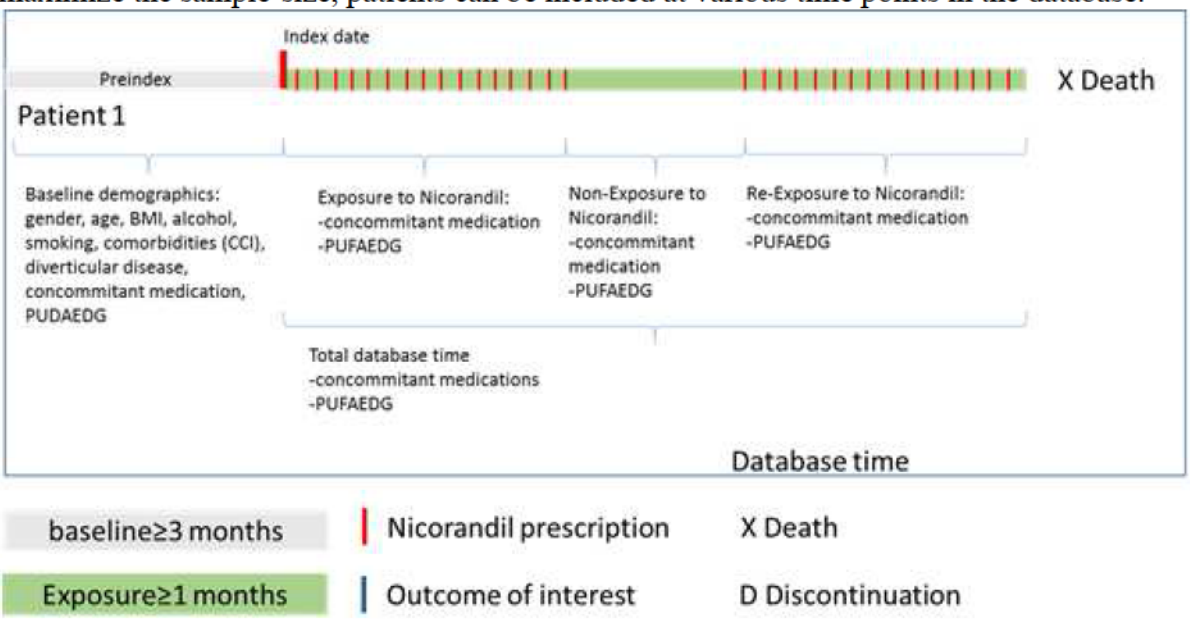
- To describe the incidences of PUFAEDG in patients with angina who are receiving Nicorandil with specific baseline or acquired conditions, including diverticular disease and concomitant treatments.

- To explore high risk subgroups for the development of PUFAEDG with angina who are receiving Nicorandil according to the following variables: age, gender, Nicorandil dose, treatment duration, calendar year, Charlson´s comorbidity index history of any outcome of interest, diabetes, Helicobacter pylori infection, Zollinger-Ellison syndrome, smoking and use of NSAIDs (including acetylsalicylic acid), diverticular disease, heart failure, diabetes, alcohol use, smoking, use of corticosteroids, NSAIDs or selective serotonin re-uptake inhibitors (SSRIs), corticosteroids use, trauma, chemical injury, contact lenses, Impaired blood circulation, bacterial, viral or fungal infections , diabetes, tumours.

9 Research Methods

9.1 Study Design

This is a retrospective cohort study, featuring accrual exposure assessment, i.e. each included patient will contribute his/her own person-time in the analysis data cut. In this study design, and to maximize the sample-size, patients can be included at various time points in the database.



Each of the patient´s contribution is summarised as key events: preindex (the period of time when the patient has angina pectoris but not on Nicorandil, which has to be minimum 3 months), index date (the exact day the patient received his/her first Nicorandil prescription), and exposure time(s). Exposure times can be classified as Nicorandil exposure time (the time patients received regular prescriptions for Nicorandil (minimum 1 month per minimum days covered by a single prescription) until death, end of database time (database censoring), or discontinuation. The database time ranges from index date to death or database censoring.

Example

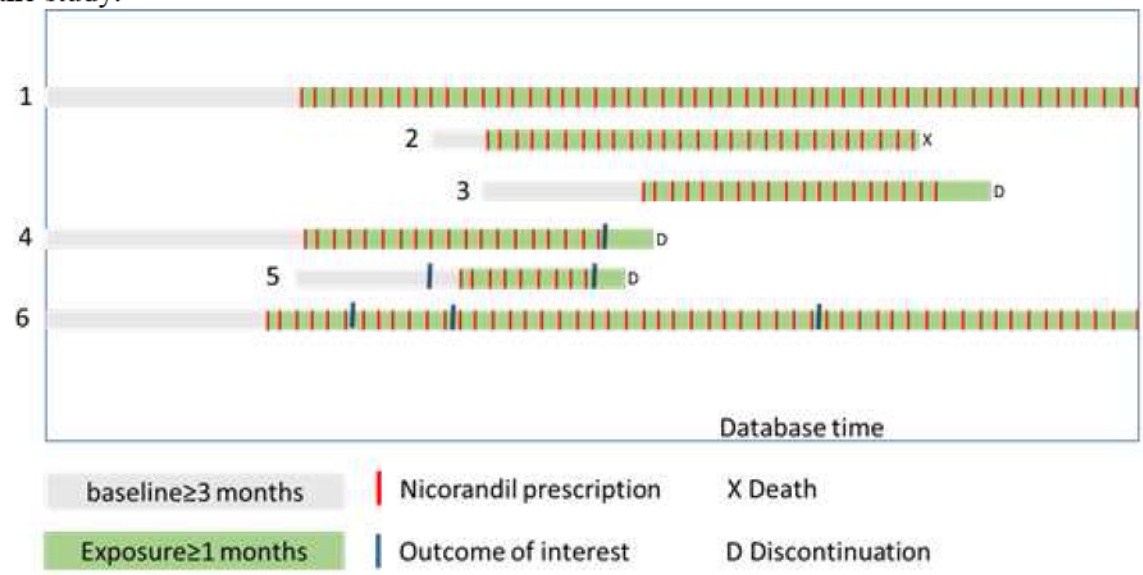
Assumptions regarding exposure and outcomes

- Patients are followed until death or database censoring. Database time consists in (Nicorandil exposure + non-exposure)
- Nicorandil exposure being calculated on the basis of prescriptions, a 60 days period is added to the last known date of prescription for patients who discontinue before Dec 31 2014. That is a conservative assumption extending Nicorandil exposure 30 days beyond most likely drug discontinuation date.
- Patients have 100% observance (i.e. patients take all the prescribed medication)
- Discontinuation is defined as a period of 3 or more consecutive months (3 DAYSUPP) without Nicorandil prescription
- An outcome of interest (PUFAEDG) is counted in the numerator only if it occurs during

Nicorandil exposure (accounting for the potential 60 days post discontinuation period).

Examples

This chart below represents the various patterns of inclusion and censoring of patients, while taking events into account. The following fictive verbatims explain the inclusion and outcome logic within the study.



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9.2 Setting, Inclusion and Exclusion Criteria

Setting

This study will be conducted using the Clinical Practice Research Datalink (CPRD), including data collected by General Practitioners of 681 practices around the UK accounting for 13 million total patients, 5.7 million of which are currently active. This is a patient-level data study including any individual aged 18 years registered in the NHS seen in a representative sample of primary practises in the UK. CPRD being part of the NHS, the data collection is systematic and the language used (READ codes) very specific. The database includes demographics, lifestyle (BMI, smoking habits, alcohol consumption, dietary guidance), diagnostics, prescriptions and procedures over time for any citizen registered into the NHS and over time. The longitudinal aspect of the licensed segment of the database (1995-2014) allows for an almost optimal capture of any patient treated in a designated geographic area, provided that the drug was launched in the UK in 1994.

Inclusion Criteria

The proposed study will include patients:

-aged ≥18 years when they receive an initial Nicorandil prescription (index date)
-have a diagnosis of angina pectoris (see annex 3 of the present document) before index date
-who have an index date between April 1995 and Nov 2014
-who have at least 3 months of Nicorandil-free period before initial prescription
-and at least one month of eligibility after initial prescription

Exclusion Criteria
None

Study Period: 1/1/1995 to 31/12/2014 (up to 19 years)

Treatment initiation date / index date: Date of first Nicorandil prescription

Discontinuation: Discontinuation will be defined as a minimum of 3 months without Nicorandil prescriptions till death or database end (31 December 2014)

Comorbidities: The Charlson´s comorbidity index will be used over baseline and exposure period to assess patients' general medical condition [23]. Specific interest will also be given to subgroups of patients with a history of any outcome, and patient's with diverticular disease.

Nicorandil dose: The Nicorandil dose prescribed will be derived from the ATC and database information on treatment. Dose will be categorized as ≤ 20mg/day, 20-40mg/day and > 40mg/day. For patients who experience PUFAEDG the latest recorded dose and average dose prescribed will be considered. For patients without outcomes, the latest dose recorded in the Nicorandil period and the average dose will be considered.

Age: Age as on index date

Compliance: Compliance will be calculated using medication possession ratio (MPR) and a patient will be considered compliant if his/her MPR is above 80% for the last treatment pattern before study end, death or censoring due to Nicorandil discontinuation. Compliance will be used as a stratification variable in the evaluation of the risk incidences and as a variable in the multivariate approach.

Duration of therapy: Duration of therapy is derived from the prescriptions recorded in the database. Duration of therapy is the sum of the days supplied for (DAYSUPP) by prescriptions. In the eventuality of discontinuation and an event occurring after, duration of therapy is added a 1 month buffer period after the last day covered by prescription.

Outcomes of interest: Perforations, Ulcer, Fistula, Abscesses, Erosions, Diverticulosis, Diverticulitis, Death, Delayed wound healing, gastrointestinal haemorrhage. Outcomes of interest have been identified using READ codes and are provided in detail in Annex 3 of the present document. Only outcomes of interest occurring during Nicorandil exposure (+60 days after the last prescription date if discontinuation occurs before) will be recorded. Outcomes occurring before Nicorandil index date will be categorized as risk factors and used as stratification variables. Outcomes occurring after Nicorandil exposure (more than 60 days after last prescription date) will not be considered as potentially related events.

The rationale to use this 60 days buffer period post last prescription is based on:

- prescription behaviours of general practitioners, who will on average fill in 1 to 3 prescriptions per visit.
- The UK formulation for Nicorandil is mainly 60 units of 10 mg each
- a safety period of one month after the end of drug coverage (see previous paragraph)

Taxonomy of outcomes:

Type	Anatomical location	Single / Multiple Event

Any
Perforation
Ulcer
Erosion
Fistula
Diverticular Disease
Delayed wound healing
Abscess
Gastrintestinal Haemorrhage
Death
	Any
	Skin
	Genital
	Anal
	Ocular
	Gastrointestinal
	Other
		Single
		Multiple
		• Unrelated
		• Related
		  • Recurrence
		  • Progression
		  • Reversibility

In the primary analysis this will lead to the generation of a potential maximum of 316 estimates.

Incidence Rate Calculation:

- **Numerator:** Numerator will be calculated based on patients with events and based on events
  - number of patients with any PUFAEDG (i.e., only the first event of interest will be counted), which developed during nicorandil exposure
  - number of patients with a specific event PUFAEDG (specific events counted separately), which developed during nicorandil exposure**Error! Bookmark not defined.**
  - number of PUFAEDG events during the exposure time (all events counted)**Error! Bookmark not defined.**
  - number of specific PUFAEDG events during the exposure time (specific events counted separately)

- **Denominator:** the denominator will be calculated as based on Nicorandil exposure period(s)
  - the start of the exposure period is the study index date (i.e. the date of first Nicorandil prescription)
  - the end of the exposure period is the earliest of:
    - experiencing first outcome of interest
    - discontinuation of nicorandil (i.e. last prescription date record + 3 DAYSUPP
    - death
    - database cut-off Dec 31 2014
  - The individual patient exposure is calculated as the sum of (end of exposure period)-(start of exposure period)
  - The end of exposure will be calculated in relationship with the considered event of interest, e.g. for patients with 2 outcomes, exposure for "any event" will extend to the first outcome; for outcome number 2, the exposure will extend to the second outcome.

- **Incidence rate**

The incidence rates will be derived using the number of patients presenting with an outcome of interest and the number of events of interest divided by the number of person-years at risk between the index date and the end date of the exposure period as defined above, and linked to the event of interest. Incidence rates will

be expressed per 100,000 person-years and 95% CI. Person-years are the cumulative number of years between the index date and the end of exposure period(s) as defined above, for all included patients.

Incidence rate for N subjects with X outcomes

Patient level: =N/(sum of Nicorandil exposure periods till event X) * 100.000

Event level:=X/(sum of Nicorandil exposure periods till event X) * 100.000

9.3 Variables

Dependent variables will include; perforation, ulcer, fistula, abscess, erosion, diverticulosis, diverticulitis, death, delayed wound healing, gastrointestinal haemorrhage

Independent variables will be used for the stratified analysis and the multivariate analysis and will include: age, gender, Nicorandil dose, treatment duration, calendar year, Charlson´s comorbidity index, history of any outcome of interest, diabetes, Helicobacter pylori infection, Zollinger-Ellison syndrome, smoking and use of NSAIDs (including acetylsalicylic acid), diverticular disease, , heart failure, diabetes, alcohol use, smoking, use of corticosteroids, NSAIDs or selective serotonin re-uptake inhibitors (SSRIs), corticosteroids use, trauma, chemical injury, contact lenses, Impaired blood circulation, bacterial, viral or fungal infections , diabetes, tumours

9.4 Data Sources

9.4.1 Database

This study will be conducted using the Clinical Practice Research Datalink (CPRD). The CPRD is the English NHS observational data and interventional research service and will be the primary data source for patients in the United Kingdom. Its roots were establish in 1987 and now contains data collected from General Practitioners of 681 practices around the UK accounting for 13 million total patients, 5.7 million of which are currently active. This quantifies to more than 68 million patient years of quality data. CPRD is considered as the gold standard in conducting primary care observational research and its usage has resulted in over 890 clinical reviews and papers as in March 2015. A wide variety of information about each patient is available, such as demographics, medical symptoms, therapies, treatment outcomes, laboratory tests, lifestyle factors, and registration. CPRD has the ability to provide relevant information for studies in several areas, such as drug safety, epidemiology, pharmacoeconomics, or clinical trials.

CPRD contains patient registration information and all care events recorded by the respective medical practice, coded as READ codes. Prescribed drugs are coded as ATC. Nicorandil is marketed in the UK under the trade name Ikorel® as 10 and 20mg tablets and coded ATCC01DX16.

9.4.2 Coding and outcomes selection

An exhaustive search in the CPRD READ code dictionary has be performed to identify codes corresponding to potentially known or unknown iatrogenic effects linked to Nicorandil exposure to capture the following events located at various anatomical locations: perforations, ulcer, fistula, abscesses, erosions, diverticular disease. Additional outcomes will include death, delayed wound healing, and gastrointestinal haemorrhage. READ codes derived from coexisting conditions (e.g. ulcer of the diabetic foot, stercoral anal ulcer, abscess due to cellulitis) or from exposure to specific drugs (e.g. NSAID-induced gastrointestinal ulcer) or congenital (i.e. congenital diverticulum) or of traumatic aetiology (e.g. skin abrasion due to friction burn) directly related to any outcome of interest were discarded. READ codes related to family history (FH) will be discarded. Patients who had a history of traumatic lesion(s) within the 3 month before first Nicorandil prescription will be considered a subgroup (stratification analysis for this subgroup of patients) (as this is a major confounder for erosion/abrasion, delayed wound healing and death). Personal history (H/O) codes will be used to categorize the patient as having a previous episode of the target outcomes to assess recurrence during the study. The codes used can be found within the annex 3 at the end of this document.

9.5 Study Size

The overall study size should be between 30.000 and 40.000 patients in accordance with preliminary feasibility counts. As this is a descriptive study, no inferences regarding the minimum sample-size required to demonstrate an effect have been applied. All eligible patients will be included.

9.6 Data Management

The selected vendor will handle data procurement and management externally. Secondary data (i.e. the analysis dataset) will be electronic health records and will be stored and analyzed within a certified and validated SAS environment. The analysis dataset, macros and raw outputs will be stored and made available to the authorities upon request.

9.7 Data Analysis.

1- Descriptive analytics will be provided for the following variables: age, gender, Nicorandil dose, treatment duration, calendar year, Charlson´s comorbidity index history of any outcome of interest, diabetes, Helicobacter pylori infection, Zollinger-Ellison syndrome, smoking and use of NSAIDs (including acetylsalicylic acid), diverticular disease, , heart failure, diabetes, alcohol use, smoking, use of corticosteroids, NSAIDs or selective serotonin re-uptake inhibitors (SSRIs), corticosteroids use, trauma, chemical injury, contact lenses, Impaired blood circulation, bacterial, viral or fungal infections , diabetes, tumours. They will be computed, when appropriate, both the preindex period and the entire study period to reflect changes in potential counfounders.

Continuous variables will be summarized as average, standard deviation, median, Q1 and Q3.

Dichotomous variables will be summarized as sums, proportions and percentages.

2- The primary step 1 data analysis will consist of calculating incidence rates and their 95% CI per 100,000 person-years as well as time-to outcome for a) any PUFAEDG (first outcome of interest) and b) a specific event PUFAEDG in patients during Nicorandil exposure. For b) a top-down approach will be used in terms of grouping for each subcategory of events, e.g. all perforation events grouped together followed by organ-level estimates, followed by specific coding terms.

3- The primary step 2 data analysis will consist of calculating the incidence rates and their 95% CI per 100,000 person-years as well as time-to outcomes for patients with multiple during Nicorandil exposure. A top-down approach will be used in terms of grouping for each subcategory of events, i.e. all perforation events grouped together followed by organ-level estimates, followed by specific coding terms.

The following patterns of events will be considered:

- Same event recurrence: a similar event occurring at different time points in the database where the events are separated by a minimum time period of 3 months (to avoid recoding the same event). This analysis will be performed for patients who continue or discontinue nicorandil treatment.

- Different events: different events occurring at different time points in the database

- Evolution, which will follow the following gradation but not necessarily all the steps and concern same anatomical localization only:

  erosion→ulceration→perforation→fistula→death,
  diverticulosis→diverticulitis→ulceration→perforation→death

This analysis will be performed for patients who continue or discontinue nicorandil treatment.

Examples:

Patient 1 starts Nicorandil on Aug 23 2000, develops a skin erosion on Feb 2001 and then a skin ulceration in the next month. This will be considered as a pattern of evolution under Nicorandil.

- Reversibility, which will also concern same anatomical localization:

  fistula→perforation→ulceration→erosion→no code during 6 months
  perforation→ulceration→diverticulitis→diverticulosis→no code during 6 months

  This analysis will be performed for patients who continue or discontinue nicorandil treatment.

  Examples:
  Patient 1 starts Nicorandil on Jan 2 2000 then has gastrointestinal bleeding on Feb 4. His treatment is stopped immediately and on March 5 he receives a diagnosis of gastric erosion. This case could be considered as reversibility after discontinuation.
  Patient 2 starts Nicorandil on Nov 4 1998 and has a skin ulceration diagnosed on May 3 2000. He continues Nicorandil and has no more diagnostic code for any PUFAEDG in the next 6 months. This case will be considered as reversibility while drug maintenance.

4- The secondary analysis will concentrate on patients who had a first PUFAEDG within the 3 months before first Nicorandil prescription (pre-existing condition during the baseline period) versus those who did not. Incidence rates for further unique or multiple PUFAEDG and their 95% CI per 100,000 person-years as well as time-to outcome, in patients with Nicorandil will be calculated following a similar top-down approach. The identified sequences of outcomes will be processed as described in the secondary analysis (point 3 above) and this analysis will be performed for patients who continue or discontinue nicorandil treatment.

For these all analyses, the following subgroups will be considered and corresponding incidences calculated:

- Metrics: Patient-level (number of patients presenting at least one event) and event-level (number of events regardless of patients number)
- Outcome of interest class: Perforations, Ulcer, Fistula, Abscesses, Erosions, Diverticulosis, Diverticulitis, Death, Delayed wound healing, Gastrointestinal haemorrhage (see READ codes in Annex 3 of the present document)
- Gender: female, male
- Age group: 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+
- Charlson´s comorbidity index: 1 quartile, 2nd quartile, 3rd quartile, 4th quartile
- Comedications: at least within 1 month for patients with outcomes of interest (in order to make sure that exposure is present when the outcome is recorded)
- Compliance, as reflected by medication possession ratio
- Baseline outcome of interest or history of outcome: Yes, No
- Daily nicorandil dose: ≤20mg, >20-40mg or >40mg
- Dose intensity. Dose intensity will be calculated as the integration of dose and time.
- Baseline diverticular disease: Yes, No
- Risk factor present: Yes, No (see the list of variables under point 9.3)

5- The third analytic phase will focus on the determinants of events and events sequences (as dependent variable) against independent variables listed under point 9.3 and that include, amongst others, age, gender, Nicorandil dose, treatment duration, diverticular disease, comorbidities and comedications. A cox proportional hazard approach will be used.

9.8 Quality Control

Two SAS-certified analysts will perform the data collection, programming and analysis concurrently and separately. Results will be delivered when the results concur. All derived codes and derived data sets will be retained for audit and further quality control.

9.9 Limitations of the Research Methods

- The causality between nicorandil exposure and development of outcomes cannot be assessed with the same level of evidence as by a clinical trial. Because this is a descriptive study design, the study can highlight associations but cannot establish causality. This study was not designed to assess causality between nicorandil exposure and development of PUFAEDG but to quantify the risk.
- The study being descriptive and hypothesis generating, no formal inferences will be performed.
- Exposure misclassification may occur due to coding errors, errors in prescribed quantity, non-compliance, etc. However, this is expected to be non-differential with respect to outcome of interest.
- Missing information will result in variable sample-size depending on the considered analysis, and different precisions in the estimates. This will be particularly true for variables coding for life habits and over the counter drugs.
- Some level of underestimation in smoking, alcohol consumption and NSAIDs use can lead to an overestimation of the intrinsic risk carried by Nicorandil. The approach used in dealing with missing variables will include sensitivity analyses excluding those patients with missing information to investigate this potential bias. However, this cannot be done for missing information regarding the use of over the counter drugs like NSAIDs.
- The fact that data primarily arises from primary care may lead to a slight underestimation of the exposure for patients who were prescribed Nicorandil in a hospital setting: the first recorded prescription or pharmacy delivery date of Nicorandil (e.g. the index date) will be the first extra-muros record when the patient needed to have his prescription renewed. The potential impact is that for some cases the exposure duration will be reduced by up to the days supplied for by the hospital, which in turn is conservative for the estimation of incidences as this reduces the denominator, and non-differential towards the outcomes.
- CPRD contains relatively few information on the severity of medical conditions. This aspect will be proxied by using comorbidities and Charlson´s comorbidity index, as well as stratifying by outcomes of interest and the sequence of events.
- The exploratory nature of this study, as well as the high level of granularity in outcomes limits the validity of intergroup comparisons. The main results will be focused on descriptive incidences of events, while no conclusion will be derived from comparisons between subgroups.
- Despite the inclusion of a large number of patients, some very rare outcomes, or their association will not be assessed with an optimal precision.

9.10 Other Aspects

Not applicable

10 Protection of Human Subjects

All data used in this study are de-identified. Data confidentiality and individuals 'right to privacy' will be

fully protected

11 Management and Reporting of Adverse Events/Adverse Reactions

According to GVP Module VI section VI.C.1.2.1, b. *Non-interventional post-authorisation studies based on secondary use of data* " the reporting of suspected adverse reactions in the form of ICSRs is not required. Reports of adverse events/reactions should be summarised as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting". Therefore, the cases of perforations, ulcers, fistula, abscesses, erosions, diverticulosis, diverticulitis, death, delayed wound healing, and gastrointestinal hemorrhage found during the current retrospective study will only be summarized in the study report.

12 Plans for Disseminating and Communicating Study Results

The results of the study will be submitted to the regulator upon completion, 18 weeks after protocol approval. (Q1 2016)

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14 Annexes

Annex 1 List of stand-alone documents (Not applicable)
Annex 2 ENCePP checklist for study protocols
Annex 3 Additional information

Approval and Authorization Sign-Off	
Merck KGaA PPD PPD (electronic signature)……... PPD	Date ……April 21 2015……..
Merck EU PPD PPD (electronic signature)…... PPD	Date ……April 21 2015……...
Sanofi Lead Epidemiologist PPD ……...	Date …….April 21 21015……...
Chugai Lead Epidemiologist PPD	Date ……April 21 2015..……...

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

15 Annex 2
Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator 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.

This Checklist 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).

Study title:

Incidence and pattern description of gastrointestinal, skin, genital, corneal, and mucosal erosions, ulcerations , perforations, haemorrhages, fistulas, abscesses, delayed wound healing and death among patients treated with nicorandil with and without diverticular disease

Study reference number: EMR200101_502

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]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	6

[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.

Comments:

Registration in the EU PASS register is advised for PASS studies featuring a prospective data collection design, not for studies of observational nature using retrospective data

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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
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)	☒	☐	☐	8
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	8
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)	☒	☐	☐	8-14

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	13
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	13
4.2.2 Age and sex?	☒	☐	☐	13
4.2.3 Country of origin?	☒	☐	☐	13
4.2.4 Disease/indication?	☒	☐	☐	13
4.2.5 Co-morbidity?	☒	☐	☐	13
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)	☒	☐	☐	13

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)	☒	☐	☐	8-10
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)	☒	☐	☐	8-10
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	8-10
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	8-10

Comments:

The study does take into account time from therapy initiation and includes dose as a variable

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?	☒	☐	☐	8-10
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)	☒	☐	☐	8-10

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)	☒	☐	☐	14
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	14

Comments:

The subgroup section addresses the effect modifiers, assuming the intrinsic limitations of the data used

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.)	☒	☐	☐	13
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	13
8.1.3 Covariates?	☒	☐	☐	13

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	13
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	13
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	13
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	13, Annexes
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	13, Annexes
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	13, Annexes
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?	☐	☐	☒	14

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	X	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	14
10.3 Are descriptive analyses included?	☒	☐	☐	14
10.4 Are stratified analyses included?	☒	☐	☐	14
10.5 Does the plan describe methods for adjusting for confounding?	X	☐	☐	14
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	14

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?	☒	☐	☐	15-16
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	15-16
11.3 Are methods of quality assurance described?	☒	☐	☐	15-16

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	15-16
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	15-16

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	16
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)	☐	☐	☒	16
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	14,16
12.3 Does the protocol address other limitations?	☒	☐	☐	14,16

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?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	16

Comments:

Only deindentified data was used in this study

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?	☒	☐	☐	6

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)?	☒	☐	☐	17
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☒	

Comments:

Name of the main author of the protocol: _____PPD _____

Date: / /

Signature: _____

16 Annex 3

Additional Information

Appendix: List of READ codes for identification of outcomes of interest

Readcode	description
Angina	
G311.13	Unstable angina
G311100	Unstable angina
G33z700	Stable angina
Perforations	
F4A0600	Perforated corneal ulcer
2D35.00	O/E - nasal septum perforated
761J000	Closure of perforated gastric ulcer
7627000	Closure of perforated duodenal ulcer
773C600	Closure of perforated bowel ulcer NEC
J110200	Acute gastric ulcer with perforation
J110300	Acute gastric ulcer with haemorrhage and perforation
J111200	Chronic gastric ulcer with perforation
J111300	Chronic gastric ulcer with haemorrhage and perforation
J111300	Chronic gastric ulcer with haemorrhage and perforation
J11y200	Unspecified gastric ulcer with perforation
J120200	Acute duodenal ulcer with perforation
J120300	Acute duodenal ulcer with haemorrhage and perforation
J121200	Chronic duodenal ulcer with perforation
J121300	Chronic duodenal ulcer with haemorrhage and perforation
J12y200	Unspecified duodenal ulcer with perforation
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
J130300	Acute peptic ulcer with haemorrhage and perforation
J131300	Chronic peptic ulcer with haemorrhage and perforation
J13y300	Unspecified peptic ulcer with haemorrhage and perforation
Ulcers	
1485.00	H/O: corneal ulcer
F4A0.00	Corneal ulcer
F4A0000	Unspecified corneal ulcer
F4A0100	Marginal corneal ulcer
F4A0200	Ring corneal ulcer
F4A0300	Central corneal ulcer
F4A0600	Perforated corneal ulcer
F4A0z00	Corneal ulcer NOS
2523.00	O/E - angular stomatitis
2533.00	O/E - mouth ulcer present
2567.00	O/E - ulcer on tongue
2567.00	O/E - ulcer on tongue
J080000	Ulcerative stomatitis
J080100	Vesicular stomatitis
J082.11	Mouth ulcer

J082000	Minor aphthous ulceration
J082100	Major aphthous ulceration
J082200	Recurrent aphthous ulceration
J082211	Recurrent mouth ulcers
J085800	Lip ulcer
J08zF11	Ulcerative oral mucositis
H022.00	Acute ulcerative pharyngitis
H032.00	Acute ulcerative tonsillitis
H040100	Acute ulcerative laryngitis
H14y400	Tonsil ulcer
H1y7900	Ulcer of larynx
H1y1200	Nasal septum ulcer
M07z.12	Infected skin ulcer
2FF2.00	O/E - skin ulcer present
2FFZ.00	O/E - skin ulcer NOS
J574000	Solitary anal ulcer
J574200	Anal ulcer unspecified
J574300	Solitary rectal ulcer
J574500	Rectal ulcer unspecified
J574600	Anal and rectal ulcer NOS
14C1.11	H/O: duodenal ulcer
14C1.12	H/O: gastric ulcer
14C4.11	H/O: ulcerative colitis
2FFZ.00	O/E - skin ulcer NOS
J102400	Oesophageal ulcer due to medicines
J102z00	Ulcer of oesophagus NOS
J11..00	Gastric ulcer - (GU)
J110.00	Acute gastric ulcer
J110000	Acute gastric ulcer without mention of complication
J110100	Acute gastric ulcer with haemorrhage
J110111	Bleeding acute gastric ulcer
J110200	Acute gastric ulcer with perforation
J110300	Acute gastric ulcer with haemorrhage and perforation
J110400	Acute gastric ulcer with obstruction
J110y00	Acute gastric ulcer unspecified
J110z00	Acute gastric ulcer NOS
J111.00	Chronic gastric ulcer
J111000	Chronic gastric ulcer without mention of complication
J111100	Chronic gastric ulcer with haemorrhage
J111111	Bleeding chronic gastric ulcer
J111200	Chronic gastric ulcer with perforation
J111211	Perforated chronic gastric ulcer
J111300	Chronic gastric ulcer with haemorrhage and perforation
J111400	Chronic gastric ulcer with obstruction
J111y00	Chronic gastric ulcer unspecified
J111z00	Chronic gastric ulcer NOS
J11y.00	Unspecified gastric ulcer
J11y000	Unspecified gastric ulcer without mention of complication
J11y100	Unspecified gastric ulcer with haemorrhage
J11y200	Unspecified gastric ulcer with perforation

J11y300	Unspecified gastric ulcer with haemorrhage and perforation
J11y400	Unspecified gastric ulcer with obstruction
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
J11yz00	Unspecified gastric ulcer NOS
J11z.00	Gastric ulcer NOS
J11z.12	Multiple gastric ulcers
J12..00	Duodenal ulcer - (DU)
J120.00	Acute duodenal ulcer
J120000	Acute duodenal ulcer without mention of complication
J120100	Acute duodenal ulcer with haemorrhage
J120200	Acute duodenal ulcer with perforation
J120300	Acute duodenal ulcer with haemorrhage and perforation
J120400	Acute duodenal ulcer with obstruction
J120y00	Acute duodenal ulcer unspecified
J120z00	Acute duodenal ulcer NOS
J121.00	Chronic duodenal ulcer
J121000	Chronic duodenal ulcer without mention of complication
J121100	Chronic duodenal ulcer with haemorrhage
J121111	Bleeding chronic duodenal ulcer
J121200	Chronic duodenal ulcer with perforation
J121211	Perforated chronic duodenal ulcer
J121300	Chronic duodenal ulcer with haemorrhage and perforation
J121400	Chronic duodenal ulcer with obstruction
J121y00	Chronic duodenal ulcer unspecified
J121z00	Chronic duodenal ulcer NOS
J122.00	Duodenal ulcer disease
J124.00	Recurrent duodenal ulcer
J12y.00	Unspecified duodenal ulcer
J12y000	Unspecified duodenal ulcer without mention of complication
J12y100	Unspecified duodenal ulcer with haemorrhage
J12y200	Unspecified duodenal ulcer with perforation
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
J12y400	Unspecified duodenal ulcer with obstruction
J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
J12yz00	Unspecified duodenal ulcer NOS
J12z.00	Duodenal ulcer NOS
J13..00	Peptic ulcer - (PU) site unspecified
J130100	Acute peptic ulcer with haemorrhage
J130y00	Acute peptic ulcer unspecified
J130z00	Acute peptic ulcer NOS
J131100	Chronic peptic ulcer with haemorrhage
J131y00	Chronic peptic ulcer unspecified
J131z00	Chronic peptic ulcer NOS
J13y.00	Unspecified peptic ulcer
J13y000	Unspecified peptic ulcer without mention of complication
J13y100	Unspecified peptic ulcer with haemorrhage
J13y200	Unspecified peptic ulcer with perforation
J13y300	Unspecified peptic ulcer with haemorrhage and perforation
J13y400	Unspecified peptic ulcer with obstruction
J13yz00	Unspecified peptic ulcer NOS

J13z.00	Peptic ulcer NOS
J14..11	Anastomotic ulcer
J14..15	Stomal ulcer
J140100	Acute gastrojejunal ulcer with haemorrhage
J140z00	Acute gastrojejunal ulcer NOS
J14y.00	Unspecified gastrojejunal ulcer
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J14y200	Unspecified gastrojejunal ulcer with perforation
J14yz00	Unspecified gastrojejunal ulcer NOS
J14z.00	Gastrojejunal ulcer NOS
J41..12	Ulcerative colitis and/or proctitis
J410.00	Ulcerative proctocolitis
J410000	Ulcerative ileocolitis
J410100	Ulcerative colitis
J410200	Ulcerative rectosigmoiditis
J410400	Exacerbation of ulcerative colitis
J410z00	Ulcerative proctocolitis NOS
J411.00	Ulcerative (chronic) enterocolitis
J412.00	Ulcerative (chronic) ileocolitis
J57y900	Ulceration of colon
J57yA00	Ulceration of intestine NOS
Jyu4100	[X]Other ulcerative colitis
M271.13	Leg ulcer NOS
M272.00	Ulcer of skin
M27..00	Chronic skin ulcer
M27y.00	Chronic ulcer of skin, other specified sites
M27z.00	Chronic skin ulcer NOS
Z174Q00	Skin ulcer care
Fistula	
M2yB.00	Fistula of skin
J53..00	Anal fissure and fistula
J53..00	Anal fissure and fistula
J531000	Sub-mucosal anal fistula
J531100	Inter-muscular anal fistula
J531z00	Fistula-in-ano NOS
J53z.00	Anal fissure and fistula NOS
J53z.00	Anal fissure and fistula NOS
J53z.00	Anal fissure and fistula NOS
J57y.11	Fistula of intestine NOS
J57y100	Enterocutaneous fistula
J57y600	Colonic fistula
J57y700	Intestinal fistula NOS excluding ano-rectal fistula
J57y700	Intestinal fistula NOS excluding ano-rectal fistula
J664z00	Fistula of bile duct NOS
K161.00	Intestinovesical fistula
K161000	Enterovesical fistula
K161000	Enterovesical fistula
K161z00	Intestinovesical fistula NOS
K161z00	Intestinovesical fistula NOS
K162.00	Vesical fistula NEC

K162200	Urethrovesical fistula
K162z00	Vesical fistula NEC NOS
K162z00	Vesical fistula NEC NOS
K191z00	Urethral fistula NOS
K52..00	Female genital tract fistula
K520000	Cervicovesical fistula
K520100	Ureterovaginal fistula
K520200	Urethrovaginal fistula
K520500	Uterovesical fistula
K520600	Vesicocervicovaginal fistula
K520700	Vesicovaginal fistula
K520z00	Female urinary - genital tract fistula NOS
K521000	Intestinouterine fistula
K521100	Intestinovaginal fistula
K521200	Rectovaginal fistula
K521200	Rectovaginal fistula
K521200	Rectovaginal fistula
K521400	Sigmoidovaginal fistula
K521z00	Female digestive - genital tract fistula NOS
K522.00	Female genital tract - skin fistula
K522z00	Female genital tract - skin fistula NOS
K522z00	Female genital tract - skin fistula NOS
K52z.00	Female genital tract fistula NOS
K52z.00	Female genital tract fistula NOS
Kyu9400	[X]Other female genital tract fistulae
P443z00	Preauricular sinus or fistula NOS
P44z.00	Branchial cleft,cyst,or fistula preauricular anomaly OS/NOS
P44zz00	Branchial cleft, cyst or fistula preauricular anomaly NOS
PA3..00	Oesophageal atresia, stenosis and fistula
PA3y.00	Other specified oesophageal atresia, stenosis or fistula
PA3y.00	Other specified oesophageal atresia, stenosis or fistula
PA3z.00	Oesophageal atresia, stenosis or fistula NOS
PC36z00	Fistula involving uterus with digestive or urinary tract NOS
Erosion / Abrasion	
F4B4300	Recurrent erosion of cornea
SD81000	Corneal abrasion
J10y300	Oesophageal erosions
J11z.11	Gastric erosions
J123.00	Duodenal erosion
K420300	Cervicitis with erosion
K420600	Endocervicitis with erosion
K550.00	Erosion and ectropion of the cervix
K550000	Erosion of cervix
K550z00	Erosion and ectropion of the cervix NOS
SD...11	Abrasions
SD00000	Abrasion, face
SD00200	Abrasion, scalp
SD00z00	Abrasion head NOS
SD01000	Abrasion of face, infected
SD01100	Abrasion of neck, infected

SD01200	Abrasion of scalp, infected
SD10.00	Abrasion, trunk
SD10000	Abrasion, interscapular
SD10100	Abrasion, chest wall
SD10200	Abrasion, breast
SD10300	Abrasion, abdominal wall
SD10400	Abrasion, back
SD10500	Abrasion, buttock
SD10600	Abrasion, anus
SD10700	Abrasion, flank
SD10800	Abrasion, groin
SD10900	Abrasion, perineum
SD10A00	Abrasion, penis
SD10B00	Abrasion, scrotum/testis
SD10C00	Abrasion, vulva
SD10D00	Abrasion, vagina
SD11100	Abrasion of chest wall, infected
SD11200	Abrasion of breast, infected
SD11300	Abrasion of abdominal wall, infected
SD11400	Abrasion of back, infected
SD11500	Abrasion of buttock, infected
SD11600	Abrasion of anus, infected
SD11800	Abrasion of groin, infected
SD11900	Abrasion of perineum, infected
SD11A00	Abrasion of penis, infected
SD11B00	Abrasion of scrotum and testis, infected
SD11C00	Abrasion of vulva, infected
SD11D00	Abrasion of vagina, infected
SD20000	Abrasion, shoulder area
SD20100	Abrasion, scapular area
SD20200	Abrasion, axillary area
SD20300	Abrasion, upper arm
SD20400	Abrasion, clavicular area
SD20500	Abrasion of arm,unspecified level without infection
SD21000	Abrasion of shoulder, infected
SD21200	Abrasion of axilla, infected
SD21300	Abrasion of upper arm, infected
SD30000	Abrasion, elbow area
SD30100	Abrasion, forearm area
SD30200	Abrasion wrist, volar
SD30300	Abrasion wrist, dorsum
SD31000	Abrasion of elbow, infected
SD31100	Abrasion of forearm, infected
SD31200	Abrasion of wrist, infected
SD40000	Abrasion hand, palm
SD40100	Abrasion, hand, dorsum
SD50000	Abrasion, finger
SD50100	Abrasion, thumb
SD50200	Abrasion, finger, multiple
SD60000	Abrasion, hip

SD60100	Abrasion, thigh
SD60200	Abrasion, knee
SD60300	Abrasion, lower leg
SD60400	Abrasion, ankle
SD61000	Abrasion of hip, infected
SD61100	Abrasion of thigh, infected
SD61200	Abrasion of knee, infected
SD61300	Abrasion of lower leg, infected
SD61400	Abrasion of ankle, infected
SD70000	Abrasion, foot
SD70100	Abrasion, toe
SD70z00	Abrasion of foot and toe, without mention of infection, NOS
SD71000	Abrasion of foot, infected
SD71100	Abrasion of toe, infected

Diverticular disease

J510.00	Diverticulosis
J510000	Diverticulosis of the duodenum
J510100	Diverticulosis of the jejunum
J510200	Diverticulosis of the ileum
J510300	Diverticulosis of the small intestine unspecified
J510400	Diverticulosis of the small intestine NOS
J510500	Diverticulosis of the colon
J510600	Diverticulosis of the large intestine unspecified
J510700	Diverticulosis of the large intestine NOS
J510900	Bleeding diverticulosis
J510800	Divertic dis/both sml+lge intestin without perfor or abscess
J510y00	Diverticulosis unspecified
J510z00	Diverticulosis NOS
J511.00	Diverticulitis
J511000	Diverticulitis of the duodenum
J511100	Diverticulitis of the jejunum
J511200	Diverticulitis of the ileum
J511300	Diverticulitis of the small intestine unspecified
J511400	Diverticulitis of the small intestine NOS
J511500	Diverticulitis of the colon
J511600	Diverticulitis of the large intestine unspecified
J511700	Diverticulitis of the large intestine NOS
J511y00	Diverticulitis unspecified
J511z00	Diverticulitis NOS
J512.00	Perforated diverticulum
J512000	Perforated diverticulum of duodenum
J512100	Perforated diverticulum of jejunum
J512200	Perforated diverticulum of ileum
J512300	Perforated diverticulum of small intestine unspecified
J512400	Perforated diverticulum of small intestine NOS
J512500	Perforated diverticulum of colon
J512600	Perforated diverticulum of large intestine unspecified
J512700	Perforated diverticulum of large intestine NOS
J512y00	Perforated diverticulum unspecified
J512z00	Perforated diverticulum of intestine NOS
J512800	Divertic disease/both sml+lge intestin with perforat+abscess

ABSCESS	
F4A5300	Corneal abscess
J073.00	Abscess of salivary gland
J073000	Abscess of parotid gland
J073100	Abscess of submandibular gland
J073200	Abscess of sublingual gland
J073z00	Abscess of salivary gland NOS
J085000	Abscess of lip
J090000	Abscess of tongue
J101000	Abscess of oesophagus
J512800	Divertic disease/both sml+lge intestin with perforat+abscess
J513.00	Diverticular abscess
J54..12	Rectal abscess
J540.00	Perianal abscess
J543.00	Pelvi-rectal abscess
J544.00	Ano-rectal fissure abscess
J545.00	Intrasphincteric abscess
J546.00	Rectal abscess
J54z.00	Ano-rectal abscess NOS
K272000	Penile abscess
K284000	Abscess of scrotum
K310.11	Abscess, breast, non puerperal
K403111	Acute pelvic abscess - female
K404300	Chronic abscess of the female pelvis
K424.00	Other abscess of vulva
K424000	Abscess of vulva
K424011	Abscess of labia
K424z00	Other abscess of vulva NOS
M020100	Finger pulp abscess
M03..11	Abscess of skin area excluding digits of hand or foot
M034011	Abscess of dorsum of hand
M034012	Abscess of palm of hand
M03y011	Abscess of scalp
M03z100	Abscess NOS
M03zz00	Cellulitis and abscess NOS
M09..00	Cutaneous abscess
M090.00	[X]Abscess of face
M091.00	[X]Abscess of neck
M092.00	[X]Abscess of trunk
M092000	[X]Abscess of buttock
M092100	[X]Abdominal wall abscess
M092200	[X]Perineal abscess
M093.00	[X]Abscess of buttock
M094.00	[X]Abscess of limb
M094000	[X]Abscess of axilla
M095.00	Skin abscess
Death	
22J..12	Death
22J3.00	O/E - dead - unattended death

22J4.00	O/E - dead - sudden death
22J5.00	O/E - dead - cot death
22J6.00	O/E - dead - suspicious death
22J8.00	Death - cause unknown
8HG..11	Death in hospital
945..00	Hospital death discharge notif
9451	Death notif. from hospital
945Z.00	Hospital death disch. NOS
946..00	Death notif.- non.hosp source
94D..00	Hospital notified of death
94F..00	Unexpected death
G575100	Sudden cardiac death, so described
Delayed Wound Healing	
SP23z13	Wound surgical healing delayed
SP23z11	Delayed healing surgical wound
SP23z12	Healing delayed surgical wound
22L3.00	O/E - Wound healing badly
SP25000	Postoperative stitch abscess
SP25100	Postoperative wound abscess
Gastrointestinal hemorrhage	
14CA.00	H/O: GIT haemorrhage NOS
14CD.00	H/O: upper GIT haemorrhage
J10y000	Haemorrhage of oesophagus
J110100	Acute gastric ulcer with haemorrhage
J110300	Acute gastric ulcer with haemorrhage and perforation
J111100	Chronic gastric ulcer with haemorrhage
J111300	Chronic gastric ulcer with haemorrhage and perforation
J11y100	Unspecified gastric ulcer with haemorrhage
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
J120100	Acute duodenal ulcer with haemorrhage
J120300	Acute duodenal ulcer with haemorrhage and perforation
J121100	Chronic duodenal ulcer with haemorrhage
J121300	Chronic duodenal ulcer with haemorrhage and perforation
J12y100	Unspecified duodenal ulcer with haemorrhage
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
J130100	Acute peptic ulcer with haemorrhage
J130300	Acute peptic ulcer with haemorrhage and perforation
J131100	Chronic peptic ulcer with haemorrhage
J13y100	Unspecified peptic ulcer with haemorrhage
J13y300	Unspecified peptic ulcer with haemorrhage and perforation
J140100	Acute gastrojejunal ulcer with haemorrhage
J140300	Acute gastrojejunal ulcer with haemorrhage and perforation
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J573.00	Haemorrhage of rectum and anus
J573000	Rectal haemorrhage
J573100	Anal haemorrhage
J573z00	Haemorrhage of rectum and anus NOS

J68..00	Gastrointestinal haemorrhage
J68z.00	Gastrointestinal haemorrhage unspecified
J68z000	Gastric haemorrhage NOS
J68z100	Intestinal haemorrhage NOS
J68z200	Upper gastrointestinal haemorrhage
J68zz00	Gastrointestinal tract haemorrhage NOS

Appendix: List of READ codes for identification of patienst who sustained a trauma

Readcode	description
History of trauma	
16B4.00	Post-traumatic bruising
8H2A.00	Admit trauma emergency
8H3F.00	Non-urgent trauma admission
8H5T.00	Referral to trauma surgeon
8HJA.00	Trauma self-referral
9b82.00	Trauma & orthopaedics
J08z800	Traumatic ulcer of oral mucosa
J090100	Traumatic ulceration of tongue
M271600	Traumatic leg ulcer
SC1z.11	Scarring due to trauma NOS
ZL1GR00	Under care of trauma surgeon
ZL5GR00	Referral to trauma surgeon
ZL9GQ00	Seen by trauma surgeon
ZLD4L00	Discharge by trauma surgeon
ZLEQK00	Discharge from trauma service