Post Authorization Safety Study (PASS) Information

Acronym/Title	**S**afety and **E**ffectiveness of **R**iva**r**oxaban and **A**pixaban compared to warfarin in non-valvular atrial fibrillation patients in the routine clinical practice in the UK SiERRA UK
Protocol version and date	v 1.0, 12 Nov 2018
IMPACT study number	20343
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A A03 WARFARIN
Medicinal product	Xarelto (Rivaroxaban), Eliquis (Apixaban) and Warfarin
Product reference	EU/1/08/472/001-041
Procedure number	EMEA/H/C/00944
Comparator / Reference therapy	Warfarin
Study Initiator and Funder	Bayer AG, 51368 Leverkusen
Research question and objectives	This population-based study will identify NVAF patients who initiate apixaban, rivaroxaban or warfarin as treatment for SPAF. We will compare safety and effectiveness using real world data from routine general practice in the UK, using The Health Improvement Network (THIN).**Primary Objectives** • To compare the safety of rivaroxaban (20mg and 15mg; OD) and apixaban (5mg and 2.5mg; BID) vs warfarin in patients appropriately and inappropriately receiving standard and reduced doses of each NOAC in accordance with the label for SPAF. o Intracranial hemorrhage (intracerebral hemorrhage, subarachnoid hemorrhage, subdural and epidural

	hematoma) o Hemorrhagic stroke (intracerebral hemorrhage, subarachnoid hemorrhage) • To compare the effectiveness of rivaroxaban (20mg and 15mg; OD) and apixaban (5mg and 2.5mg; BID) vs warfarin in patients appropriately and inappropriately receiving standard and reduced dose in accordance with the label for SPAF. o Ischaemic Stroke and Systemic Embolism o Myocardial Infarction **Secondary Objectives** • To evaluate the outcomes in sub-group of patients with renal impairment and diabetes • To evaluate all-cause mortality in rivaroxaban and apixaban, as compared to warfarin • Drug utilisation and patient characterization of rivaroxaban, apixaban and warfarin receiving standard and reduced dose in accordance and not in accordance with the label • Drug utilisation/prescription behaviour and patient characterization following the first Intracranial haemorrhage or Ischaemic Stroke during the study period
Country(-ies) of study	United Kingdom
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
MAH contact person	[redacted]

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.

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2. List of abbreviations

AF	Atrial fibrillation
ACR	Albumin to Creatinine Ratio
ATC	Anatomical Therapeutic Chemical (Classification System)
BMI	Body Mass Index
CEIFE	Centro Español de Investigación Farmacoepidemiológica
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DVT	Deep Vein Thrombosis
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
CPRD	Clinical Practice Research Datalink
GCP	Good Clinical Practice
HR	Hazard Ratio
IHD	Ischemic Heart Diseases
INR	International Normalized Ratio
LMWH	Low molecular weight heparins
MAH	Marketing Authorization Holder
MDRD	Modification of Diet in Renal Disease Study
MREC	Multicenter Research Ethics Committee
N/A	Not Applicable
NOACs	Non-Vitamin K Oral Anticoagulants
NVAF	Non valvular Atrial Fibrillation
OTC	Over the counter medications
PAD	Peripheral Artery Disease
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PCPs	Primary Care Physicians
SAP	Statistical Analysis Plan
SRC	Scientific Research Committee
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
THIN	The Health Improvement Network
UK	United Kingdom
VKAs	Vitamin K antagonists
NCC	Nested case-control

3. Responsible parties

3.1 Study initiator and funder

[redacted]

Contact details of the responsible parties at Bayer AG are available upon request. **3.2**

Collaborator(s)/External partner(s)/Committee(s)

[redacted]

4. Abstract

Acronym/Title	**S**afety and **E**ffectiveness of **R**iva**r**oxaban and **A**pixaban compared to warfarin in non-valvular atrial fibrillation patients in the routine clinical practice in the UK SiERRA UK
Protocol version and date	v1.0 and 12 Nov 2018
IMPACT study number	20343
Study type / Study phase	Observational Study; Phase IV
Author	[redacted]
Rationale and background	A recent cohort study in the UK showed that amongst patients with a history of NVAF using NOAC without an apparent indication for dose reduction, the reduced dose was prescribed in approximately 30% of patients receiving apixaban and 10% of patients receiving rivaroxaban in the new users of both-agents (Study 19330, unpublished data). We hypothesize that in real-world studies performed in the UK the high percentage of reduced dose apixaban use could translate into higher rates of stroke and systemic embolism than with rivaroxaban, which appears to be prescribed at reduced doses less frequently. On the other hand, patients with renal impairment receiving standard dose of NOAC are at increased risk of bleeding. Although, warfarin use has certainly decreased in the recent years, this drug remains the main oral anticoagulant used in the UK. It has also been the active comparator of choice in most clinical trials of NOAC (O'Dell et al.) and in our opinion constitutes an ideal reference drug for these analyses. Both the standard and the reduced dose of NOACs have been compared to warfarin in clinical trials and shown to be as safe and effective as warfarin. Warfarin itself does not have dose-reduction requirements however the dose needs to be adjusted to maintain INR between 2.0-3.0. Rivaroxaban and apixaban are most widely used NOACs in the UK whereas the use of dabigatran is low and declining since 2014 (Study 19330, unpublished data). Also, the appropriate and inappropriate use

	of dabigatran is difficult to estimate due to a multiple criterion in the label for dose reduction which is difficult to assess using secondary data sources. Risk of major bleeding especially GI bleeding for NOACs is extensively studied, and our research question is to study the effect of under-dosing on the risk of stroke (effectiveness outcome). However, to also study the other side of the balance which is bleeding, we included ICH because it is an event comparable to stroke in terms severity. GI bleeding is an acute event, usually followed by complete recovery in vast majority of patients. Therefore, GI Bleeding is not included as an outcome in this study. Regarding MI, results from the key trials are variable but shows protective effect of rivaroxaban. Therefore, it is important to further investigate MI as an outcome in a large population based cohort of patients.

Research question and objectives	This population-based study will identify NVAF patients who initiate apixaban, rivaroxaban or warfarin as treatment for SPAF. We will compare safety and effectiveness using real world data from routine general practice in the UK, using The Health Improvement Network (THIN).
	
	Primary Objectives
	
	• To compare the safety of rivaroxaban (20mg and 15mg; OD) and apixaban (5mg and 2.5mg; BID) vs warfarin in patients appropriately and inappropriately receiving standard and reduced doses of each NOAC in accordance with the label for SPAF.
	  o Intracranial hemorrhage (intracerebral hemorrhage, subarachnoid hemorrhage, subdural and epidural hematoma)
	  o Hemorrhagic stroke (intracerebral hemorrhage, subarachnoid hemorrhage)
	• To compare the effectiveness of rivaroxaban (20mg and 15mg; OD) and apixaban (5mg and 2.5mg; BID) vs warfarin in patients appropriately and inappropriately receiving standard and reduced dose in accordance with the label for SPAF.
	  o Ischaemic Stroke and Systemic Embolism
	  o Myocardial Infarction
	
	Secondary Objectives

	• To evaluate the outcomes in sub-group of patients with renal impairment and diabetes • To evaluate all-cause mortality in rivaroxaban and apixaban, as compared to warfarin • Drug utilisation and patient characterization of rivaroxaban, apixaban and warfarin receiving standard and reduced dose in accordance and not in accordance with the label • Drug utilisation/prescription behaviour and patient characterization following the first Intracranial haemorrhage or Ischaemic Stroke during the study period
Study design	This is a population-based retrospective cohort study with a nested case-control analysis to assess safety and effectiveness of rivaroxaban and apixaban versus warfarin in a cohort of NVAF patients from THIN database in the UK. The study period extends from 1st January 2012 up to last available database extraction (at time of writing, December 2017). Among the THIN source population, three separate cohorts of new users of rivaroxaban, apixaban and warfarin (index drug) using the date of first prescription (start date) of the respective drug will be ascertained. Event date = index date for case-control analysis This study will apply a new-users (initiators) design and will be further stratified as naïve and non-naïve users.
Population	**Inclusion criteria** • Patients aged >=18 Years of age • NVAF • New users of Rivaroxaban, Apixaban, Warfarin • At least one year enrollment with the primary care physician (PCP) • One year since first health contact recorded in THIN prior to the first prescription of a study drug **Exclusion criteria** • Patients with other recent indications of OAC initiation as described in section 9.1. • Individuals on more than one OAC on the start date.

	• Users of Rivaroxaban apart from 15/20mg daily dose • Users of Apixaban apart from 5/10mg daily dose
Variables	Detailed descriptive variables including baseline characteristics will be captured for the population, including co-medications and comorbidities at start date. Renal disease using estimated glomerular filtration rate (eGFR) as well as ACR (Albumin/Creatinine Ratio) where available will also be ascertained, as well as risk scores, lifestyle factors and healthcare utilization. Dose, posology, duration of study drugs and other anticoagulant on start date and thereafter will be ascertained.
Data sources	THIN - The population included in THIN is representative of the UK as a whole in terms of age, sex and geographic distribution. THIN currently collects data from close to 500 practices, covering 6% of the general population of the UK population.
Study size	Study 19330 (unpublished data) conducted in UK identified 8,629 initiators of apixaban and 12,353 initiators of rivaroxaban among patients with NVAF from 2011 through 2016 within the THIN database.
Data analysis	Describe the three study cohorts i.e. patients prescribed with rivaroxaban, apixaban, warfarin by baseline characteristics, use of medications, comorbidities and healthcare utilization among the three study cohorts and contrast them with the baseline characteristics of patients in relevant, phase III clinical trials. Two independent follow-ups will be performed, one for each analysis. **Safety and Effectiveness**: In this follow-up members of all three study cohorts will be followed from the day after start date up until the earliest of: a) first occurrence of Intracranial hemorrhage (intracerebral hemorrhage, subarachnoid hemorrhage, subdural and epidural hematoma), b) an ischemic event (Ischaemic Stroke /Systemic Embolism), c) Myocardial Infarction, d) death, and e) end of study period. **All-cause mortality:** the follow-up of members of all three study cohorts will be followed from the day after start date up until the earliest of: a) date of death, and b) end of study period. The end of study period is defined as end of last data collection

	in each practice. Analyze safety, effectiveness, and all-cause mortality associated to use of the study drugs in three independent nested-case control analyses. Estimates for standard as well as for reduced dose of study drugs will be obtained. These three analyses will include all cases identified in each follow-up (respectively: intracranial hemorrhage events, ischemic events, and deaths) and an analysis-specific group of controls. These control groups will comprise a random sample of members of all three cohorts, frequency-matched by age, sex and calendar year to each set of cases. Under our study design of incidence density sampling, the odds ratio (OR) is an unbiased estimator of the incidence rate ratio (RR). Unconditional logistic regression models will be used to obtain OR estimates adjusted by baseline variables described above and OAC use at index date. Outcomes will be analysed for the sub-group of NOAC users appropriately and inappropriately receiving standard and reduced dose. Outcomes will be analysed in the sub-group of diabetics and by renal function (CKD-EPI). Further, the patterns of use of study medication before and after intracranial hemorrhage events, and ischemic events that occurred during the study period will be described.
Milestones	The project is planned to begin in December 2018 and will end in December 2019

5. Amendments

None

6. Milestones

Table 1: Milestones

Milestone	**Planned date**
Study Start	December 2018

Registration in the EU PAS register	December 2018
Study End	October 2019
Final report of study results	December 2019

7. Rationale and background

The prevalence of AF in England in 2016-17 was estimated to be 1.8% using Quality and Outcomes Framework (QOF) data (NHS Digital 2016). QOF is a voluntary incentive and reward system for general practice and includes an estimate of disease prevalence based on the number of patients with certain conditions, including AF, within practices lists. Other estimates based upon the GRASP (Guidance on Risk Assessment and Stroke Prevention) risk assessment tool of NHS Improvement estimates AF prevalence to be 1.76% (Cowan et al. 2013).

Bayer currently markets rivaroxaban in the UK which is indicated for the prevention of stroke and systemic embolism in adult patients with NVAF as well as the treatment and prevention of VTE. Other NOACs indicated for prevention of stroke and systemic embolism, include apixaban and dabigatran. In the UK, warfarin remains a widespread AF therapy although following the introduction of NOACs, its use in usual clinical practice has diminished significantly. Rivaroxaban was first marketed in 2008 in the UK, whereas apixaban was introduced in 2011. By choosing this study period, we ensure that all three study drugs were available throughout the study. Each individual NOAC licensed for the prevention of stroke in AF has different dosing recommendations and some anecdotal reports have previously indicated that there may be a clinically meaningful difference in the rates of lower doses of these agents as would be expected based on clinical trial data or the known prevalence of indications for reduced dose reflected in the respective drug labels.

The currently marketed NOACs have been extensively investigated in numerous post-marketing cohort studies. However, the methodologies employed and the sources of data adopted for these studies have been highly variable including data captured from both administrative databases as well as research databases. Previous work by Fay et al (Fay, Martins, and Czekay 2016) investigated the dosing patterns of NOACs for stroke prevention in AF using prescription data obtained from the UK, Germany and France. The outcomes indicated a greater use of lower doses of NOACs for AF therapy than were observed in the Phase III trials. Further work in the U.S. by Yao et al (Yao et al. 2017) has investigated dosing of NOACs in a large administrative database and the associated outcomes of patients administered lower doses of these agents with respect to stroke and major bleeding in patients with or without renal dysfunction. Those patients with no renal indication for dose reduction were potentially under dosed and this was associated with a higher risk of stroke but no significant difference in major bleeding. Of interest, potential under dosing with apixaban was associated with higher rates of stroke and systemic embolism compared to the standard dose whilst there was no significant difference between the reduced dose and standard dose with respect to rivaroxaban. A limitation of this study was the inability to account for other factors associated with

dose reduction for apixaban, a limitation which may be overcome by using the THIN database and consequently better reflecting the appropriate use of these agents in usual clinical practice.

Bayer has recently conducted a retrospective cohort study on prescription patterns of NOACs in NVAF patients in UK general practice using a combination of the THIN and CPRD databases. Amongst patients without an apparent indication for dose reduction, the reduced dose was prescribed in approximately 30% of patients receiving apixaban and 10% of patients receiving rivaroxaban in the new-users of both agents (Study 19330, unpublished data). We therefore hypothesize that in the UK, the higher than expected rates of reduced dose apixaban use as compared to the Phase III trials will exhibit higher rates of stroke and systemic embolism versus warfarin than rivaroxaban, which appears to be prescribed at the reduced dose less frequently. Also, patients with renal impairment receiving standard dose are at increased risk of bleeding. Although, warfarin use has certainly decreased in the recent years, this drug remains the main oral anticoagulant used in the UK. It has also been the active comparator of choice in most clinical trials of NOAC (O'Dell et al.) and in our opinion constitutes an ideal reference drug for these analyses. Both the standard and the reduced dose of NOACs have been compared to warfarin in clinical trials and shown to be as safe and effective as warfarin. Warfarin itself does not have dose-reduction requirements however the dose needs to be adjusted to maintain INR between 2.0-3.0. Rivaroxaban and apixaban are most widely used NOACs in the UK whereas the use of dabigatran is low and declining since 2014 (Study 19330, unpublished data). Also, the appropriate and inappropriate use of dabigatran is difficult to estimate due to a multiple criterion in the label for dose reduction which is difficult to assess using secondary data sources. Risk of major bleeding especially GI bleeding for NOACs is extensively studied, and our research question is to study the effect of under-dosing on the risk of stroke (effectiveness outcome). However, to also study the other side of the balance which is bleeding, we included ICH because it is an event comparable to stroke in terms severity. GI bleeding is an acute event, usually followed by complete recovery in vast majority of patients. In terms of the balanced outcomes, it is important to take account of the severity of the disease events prevented and caused by the intervention, and not just the frequencies of the events. Thus GI bleeds, which are sometimes severe, are acute events usually followed by recovery without sequelae, while strokes and ICH can leave residual physical and/or cognitive impairments in those who survive, and may require complex and lifelong interventions. Therefore, GI Bleeding is not included as an outcome in this study.

Regarding MI, here are some of the results from the key trials:-

- Chatterjee et al reported (2013) that rivaroxaban was associated with a reduction in MI across ATLAS EINSTEN RECORD and ROCKET trials (OR in ROCKET AF was 0.8 (0.61-1.04).
- Pioneer indicated high rates coronary revascularization in AF patients with CAD (20-45%) but major adverse CV event (CV death, MI, stroke) were similar to VKA at both doses of rivaroxaban.

- Results of ATLAS ACS TIMI 46 suggested that rivaroxaban may meaningfully reduce major CV events with an acceptable incremental bleeding profile. In ATLAS ACS 2 TIMI 51 the 5mg dose was observed to reduce the rate of MI versus placebo although this dose level did not reduce death from cardiovascular causes.
- Danish registry (Lee 2018) observed that NOACs were associated with a significant reduction of MI compared with VKA – the highest absolute risk difference was observed between rivaroxaban and VKA

Therefore, it is important to further investigate MI as an outcome in a large population based cohort of patients.

Further, it is important to understand how are the OACs used after a patient experiences an event on the index OACs for e.g. major bleeding or stroke.

This will be the first study which will evaluate the safety and effectiveness of rivaroxaban and apixaban comparted to warfarin in patients appropriately and inappropriately receiving standard and reduced doses of each NOAC in accordance with the label in a large-population based cohort of NVAF patients.

8. Research questions and objectives

This population-based study will identify NVAF patients who initiate apixaban, rivaroxaban or warfarin as treatment for SPAF. We will compare safety and effectiveness using real world data from routine general practice in the UK, using The Health Improvement Network (THIN).

8.1 Primary objective

- To compare the safety of rivaroxaban (20mg and 15mg; OD) and apixaban (5mg and 2.5mg; BID) vs warfarin in patients appropriately and inappropriately receiving standard and reduced doses of each NOAC in accordance with the label for SPAF.
    - Intracranial hemorrhage (intracerebral hemorrhage, subarachnoid hemorrhage, subdural and epidural hematoma)
    - Hemorrhagic stroke (intracerebral hemorrhage, subarachnoid hemorrhage)
- To compare the effectiveness of rivaroxaban (20mg and 15mg; OD) and apixaban (5mg and 2.5mg; BID) vs warfarin in patients appropriately and inappropriately receiving standard and reduced dose in accordance with the label for SPAF.
    - Ischaemic Stroke and Systemic Embolism
    - Myocardial Infarction

8.2 Secondary objectives

- To evaluate the outcomes in sub-group of patients with renal impairment and diabetes
- To evaluate all-cause mortality in rivaroxaban and apixaban, as compared to warfarin

- Drug utilisation and patient characterization of rivaroxaban, apixaban and warfarin receiving standard and reduced dose in accordance and not in accordance with the label
- Drug utilisation/prescription behaviour and patient characterization following the first Intracranial haemorrhage or Ischaemic Stroke during the study period

9. Research methods

9.1 Study design

This is a population-based retrospective cohort study with a nested case-control analysis to assess safety and effectiveness of new users of rivaroxaban and apixaban versus new users of warfarin in a cohort of NVAF patients from THIN database (secondary data) in the UK.

All patients aged 18 and above and who have been enrolled in the databases for at least 1 year and had their first prescription recorded in the databases at least 1 year ago will be included in source population. A patient will be considered eligible to enter a study cohort as a new-user of one of the three study drugs when he or she has a first prescription of the index drug recorded during the enrollment period. Individuals meeting the criteria of new user of more than one study drug during the enrollment period will be assigned to the study cohort with the earliest start date. Among the three study cohorts, we will further identify patients with Non-valvular Atrial Fibrillation (NVAF) defined as: Patients with a record of Atrial fibrillation (AF) any time prior start date or within the 2 weeks after the start date, and free of valvular replacement or mitral stenosis prior to start date or 2 weeks after start date.

Additionally, NVAF patients with other recent indications of OAC initiation will be excluded. Thus patients with an entry of venous thromboembolism or orthopedic arthroplasty recorded in the last 3 months before the date of first time use of OAC or in the week after the start date will be excluded from the study cohort. Individuals on more than one OAC on the start date will also be excluded.

The validity of a nested case-control (NCC) study that follows the incidence-density based NCC paradigm is equivalent to the corresponding cohort study. NCC is simply described as an efficient person-time sampling strategy to obtain the same results as in a cohort study. In this study, this efficiency gain is quite substantial. It is quite common that daily-dose of these drugs changes during follow-up time. As described in the section 9.3.1.1, the algorithm to be used to ascertain daily dose at one specific time-point (one unit of person-time) is already quite complex. An attempt to classify the daily dose of every single unit of person-time of follow-up for the entire cohort would be not only be time-consuming but also prone to misclassification. The reason is that the algorithm is not entirely automated but requires some fine tuning based on recent prescription history. Thus, using a NCC approach enables us to minimize misclassification using all available information to estimate the daily-dose at the two most important time points: a) at index date (date of the event among cases or random date among controls) and b) at start date.

9.1.1 Primary end-points

- Safety: Risk of intracranial hemorrhage (intracerebral hemorrhage, subarachnoid hemorrhage, subdural and epidural hematoma), among NVAF patients in the UK associated with appropriately and inappropriately receiving standard and reduced dose in new-users of apixaban, rivaroxaban, or warfarin for stroke prevention.
- Effectiveness: Risk of ischemic events (ischaemic stroke /systemic embolism, myocardial infarction), among NVAF patients in the UK associated with appropriately and inappropriately receiving standard and reduced dose in new-users apixaban, rivaroxaban, or warfarin for stroke prevention.

9.1.2 Secondary end-points

- To evaluate the above mentioned outcomes in the sub-groups of patients with renal impairment and diabetes
- To evaluate all-cause mortality in rivaroxaban and apixaban, as compared to warfarin
- Drug utilisation and patient characterization of rivaroxaban, apixaban and warfarin receiving standard and reduced dose in accordance and not in accordance with the label
- Drug utilisation/prescription behaviour and patient characterization following the first Intracranial haemorrhage or Ischaemic Stroke during the study period

9.2 Setting

9.2.1 Study population

In the UK, nearly all residents are registered in a general medical practice that uses a system of electronic medical records. THIN is a structured, de-identified electronic medical record database in the UK. The population included in THIN is representative of the UK as a whole in terms of age, sex and geographic distribution. THIN now collects data from around 500 practices, covering about 5% of the general population of the UK population (including practices in England, Wales, Scotland, and Northern Ireland). One of the advantages of using THIN for this project is that the knowledge acquired in study 19330, which was recently completed, in a similar population using this database and the possibility to validate the outcomes using manual review of cases and free text comments is key in managing this complex issue of classifying daily-dose of these drugs.

9.2.2 Study time frame

The study period extends from 1st January 2012 up to last available database extraction (at time of writing, December 2017). Rivaroxaban was first marketed in 2008 in the UK, whereas apixaban was introduced in 2011. By choosing this study period we ensure that all three study drugs were available throughout the study.

9.2.3 Selection criteria

Inclusion criteria

- Patients aged >=18 years of age
- NVAF
- New users of Rivaroxaban, Apixaban, Warfarin
- At least one year enrollment with the general practice (GP)
- One year since first health contact recorded in THIN prior to the first prescription of a study drug

Exclusion criteria

- Patients with other recent indications of OAC initiation as described in section 9.1.
- Individuals on more than one OAC on the start date.
- Users of Rivaroxaban apart from 15/20mg daily dose
- Users of Apixaban apart from 5/10mg daily dose

9.2.4 Representativeness

The population included in THIN is representative of the UK as a whole in terms of age, sex and geographic distribution (Blak et al. 2011; Bourke, Dattani, and Robinson 2004). THIN has been extensively validated for use in pharmacoepidemiology (Lewis et al. 2007).

9.3 Variables

9.3.1 Exposure definition

Among the source population resulting from the THIN database, we will ascertain three separate/mutually exclusive cohorts of new-users of rivaroxaban, apixaban and warfarin (index drug) using the date of first prescription (start date) among the three study drugs. Index date=event date in the nested case-control analysis.

This study will apply a new-users (initiators) design (Ray 2003) and then further stratify the new users into naïve and non-naive. A patient is considered eligible as new user of rivaroxaban, apixaban or warfarin if he or she had a first prescription of the respective drug recorded during the enrolment period and never received one prior for that index OAC. Further, naïve users are individuals with no previous recorded use of any OAC in the database before the start date. Non-naïve patients are those with one or more oral anticoagulant prescriptions other than the index drug recorded before the start date.

The study drug will be further stratified to Current, recent, past and non-use specified in section 9.3.3

Among cases of intracranial haemorrhage or ischemic events during the study period, use of the study drugs after index date (index date=event date in the nested case-control analysis) will also be ascertained within one year after the index date.

9.3.1.1 Strategy for dose estimation

Apixaban, rivaroxaban and warfarin tablet strength will be derived from the description of the prescribed product. Dosing frequency/posology per day will be derived from the free text recorded instructions for the prescription.
For NOAC, a posology of three or more doses per day (derived from instructions) will not be considered valid. Furthermore, the daily dose of NOAC prescriptions will be assigned by applying the algorithms for deduplication and daily dose assignment as described below.

Deduplication
For any two or more prescriptions for the same NOAC issued on the same day (concurrent), a deduplication will be performed based on the following criteria:
1 – If all concurrent prescriptions are of the same strength, then the one with the greatest quantity (total number) of tablets will be selected.
If not:
2 – If the concurrent prescriptions are for rivaroxaban and one of the concurrent prescriptions is for a tablet strength of 15 mg then this prescription will be selected.
If not:
3 – If there is another prescription of the same NOAC within a window of 30 days after the end of supply of the longest concurrent prescription that matched the strength of one of the original concurrent prescriptions, then this strength will be selected.
If not:
4 –The first prescription as ordered in the database will be selected.

Daily dose assignment

After deduplication, if required, daily dose will be computed with the following rules:
1– If the directly derived posology from text-based dosage instructions have a value of 1 or 2, then the corresponding value of posology of 1 or 2 will be assigned.
If not:
2 – If the NOAC is apixaban, then posology will be assigned to 2.
If not:

3 – If the NOAC is rivaroxaban then the posology is assigned to 1, unless one of the following scenarios are present:

A – When there is concurrent prescription of 15 mg strength and 20 mg strength tablets, then posology will be assigned to 2 for the 15 mg strength. This particular rule applied even when dosage instructions gave valid values of 1 (see rule 1 above).

B – When the rivaroxaban prescription is for 15 mg strength with a quantity of 42 tablets (irrespective of another concurrent rivaroxaban prescription), then posology will be assigned to 2.

Once all these steps are applied, then daily dose will be derived as the simple product of posology value and strength of the selected prescription. Once the daily dose is computed for all NOACs following the rules described above, we will change the daily dose of rivaroxaban assigned to 40 mg to 20 mg when the posology derived from dividing the quantity (number of tablets) by days of time interval between consecutive prescriptions (gap between prescriptions less than 90 days) results in 20 mg daily dose: consequently, correcting the information indentified from the instructions field of the database in this scenario. This amendment to the algorithm was introduced as a result of our exercise in Study 19330, unpublished data. In the case of rivaroxaban, we found that estimating daily dose based on dose instructions (those recorded in the free text field) sometimes results in misclassifying as 40mg daily dose, usage that should be classified as 20mg daily dose according to pill count.

Furthermore estimated daily doses for both start date and index date, will be classified according to whether or not estimated daily dose corresponded to a standard dose. When estimated daily dose at index date, only prior prescriptions will be taken into account. For rivaroxaban a daily dose of 20mg will be considered as “standard dose”. Daily doses of 15mg will be considered a “reduced dose”. For apixaban a daily dose of 10mg will be considered as “standard dose”. Daily doses of 5mg will be considered as “reduced dose”.

For warfarin we will also obtain posology from free text recorded instructions for the prescription using the following criteria:
1.- When instructions assign 1, 2 or 3 per day we will consider them as valid and apply that posology.
2.- If instructions are missing, not mapped to a value, or mapped to posology other than 1,2, 3 per day, we will assign a value of 1 per day.

Warfarin daily dose will be derived as the simple product of posology value and strength of the selected prescription. In the case of more than one prescription of warfarin on same day (usually different strengths) the daily dose will be the sum of daily doses of all different prescriptions recorded on that day, and the length of supply the largest supply among all different prescriptions recorded on that day.

9.3.1.2 Dose Reduction Criterion

- **Apixaban**:
  - The recommended dose of apixaban is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).
  - NVAF patients with severe renal impairment (creatinine clearance 15-29 mL/min) patients should receive the lower dose of apixaban 2.5 mg twice daily for the prevention of stroke and systemic embolism.
- **Rivaroxaban**:
  - In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment, the recommended dose is 15 mg once daily for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
- **Warfarin**:
  - Warfarin itself does not have dose-reduction requirements however the dose needs to be titrated to maintain INR between 2.0-3.0. In this study, we would not use the dose adjusting criterion for warfarin as it is variable and difficult to take in to account.

9.3.2 Outcomes definition

The outcomes include

- Intracranial hemorrhage (intracerebral hemorrhage, subarachnoid hemorrhage, subdural and epidural hematoma)
- Ischemic event (Ischaemic Stroke /Systemic Embolism),
- Myocardial Infarction
- All cause-mortality

See section Annex 3: Additional information for corresponding codes.

9.3.2.1 Validation of outcomes

Anonymized free text will be obtained for all individuals experiencing safety or effectiveness events (as defined above) during the study period. We will manually review their clinical profiles with available free text to confirm or discard these events. Since the study cohort will include individuals with a history of ischemic and/or hemorrhagic events before the study period, this manual review of clinical profiles would be essential to discard diagnosis recorded during the study period that actually refer to episodes that occurred before start date. Furthermore, only events that required

hospitalization will be considered. For this process of validation of the outcomes, all patient personal identifiers will be suppressed and information on drug use removed to allow for a blinded revision of patient profiles. Additionally we will obtain anonymized free text from a random sample of individuals (n=100) that allegedly do not experience safety or effectiveness events (i.e. no event codes recorded). We will manually review their clinical profiles with available free text to identify any signs of safety or effectiveness events (meeting our operational definition) that had not been identified through the code search.

9.3.3 Covariate definition

The following variables will be collected among the three study cohorts (apixaban, rivaroxaban and warfarin) both at start and index date (the date among cases and controls):

- Age and sex distribution at start date/index date
- Naïve/Non-Naïve at index date: Use of OAC other than the index OAC before index date
- Frailty: we will estimate an electronic frailty index (eFI) at start date/index date by using an algorithm developed and validated in THIN (Clegg et al. 2016). Briefly the eFI score is simply an equally weighted calculation of deficits present out of the total 36 deficits identified. Patients will be classified into four mutually exclusive categories based on this score: a) Fit = 0-0.12, b) Mild frailty = 0.12-0.24, c) Moderate frailty = 0.24-0.36, and d) Severe frailty = >0.36.
- Renal disease: estimated glomerular filtration rate (eGFR) before start date/index date will be calculated using the formula described in Table S1 (Annex 3). In prior studies we found that eGFR could not be estimated in less than 5% of AF patients. ACR (Albumin/Creatinine Ratio) will also be ascertained.
- Comorbidity: history of haemorrhagic disease and history of intracranial haemorrhage, urogenital bleeding and gastrointestinal bleeding. Liver disease, pancreatic disease, cancer, cardiovascular disease (acute MI, coronary artery disease, congestive heart failure, ventricular arrhythmia, peripheral arterial disease) cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia and obesity), stroke/TIA, respiratory disease (asthma and chronic obstructive pulmonary disease), rheumatoid arthritis, osteoarthritis, gastrointestinal disease, liver disease and pancreatic, alcohol-related disorders before start date/index date.
- CHADS2 (0-6) and CHA_2DS_2Vasc (0-9) scores will be calculated at start and index date based on the presence/ history of congestive heart failure, hypertension, age, diabetes mellitus and prior stroke or transient ischaemic attack. HAS-BLED (0-9) score for major bleeding risk (hypertension, renal disease, liver disease, stroke history, prior major bleeding or predisposition to bleeding, age > 65, medication usage predisposing to bleeding, alcohol usage history), will also be calculated. Numbers and proportion will be calculated per value.
- Smoking status, body mass index (BMI) and Townsend score: most recently recorded value before the start date/index date.

- Healthcare utilization in the year prior to the start date/index date (e.g. GP visits, outpatient visits and hospital admissions where available).
- Use of following medications in the three months before the start date: antiplatelet drugs (low-dose acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor), antiarrhythmic drugs, antihypertensive drugs, statins, anti-diabetic agents, non-steroidal anti-inflammatory drugs, oral steroids, acid-suppressive drugs, disease-modifying anti-rheumatic drugs, antidepressants, antipsychotic drugs, oral contraceptives, hormone-replacement therapy, strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein (e.g. the systemic azole antimycotics ketoconazole, itraconazole, voriconazole and posaconazole and the HIV-protease inhibitor ritonavir), strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine or phenobarbital) and fluconazole.
- Recency of use of medications listed above as well as study drugs on index date will be categorized as:
  - Current use (when the drug supply lasts until index date or supply ends in the 30 days before index date)
  - Recent use (when the drug supply ends 30-90 days before index date)
  - Past use (when the drug supply ends 91-365 days before index date)
  - Non-use: no use in year before index date

  Note that for medications other than study drugs, recent and past will be collapsed into one category
- Duration of use will be defined among current users of study drugs at index date as the time from the first consecutive prescription of that drug to index date. Consecutive prescriptions will be considered those separated by a gap of less than 30 days between end of supply and the date of the next prescription. Duration of use will be classified as: up to 90 days, 91 days up to one year, 1-3 years, more than 3 years. Furthermore, these individuals (i.e. current users of study drugs at index date) will be classified as "Continuers" if the first consecutive prescription corresponds to the patient's start date (i.e. the patient maintained the same drug initiated at start date up until the index date), or "Discontinuers/Switchers" if the patient was not continuously taking the starting OAC between start and index date (i.e. either the patient has interrupted the drug at some point or the patient switched from one OAC to another).

9.4 Data sources

THIN

Established in 2002, THIN now collects data from close to 500 practices, covering about 5% of the general population, with more than 65 million patient-years of experience (CSD Medical Research, 2012). Eleven million individual patients are represented in the data; of those, approximately one-third are active at any one time. THIN records information on all services provided by the PCP, and information on specialist visits and hospitalizations are routinely forwarded to the PCP, who enters that information into the medical record. The population included in THIN is representative of the UK as a whole in terms of age, sex and geographic distribution (Blak et al. 2011; Bourke, Dattani, and Robinson 2004). THIN has been extensively validated for use in pharmacoepidemiology (Lewis et al. 2007).

The Read classification is used to code specific diagnoses as reasons for each consultation (Stuart-Buttle et al. 1996), and a drug dictionary based on data from the MULTILEX classification is used to record prescriptions (FDB (First Databank) n.d.).

9.5 Study size

Study 19330 (unpublished data) conducted in UK identified 8,629 initiators of apixaban and 12,353 initiators of rivaroxaban among patients with NVAF from 2011 through 2016 within the THIN database. A study conducted in UK between 1 December 2012 and 31 October 2014 using CPRD, reported 10,218 naïve users of warfarin (Johnson at al. 2016). With an additional year up to 2017, the expected numbers of Rivaroxaban, Apixaban and Warfarin users will be greater than numbers reported above. Thus, assuming the study will include at least 10,000 initiators of each study drug and annual rates of intracranial hemorrhage, ischemic stroke, and all-cause mortality of 1%, 2%, and 4%, we expect the study to identify at least a total of 900, 1800, and 3600 events respectively. In case only 50% of initiators continue drug use at index date (i.e. current users at index date), we should be able to detect, with a statistical power greater than 80%, odds ratios of 1.5 associated to current use of each study drugs for intracranial haemorrhage, odds ratios of 1.3 for ischemic stroke, and odds ratios of 1.2 for all-cause mortality.

Regarding the daily dose analyses, power calculation will depend largely on the percentage of individuals we found in each daily dose category. For instance in, if we assume that 30% of current users of apixaban will use a reduced dose (2.5mg Bid), half of them appropriately, for the comparison between “appropriate” and “inappropriate” reduced dose of apixaban we would be able to detect odds ratios of 3.5 when exploring intracranial hemorrhage, odds ratios of 2.4 for ischemic stroke, or odds ratios 1.8 for all-cause death. On the other hand for the comparison between “inappropriate” reduced dose of apixaban versus warfarin current use, if the assumptions described above hold, we should be able to detect with a power of at least 80% odds ratios of 2.3,1.8, and 1.6 for ICH, IS, and all-cause mortality respectively. Note that all these calculations have assumed a two-sided type I error of 5%.

9.6 Data management

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 a minimum of 10 years.

As a standard process, one researcher prepares the list of codes, test the computer algorithms to be used and runs statistical analysis after agreement on all phases of analyses with the rest of the team. As one measure of quality control, another researcher independently performs several checks in reviewing commands and analyses performed in order to minimize data errors.

9.7 Data Analysis

We will first describe the three cohorts according baseline characteristics, use of medications, comorbidities and healthcare utilization services (see variables in section 9.3). This analysis will be based on descriptive statistics: frequencies and percentages will be calculated to the variables of interests, continuous and count variables will be described using mean (±standard deviation), proportions, median (quartiles) and minimum and maximum values. 95% confidence intervals will be computed for descriptive variables.

Two independent follow-ups will be performed, one for each analysis. **Safety and effectiveness**: In this follow-up members of all three study cohorts will be followed from the day after start date up until the earliest of: a) first occurrence of Intracranial hemorrhage (intracerebral hemorrhage, subarachnoid hemorrhage, subdural and epidural hematoma), b) an ischemic event (Ischaemic Stroke /Systemic Embolism), c) Myocardial Infarction, d) death, and e) end of study period. **All-cause Mortality:** the follow-up of members of all three study cohorts will be followed from the day after start date up until the earliest of: a) date of death, and b) end of study period. The end of study period is defined as end of last data collection in each practice.

We will then analyze safety, effectiveness, and all-cause mortality associated to use of the study drugs in three independent nested-case control analyses. These three analyses will include all cases identified in each follow-up (respectively: intracranial hemorrhage events, ischemic events, and deaths) and an analysis-specific group of controls. These control groups will comprise a random sample of members of all three cohorts, frequency-matched by age, sex and calendar year to each set of cases (Walker 1991). Briefly, each cohort member is assigned a random date within the study period. We will consider "eligible controls" all those individuals who are being followed at the time of the random date (e.g. random date included between their start of follow-up and end of follow-up). This process (similar to incidence density sampling) ensures that the likelihood of being selected as control is proportional to the amount of person-time contributed by each patient: as an example a person who contributes all the time included between beginning of study period and end of study period has a 100% likelihood of being an eligible control. Then we will sample "eligible

controls" in such a way that the frequency of matching factors (age categories, sex, and calendar year) among selected controls at their random dates matches that of the cases at the index date (i.e. frequency-matched controls). In other words, if 2% of cases are males, belong to the age category 40-49 and have 2010 as year of their index date, then 2% of controls are males, belong to the age category 40-49 and have 2010 as year of their random date. Under our study design of incidence density sampling, the odds ratio (OR) is an unbiased estimator of the incidence rate ratio (RR) (Rothman 2012). Unconditional logistic regression models will be used to obtain OR estimates of OAC use adjusted by baseline variables described above and OAC use at index date. The model will include all covariates described in section 9.3.3 in the logistic regression model (fully-adjusted model). Additionally, and depending on the number of cases ascertained, we could explore simpler models based on either change-in-estimate or statistical significance approaches. Specifically the following analyses will be performed for each outcome:

a) OAC daily dose: We will use the daily dose criteria described in 9.3.1.2 to classify current users of rivaroxaban and apixaban and compare with warfarin as follows:

   Rivaroxaban

   - Overall Rivaroxaban (both doses) vs warfarin
   - 20mg OD – No dose reduc. criteria – Appropriate vs warfarin
   - 20mg OD – Dose reduction criteria – Inappropriate vs warfarin
   - 15mg OD - No dose reduc. criteria – Inappropriate vs warfarin
   - 15mg OD – Dose reduction criteria – Appropriate vs warfarin
   - Overall Appropriate use vs warfarin

   Apixaban

   - Overall Apixaban (both doses) vs warfarin
   - 5mg Bid - No dose reduc. criteria – Appropriate vs warfarin
   - 5mg Bid – Dose reduction criteria – Inappropriate vs warfarin
   - 2.5mg Bid - No dose reduc. criteria – Inappropriate vs warfarin
   - 2.5mg Bid – Dose reduction criteria – Appropriate vs warfarin
   - Overall Appropriate use vs warfarin

b) Outcomes will also be analysed in the sub-group of diabetes and by renal function (CKD-EPI) (creatinine clearance or serum creatinine as described in the label of the respective NOAC). Since renal function is taken into account in this classification, individuals without

renal function values available (expected to be less than 5%) will be excluded from these analyses. Using warfarin current use as the reference category, we will estimate the risk of the study outcomes associated to the rivaroxaban and apixaban daily dose categories described above.

c) OAC duration: We will use the duration variable described in section 9.3.3. to compare different drug durations of current use with non-use of each study drug. Additionally we will compare "Continuers" and "Discontinuers/Switchers" with non-use of each study drug.

d) Stratified analysis: The above described analyses will also be conducted separately for naïve, and non-naïve patients at start date.

Comparisons will be done based on adjusted point estimates and confidence intervals obtained from multivariable regression.

We will describe the patterns of use of study medication or other NOACs (edoxaban/dabigatran) after intracranial hemorrhage events, and ischemic events that occurred during the study period. The current hypothesis is that a patient will restart with anticoagulation within 1-3 months of an event.

Strategy for handling missing data

As a general strategy, no data imputation strategies will be applied to supplement missing data. However, missing values may occur in a small proportion. In this case, individuals with missing values will be kept in the analysis and a separate category will be created for missing values of that variable.

9.8 Quality control

Standard operating procedures at 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 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 Sponsor will not receive any patient or provider identifiable information from CEIFE at any time. We will abide by the Guidelines for Good Pharmacoepidemiology Practices (ISPE n.d.). The study protocol is dependent on approval by a Scientific Research Committee (SRC) that review studies performed in THIN

9.9 Limitations of the research methods

- Given the nature of real-world data, missing data are likely to be present in a minority of instances. As a general strategy, no data imputation strategies will be applied to supplement missing data. However, missing values may occur in a small proportion. In this case, individuals with missing values will be kept in the analysis and a separate category will be created for missing values of that variable.
- Only prescriptions captured in THIN dataset will be available. Medications prescribed at hospital will not be captured nor will over the counter medications (OTC). This might induce some exposure misclassification that we expect to be non-differential. This might introduce to some bias towards the null in study estimates. While bias towards the null is generally considered as conservative in effectiveness analyses, it is considered as anticonservative in safety analyses (tends to conclude treatment strategies are similar even if they are not). We should take this into account when interpreting study results.
- Incomplete data concerning medication compliance: drug use is based on prescriptions written by the treating physician, but no information is available to confirm if the drug was actually taken by the patient (common to virtually any computerized clinical database).
- There may be some missing data if GPs may not enter the hospitalization data however we expect that the vast majority of GPs will record information on hospitalization into THIN.
- Some lifestyle variables such as smoking, BMI and alcohol consumption is not consistently recorded for all patients.
- The results from observational analyses should be interpreted with care, as in the presence of remaining confounding, any findings cannot simply be attributed to use of study drugs.

9.10 Other aspects

Not applicable

10. Protection of human subjects

The study will be conducted in accordance with Good Pharmacoepidemiology Practices.. 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. The study protocol is dependent on approval by a Scientific Research Committee (SRC) for studies performed in THIN

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.

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 (European Medicines Agency n.d.).

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. Reports of adverse events/reactions will be summarized in the study report (European Medicines Agency 2012).

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.

Study results will be published following guidelines of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors n.d.), and communication in appropriate scientific venues will be considered.

When reporting results of this study, the appropriate STROBE checklist (Elm et al. 2007) will be followed

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Annex 1: List of stand-alone documents

None

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

ENCePP Checklist for Study Protocols (Revision 3)

Study title:

Safety and **E**ffectiveness of **R**iva**r**oxaban and **A**pixaban compared to warfarin in non valvular atrial fibrillation patients in the routine clinical practice in the UK

SiERRA UK

Study reference number: 20343

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☒	6
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7, 8
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[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:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☒	☐	☐	9.1, 9.2.2
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Duration of follow-up?	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.1, 9.3.3
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.2.1
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.3.2.1, 9.7
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3 Covariates?	☒	☐	☐	9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

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

Comments:

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

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☐	☒	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Date: 13/August/2018

Signature: _____

Annex 3: Additional information

List of Read Codes

Table S1:
Operational definitions for subpopulations:

Non-valvular Atrial Fibrillation (NVAF)	Patients with a record of Atrial fibrillation (AF) any time prior index date or within the 2 weeks after the index date, and free of valvular replacement or mitral stenosis (see table codes below) prior to index date or 2 weeks after index-date
Renal Impairment	We will obtain eGFR values from creatinine values (AHD code 1400019) using the CDK-EPI* formula. Furthermore we will define four levels of decreasing severity of Renal impairment (CKD–EPI) eGFR >50 mL/min eGFR 30–49 mL/min eGFR 15–29 mL/min eGFR <15 mL/min Unknown -

***CDK-EPI Formula:**eGFR = 141 * min(Scr/κ,1)α * max(Scr/κ, 1)-1.209 * 0.993Age * 1.018 [if female] * 1.159 [if black]*
Scr: serum creatinine (mg/dL)
κ : 0.7 for females and 0.9 for males
α: 0.329 for females and 0.411 for males
min : the minimum of Scr/κ or 1
max : the maximum of Scr/κ or 1.

Table S3- AF READ codes

READ	Description
3272.00	Ecg: atrial fibrillation
3273.00	Ecg: atrial flutter
3274.00	Ecg: paroxysmal atrial tachy.
7936A00	Implant intravenous pacemaker for atrial fibrillation
G570.00	Paroxysmal supraventricular tachycardia
G570000	Paroxysmal atrial tachycardia
G573.00	Atrial fibrillation and flutter
G573000	Atrial fibrillation
G573100	Atrial flutter
G573200	Paroxysmal atrial fibrillation
G573z00	Atrial fibrillation and flutter nos

14AN.00	H/o: atrial fibrillation
212R.00	Atrial fibrillation resolved
662S.00	Atrial fibrillation monitoring
6A9..00	Atrial fibrillation annual review
9hF..00	Exception reporting: atrial fibrillation quality indicators
9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
9Os..00	Atrial fibrillation monitoring administration
9Os0.00	Atrial fibrillation monitoring first letter
9Os1.00	Atrial fibrillation monitoring second letter
9Os2.00	Atrial fibrillation monitoring third letter
9Os3.00	Atrial fibrillation monitoring verbal invite
9Os4.00	Atrial fibrillation monitoring telephone invite
G573300	Non-rheumatic atrial fibrillation

Table s4 READ Codes for mitral stenosis (to exclude from AF patients)

READ	Description
G11..11	Rheumatic mitral valve disease
G110.00	Mitral stenosis
G110.11	Rheumatic mitral stenosis
G112.00	Mitral stenosis with insufficiency
G112.12	Mitral stenosis with incompetence
G112.13	Mitral stenosis with regurgitation
G113.00	Nonrheumatic mitral valve stenosis
G130.00	Mitral and aortic stenosis
G131.00	Mitral stenosis and aortic insufficiency
G131.13	Mitral stenosis and aortic incompetence
G131.14	Mitral stenosis and aortic regurgitation
P65..00	Congenital mitral stenosis
P650.00	Congenital mitral stenosis, unspecified
P651.00	Fused commissure of the mitral valve
P65z.00	Congenital mitral stenosis NOS
P6yyC00	Fusion of mitral valve cusps

Table S5 READ Codes for valvular replacement- to exclude from AF patients)

READ	Description
7910.12	Replacement of mitral valve
7910000	Allograft replacement of mitral valve
7910100	Xenograft replacement of mitral valve
7910200	Prosthetic replacement of mitral valve
7910211	Bjork-Shiley prosthetic replacement of mitral valve
7910212	Bjork-Shiley prosthetic replacement of mitral valve

7910213	Carpentier prosthetic replacement of mitral valve
7910214	Edwards prosthetic replacement of mitral valve
7910300	Replacement of mitral valve NEC
7911.12	Replacement of aortic valve
7911000	Allograft replacement of aortic valve
7911100	Xenograft replacement of aortic valve
7911200	Prosthetic replacement of aortic valve
7911300	Replacement of aortic valve NEC
7911500	Transapical aortic valve implantation
7911600	Transluminal aortic valve implantation
7912.11	Replacement of tricuspid valve
7912000	Allograft replacement of tricuspid valve
7912100	Xenograft replacement of tricuspid valve
7912200	Prosthetic replacement of tricuspid valve
7912300	Replacement of tricuspid valve NEC
7913.12	Replacement of pulmonary valve
7913000	Allograft replacement of pulmonary valve
7913100	Xenograft replacement of pulmonary valve
7913200	Prosthetic replacement of pulmonary valve
7913300	Replacement of pulmonary valve NEC
7914.11	Replacement of unspecified valve of heart
7914000	Allograft replacement of valve of heart NEC
7914100	Xenograft replacement of valve of heart NEC
7914200	Prosthetic replacement of valve of heart NEC
7914211	Edwards prosthetic replacement of valve of heart
7914212	Starr prosthetic replacement of valve of heart
7914300	Replacement of valve of heart NEC
7914600	Replacement of truncal valve
7919600	Percutaneous transluminal pulmonary valve replacement
791C000	Aortic root replac us pul val auto ri vent pulm art val cond
791C100	Ao ro repl us pulm val auto ri vent pul art val cond aortov
791C200	Aortic root replacement using homograft
791C300	Aortic root replacement using mechanical prosthesis
791C400	Aortic root replacement
14S4.00	H/O: heart valve recipient
14T3.00	H/O: artificial heart valve
SP00200	Mechanical complication of heart valve prosthesis
SP00400	Infect and inflammatory reaction due to cardiac valve pros
SyuK611	[X] Embolism from prosthetic heart valve

TB01200	Implant of heart valve prosthesis + complication, no blame
ZV42200	[V]Heart valve transplanted
ZV43300	[V]Has artificial heart valve
ZV45H00	[V]Presence of prosthetic heart valve
ZVu6e00	[X]Presence of other heart valve replacement

Table S6. Read codes of Dialysis (renal Impairment)

Read	Description
14V2.00	H/O: renal dialysis
14V2.11	H/O: kidney dialysis
4I29.00	Peritoneal dialysis sample
4N3..00	Peritoneal dialysis fluid cell count
4N4..00	Dialysis fluid potassium level
4N5..00	Dialysis fluid sodium level
7A60600	Creation of graft fistula for dialysis
7A61900	Ligation of arteriovenous dialysis fistula
7A61A00	Ligation of arteriovenous dialysis graft
7L1A.11	Dialysis for renal failure
7L1A000	Renal dialysis
7L1A011	Thomas intravascular shunt for dialysis
7L1A100	Peritoneal dialysis
7L1A200	Haemodialysis NEC
7L1A400	Automated peritoneal dialysis
7L1A500	Continuous ambulatory peritoneal dialysis
7L1A600	Peritoneal dialysis NEC
7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail
7L1B000	Insertion of ambulatory peritoneal dialysis catheter
7L1B100	Removal of ambulatory peritoneal dialysis catheter
7L1B200	Flushing of peritoneal dialysis catheter
7L1C000	Insertion of temporary peritoneal dialysis catheter
7L1f000	Extracorporeal albumin haemodialysis
8882.00	Intestinal dialysis
SP05613	[X] Peritoneal dialysis associated peritonitis
SP06B00	Continuous ambulatory peritoneal dialysis associated perit
TA02.00	Accid cut,puncture,perf,h'ge - kidney dialysis/oth perfusion
TA02000	Accid cut,puncture,perf,h'ge - kidney dialysis
TA02011	Accidental cut/puncture/perf/haem'ge during renal dialysis
TA12000	Foreign object left in body during kidney dialysis
TA12011	Foreign object left in body during renal dialysis
TA22000	Failure of sterile precautions during kidney dialysis
TA22011	Failure of sterile precautions during renal dialysis

TA42000	Mechanical failure of apparatus during kidney dialysis
TA42011	Mechanical failure of apparatus during renal dialysis
TB11.00	Kidney dialysis with complication, without blame
TB11.11	Renal dialysis with complication, without blame
U611200	[X]Foreign obj accid left body dur kidney dialys/oth perfus
U612200	[X]Failure sterile precautions dur kidney dialys/other perf
U641.00	[X]Kidny dialysis caus abn reac pt/lat comp no misad at time
Z131500	Warming patient with warm haemodialysis
Z131600	Warming patient with warm peritoneal dialysis
Z1A2.00	Haemodialysis training
Z1A2.11	HD - Haemodialysis training
Z919.00	Care of haemodialysis equipment
Z919100	Priming haemodialysis lines
Z919200	Washing back through haemodialysis lines
Z919300	Reversing haemodialysis lines
Z91A.00	Peritoneal dialysis bag procedure
Z91A100	Putting additive into peritoneal dialysis bag
ZV45100	[V]Renal dialysis status
ZV56.00	[V]Aftercare involving intermittent dialysis
ZV56000	[V]Aftercare involving extracorporeal dialysis
ZV56011	[V]Aftercare involving renal dialysis NOS
ZV56100	[V]Preparatory care for dialysis
ZV56y00	[V]Other specified aftercare involving intermittent dialysis
ZV56y11	[V]Aftercare involving peritoneal dialysis
ZV56z00	[V]Unspecified aftercare involving intermittent dialysis
4N...00	Dialysis fluid examination
4N0..00	Dialysis fluid urea level
4N1..00	Dialysis fluid creatinine level
4N2..00	Dialysis fluid glucose level
SP01500	Mechanical complication of dialysis catheter
Z131400	Warming patient by dialysis therapy
Z132800	Cooling patient using cool peritoneal dialysis
Z1A..00	Dialysis training
Z1A1.00	Peritoneal dialysis training
Z1A1.11	PD - Peritoneal dialysis training
Z919400	Recirculation of the dialysis machine
ZVu3G00	[X]Other dialysis

Table S7. Read codes of Kidney transplant (renal Impairment)

Read	**Description**
7B00.00	Transplantation of kidney

7B00000	Autotransplant of kidney
7B00100	Transplantation of kidney from live donor
7B00111	Allotransplantation of kidney from live donor
7B00200	Transplantation of kidney from cadaver
7B00211	Allotransplantation of kidney from cadaver
7B00300	Allotransplantation of kidney from cadaver, heart-beating
7B00400	Allotransplantation kidney from cadaver, heart non-beating
7B00500	Allotransplantation of kidney from cadaver NEC
7B00y00	Other specified transplantation of kidney
7B00z00	Transplantation of kidney NOS
7B01500	Transplant nephrectomy
7B01511	Excision of rejected transplanted kidney
7B06300	Exploration of renal transplant
7B0F.00	Interventions associated with transplantation of kidney
7B0F100	Pre-transplantation of kidney work-up, recipient
7B0F200	Pre-transplantation of kidney work-up, live donor
7B0F300	Post-transplantation of kidney examination, recipient
7B0F400	Post-transplantation of kidney examination, live donor
7B0Fy00	OS interventions associated with transplantation of kidney
7B0Fz00	Interventions associated with transplantation of kidney NOS
8L50.00	Renal transplant planned
SP08011	Det.ren.func.after ren.transpl
SP08300	Kidney transplant failure and rejection
TB00100	Kidney transplant with complication, without blame
ZV42000	[V]Kidney transplanted
14S2.00	H/O: kidney recipient

CKD stage 1

1Z10.00	Chronic kidney disease stage 1
1Z17.00	Chronic kidney disease stage 1 with proteinuria
1Z17.11	CKD stage 1 with proteinuria
1Z18.00	Chronic kidney disease stage 1 without proteinuria

CKD Stage 2

1Z11.00	Chronic kidney disease stage 2
1Z19.00	Chronic kidney disease stage 2 with proteinuria
1Z19.11	CKD stage 2 with proteinuria
1Z1A.00	Chronic kidney disease stage 2 without proteinuria

1Z1A.11	CKD stage 2 without proteinuria

CKD stage 3

1Z12.00	Chronic kidney disease stage 3
1Z15.00	Chronic kidney disease stage 3A
1Z16.00	Chronic kidney disease stage 3B
1Z1B.00	Chronic kidney disease stage 3 with proteinuria
1Z1B.11	CKD stage 3 with proteinuria
1Z1C.00	Chronic kidney disease stage 3 without proteinuria
1Z1C.11	CKD stage 3 without proteinuria
1Z1D.00	Chronic kidney disease stage 3A with proteinuria
1Z1D.11	CKD stage 3A with proteinuria
1Z1E.00	Chronic kidney disease stage 3A without proteinuria
1Z1E.11	CKD stage 3A without proteinuria
1Z1F.00	Chronic kidney disease stage 3B with proteinuria
1Z1F.11	CKD stage 3B with proteinuria
1Z1G.00	Chronic kidney disease stage 3B without proteinuria
1Z1G.11	CKD stage 3B without proteinuria

CKD stage 4

1Z13.00	Chronic kidney disease stage 4
1Z1H.00	Chronic kidney disease stage 4 with proteinuria
1Z1H.11	CKD stage 4 with proteinuria
1Z1J.00	Chronic kidney disease stage 4 without proteinuria
1Z1J.11	CKD stage 4 without proteinuria

Dialysis Stage 4

14V2.00	H/O: renal dialysis
14V2.11	H/O: kidney dialysis
4I29.00	Peritoneal dialysis sample
4N3..00	Peritoneal dialysis fluid cell count
4N4..00	Dialysis fluid potassium level
4N5..00	Dialysis fluid sodium level
7A60600	Creation of graft fistula for dialysis
7A61900	Ligation of arteriovenous dialysis fistula

7A61A00	Ligation of arteriovenous dialysis graft
7L1A.11	Dialysis for renal failure
7L1A000	Renal dialysis
7L1A011	Thomas intravascular shunt for dialysis
7L1A100	Peritoneal dialysis
7L1A200	Haemodialysis NEC
7L1A400	Automated peritoneal dialysis
7L1A500	Continuous ambulatory peritoneal dialysis
7L1A600	Peritoneal dialysis NEC
7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail
7L1B000	Insertion of ambulatory peritoneal dialysis catheter
7L1B100	Removal of ambulatory peritoneal dialysis catheter
7L1B200	Flushing of peritoneal dialysis catheter
7L1C000	Insertion of temporary peritoneal dialysis catheter
7L1f000	Extracorporeal albumin haemodialysis
8882.00	Intestinal dialysis
SP05613	[X] Peritoneal dialysis associated peritonitis
SP06B00	Continuous ambulatory peritoneal dialysis associated perit
TA02.00	Accid cut,puncture,perf,h'ge - kidney dialysis/oth perfusion
TA02000	Accid cut,puncture,perf,h'ge - kidney dialysis
TA02011	Accidental cut/puncture/perf/haem'ge during renal dialysis
TA12000	Foreign object left in body during kidney dialysis
TA12011	Foreign object left in body during renal dialysis
TA22000	Failure of sterile precautions during kidney dialysis
TA22011	Failure of sterile precautions during renal dialysis
TA42000	Mechanical failure of apparatus during kidney dialysis
TA42011	Mechanical failure of apparatus during renal dialysis
TB11.00	Kidney dialysis with complication, without blame
TB11.11	Renal dialysis with complication, without blame
U611200	[X]Foreign obj accid left body dur kidney dialys/oth perfus
U612200	[X]Failure sterile precautions dur kidney dialys/other perf
U641.00	[X]Kidny dialysis caus abn reac pt/lat comp no misad at time
Z131500	Warming patient with warm haemodialysis
Z131600	Warming patient with warm peritoneal dialysis
Z1A2.00	Haemodialysis training
Z1A2.11	HD - Haemodialysis training
Z919.00	Care of haemodialysis equipment
Z919100	Priming haemodialysis lines
Z919200	Washing back through haemodialysis lines

Z919300	Reversing haemodialysis lines
Z91A.00	Peritoneal dialysis bag procedure
Z91A100	Putting additive into peritoneal dialysis bag
ZV45100	[V]Renal dialysis status
ZV56.00	[V]Aftercare involving intermittent dialysis
ZV56000	[V]Aftercare involving extracorporeal dialysis
ZV56011	[V]Aftercare involving renal dialysis NOS
ZV56100	[V]Preparatory care for dialysis
ZV56y00	[V]Other specified aftercare involving intermittent dialysis
ZV56y11	[V]Aftercare involving peritoneal dialysis
ZV56z00	[V]Unspecified aftercare involving intermittent dialysis
4N...00	Dialysis fluid examination
4N0..00	Dialysis fluid urea level
4N1..00	Dialysis fluid creatinine level
4N2..00	Dialysis fluid glucose level
SP01500	Mechanical complication of dialysis catheter
Z131400	Warming patient by dialysis therapy
Z132800	Cooling patient using cool peritoneal dialysis
Z1A..00	Dialysis training
Z1A1.00	Peritoneal dialysis training
Z1A1.11	PD - Peritoneal dialysis training
Z919400	Recirculation of the dialysis machine
7B00.00	Transplantation of kidney
7B00000	Autotransplant of kidney
7B00100	Transplantation of kidney from live donor
7B00111	Allotransplantation of kidney from live donor
7B00200	Transplantation of kidney from cadaver
7B00211	Allotransplantation of kidney from cadaver
7B00300	Allotransplantation of kidney from cadaver, heart-beating
7B00400	Allotransplantation kidney from cadaver, heart non-beating
7B00500	Allotransplantation of kidney from cadaver NEC
7B00y00	Other specified transplantation of kidney
7B00z00	Transplantation of kidney NOS
7B01500	Transplant nephrectomy
7B01511	Excision of rejected transplanted kidney
7B06300	Exploration of renal transplant
7B0F.00	Interventions associated with transplantation of kidney
7B0F100	Pre-transplantation of kidney work-up, recipient
7B0F200	Pre-transplantation of kidney work-up, live donor

7B0F300	Post-transplantation of kidney examination, recipient
7B0F400	Post-transplantation of kidney examination, live donor
7B0Fy00	OS interventions associated with transplantation of kidney
7B0Fz00	Interventions associated with transplantation of kidney NOS
8L50.00	Renal transplant planned
SP08011	Det.ren.func.after ren.transpl
SP08300	Kidney transplant failure and rejection
TB00100	Kidney transplant with complication, without blame
ZV42000	[V]Kidney transplanted
14S2.00	H/O: kidney recipient

Table S8. Read codes of intracranial hemorrhage (safety analysis)

Read	Description
14AF.00	H/O sub-arachnoid haemorrhage
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
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
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

G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G62..00	Other and unspecified intracranial haemorrhage
G62z.00	Intracranial haemorrhage NOS
G682.00	Sequelae of other nontraumatic intracranial haemorrhage
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6B00	[X]Sequelae of other nontraumatic intracranial haemorrhage
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
G600.00	Ruptured berry aneurysm
Q200.00	Subdural and cerebral haemorrhage due to birth trauma
Q200000	Cerebral haemorrhage unspecified
Q200011	Intracerebral haemorrhage in fetus or newborn
Q200012	Intracranial haemorrhage in fetus or newborn
Q200700	Cerebral haemorrhage due to birth injury
Q200y00	Subdural or cerebral haemorrhage due to birth trauma os
Q200z00	Subdural or cerebral haemorrhage due to birth trauma nos
Q208.00	Cerebral oedema due to birth injury
Q313100	Perinatal lung intra-alveolar haemorrhage
Q412.00	Perinatal subarachnoid haemorrhage
Q412000	Subarachnoid haemorrhage due to birth injury
Q417.00	Intracranial nontraumatic haemorrhage of fetus and newborn
Q417000	Intracerebral (nontraumatic) haemorrhage of fet and newborn
Qyu5F00	[X]intracranial nontraumatic haemorrhage fetus newborn unsp
S62..00	Cerebral haemorrhage following injury
S62..12	Subarachnoid haemorrhage following injury
S62..14	Traumatic cerebral haemorrhage
S620.00	Closed traumatic subarachnoid haemorrhage
S621.00	Open traumatic subarachnoid haemorrhage
S627.00	Traumatic subarachnoid haemorrhage
S62z.00	Cerebral haemorrhage following injury nos
S63..00	Other cerebral haemorrhage following injury
S63z.00	Other cerebral haemorrhage following injury nos
7017000	Evacuation of subdural haematoma
7032000	Evacuation of extradural haematoma

G622.00	Subdural haematoma - nontraumatic
Q200200	Local subdural haematoma due to birth trauma
S624.11	Epidural haematoma following injury
S629.00	Traumatic subdural haematoma
S629000	Traumatic subdural haematoma without open intracranial wound
S629100	Traumatic subdural haematoma with open intracranial wound
S62A.00	Traumatic extradural haematoma
S62A100	Traumatic extradural haematoma with open intracranial wound

Table S9. Read codes of ischemic events (effectiveness analysis)

Read	Description
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
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
14A7.00	H/O: CVA/stroke
14A7.11	H/O: CVA
14A7.12	H/O: stroke
14AK.00	H/O: Stroke in last year
662M100	Stroke 6 month review
662M200	Stroke initial post discharge review
8HBJ.00	Stroke / transient ischaemic attack referral
G63..11	Infarction - precerebral
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
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
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G654.00	Multiple and bilateral precerebral artery syndromes
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
G676.00	Nonpyogenic venous sinus thrombosis
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G683.00	Sequelae of cerebral infarction
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
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6C00	[X]Sequelae of stroke, not specfd as h'morrhage or infarction
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
L440.12	Stroke in the puerperium
ZLEP.00	Discharge from stroke serv
ZV12511	[V]Personal history of stroke
ZV12512	[V]Personal history of cerebrovascular accident (CVA)
G63y100	Cerebral infarction due to embolism of precerebral arteries
G641000	Cerebral infarction due to embolism of cerebral arteries

	Proposed Systemic Embolism codes
G742z00	Peripheral arterial embolism and thrombosis NOS
K138000	Renal artery embolism
K138011	Renal artery embolus
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
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
Gyu7500	[X]Embolism and thrombosis of other arteries
G74..00	Arterial embolism and thrombosis
G74..11	Arterial embolus and thrombosis
G74..12	Thrombosis - arterial
G74..13	Arterial embolic and thrombotic occlusion
G740.00	Embolism and thrombosis of the abdominal aorta
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

G74z.00	Arterial embolism and thrombosis NOS

Table S10. Read codes of venous thromboembolism

Read	Description
G801.00:G80zz00	Code range
G80..00	Phlebitis and thrombophlebitis
G800.11	Saphenous vein phlebitis
G800.12	Saphenous vein thrombophlebitis
G800000	Phlebitis of the long saphenous vein
G800100	Phlebitis of the short saphenous vein
G800300	Thrombophlebitis of the long saphenous vein
G800400	Thrombophlebitis of the short saphenous vein
G401.00	Pulmonary embolism
G401.12	Pulmonary embolus
14A8.12	H/o: thrombosis
2I17.00	O/e - phlebitis
G402.00	Pulmonary infarct
G82..00	Other venous embolism and thrombosis
L096400	Pulmonary embolism following abortive pregnancy
L414.12	Phlegmasia alba dolens - obstetric
L43..00	Obstetric pulmonary embolism
L432.00	Obstetric blood-clot pulmonary embolism
L432000	Obstetric blood-clot pulmonary embolism unspecified
L432100	Obstetric blood-clot pulmonary embolism - delivered
L432300	Obstetric blood-clot pulmonary embolism + a/n complication
L432400	Obstetric blood-clot pulmonary embolism + p/n complication
L432z00	Obstetric blood-clot pulmonary embolism nos
L43y.00	Other obstetric pulmonary embolism
L43y000	Other obstetric pulmonary embolism unspecified
L43y100	Other obstetric pulmonary embolism - delivered
L43y200	Other obstetric pulmonary embolism - delivered + p/n comp
L43y300	Other obstetric pulmonary embolism with antenatal comp
L43y400	Other obstetric pulmonary embolism with postnatal comp
L43yz00	Other obstetric pulmonary embolism nos
L43z.00	Obstetric pulmonary embolism nos
L43z000	Obstetric pulmonary embolism nos
L43z100	Obstetric pulmonary embolism nos - delivered
L43z200	Obstetric pulmonary embolism nos - delivered with p/n comp
L43z300	Obstetric pulmonary embolism nos with antenatal complication
L43z400	Obstetric pulmonary embolism nos with postnatal complication

L43zz00	Obstetric pulmonary embolism nos
ZV12900	[V] personal history of pulmonary embolism

Table S11. Read codes of orthopedic arthroplasty

Read	Description
7K2..00	Hip joint operations
7K20.00	Total prosthetic replacement of hip joint using cement
7K20.12	Aufranc total replacement of hip joint using cement
7K20.13	Charnley total replacement of hip joint using cement
7K20.14	Exeter total replacement of hip joint using cement
7K20.15	Farrer total replacement of hip joint using cement
7K20.16	Freeman total replacement of hip joint using cement
7K20.17	Furlong total replacement of hip joint using cement
7K20.18	Howse total replacement of hip joint using cement
7K20.19	Ilch total replacement of hip joint using cement
7K20.1A	Mckee total replacement of hip joint using cement
7K20.1B	Monk total replacement of hip joint using cement
7K20.1C	Muller total replacement of hip joint using cement
7K20.1D	Pretoria total replacement of hip joint using cement
7K20.1E	Stanmore total replacement of hip joint using cement
7K20.1F	Turner total replacement of hip joint using cement
7K20.1G	Thr - total prosthetic replacement of hip joint using cement
7K20000	Primary cemented total hip replacement
7K20011	Charnley cemented total hip replacement
7K20100	Conversion to cemented total hip replacement
7K20200	Revision cemented total hip replacement
7K20300	Primary hybrid total replacement of hip joint nec
7K20400	Conversion to hybrid total hip replacement nec
7K20500	Revision of hybrid total hip replacement nec
7K20x00	Conversion from cemented total hip replacement
7K20x11	Removal prev cemented total prosthetic replacement hip joint
7K20y00	Total prosthetic replacement of hip joint using cement os
7K20z00	Total prosthetic replacement of hip joint using cement nos
7K21.00	Total prosthetic replacement of hip joint not using cement
7K21.11	Freeman total replacement of hip joint not using cement
7K21.12	Furlong total replacement of hip joint not using cement
7K21.13	Lord total replacement of hip joint not using cement
7K21.14	Madreporique total replacement of hip joint not using cement
7K21.15	Monk total replacement of hip joint not using cement
7K21.16	Ring total replacement of hip joint not using cement
7K21.17	Thr - total prosthetic replacement hip joint without cement

7K21000	Primary uncemented total hip replacement
7K21100	Conversion to uncemented total hip replacement
7K21200	Revision uncemented total hip replacement
7K21x00	Conversion from uncemented total hip replacement
7K21x11	Removal previous uncement total prosthet replacem hip joint
7K21y00	Total prosthetic replacement hip joint not using cement os
7K21z00	Total prosthetic replacement hip joint not using cement nos
7K22.00	Other total prosthetic replacement of hip joint
7K22.12	Thr - other total prosthetic replacement of hip joint
7K22000	Primary total prosthetic replacement of hip joint nec
7K22011	Primary hybrid total replacement of hip joint nec
7K22100	Conversion to total prosthetic replacement of hip joint nec
7K22112	Conversion to hybrid total hip replacement nec
7K22200	Revision of total prosthetic replacement of hip joint nec
7K22211	Revision of hybrid total hip replacement nec
7K22300	Attention to total hip replacement nec
7K22x00	Conversion from prev total pros replace hip joint nec
7K22x11	Removal previous total prosthetic replacement hip joint nec
7K22x12	Conver from hybrid total prosth hip joint replace nec
7K22y00	Other specified total prosthetic replacement of hip joint
7K22z00	Total prosthetic replacement of hip joint nos
7K23.00	Prosthetic cemented hemiarthroplasty of hip
7K23.12	Austin - moore hemiarthroplasty of hip joint using cement
7K23.13	Hastings hemiarthroplasty of hip joint using cement
7K23.14	Monk hemiarthroplasty of hip joint using cement
7K23.16	Thompson hemiarthroplasty of hip joint using cement
7K23000	Primary cemented hemiarthroplasty of hip
7K23100	Conversion to cemented hemiarthroplasty of hip
7K23200	Revision cemented hemiarthroplasty of hip
7K23x00	Conversion from cemented hemiarthroplasty of hip
7K23y00	Other specified prosthetic cemented hemiarthroplasty of hip
7K23z00	Prosthetic cemented hemiarthroplasty of hip nos
7K24.00	Prosthetic uncemented hemiarthroplasty of hip
7K24.12	Austin moore hemiarthroplasty of hip joint not using cement
7K24.13	Bateman hemiarthroplasty of hip joint not using cement
7K24.14	Brown hemiarthroplasty of hip joint not using cement
7K24.15	Judet hemiarthroplasty of hip joint not using cement
7K24.16	Matchett hemiarthroplasty of hip joint not using cement
7K24.17	Monk hemiarthroplasty of hip joint not using cement
7K24.18	Austin moore hemiarthroplasty of hip joint not using cement
7K24.19	Thompson hemiarthroplasty of hip joint not using cement

7K24000	Primary uncemented hemiarthroplasty of hip
7K24100	Conversion to uncemented hemiarthroplasty of hip
7K24200	Revision uncemented hemiarthroplasty of hip
7K24x00	Conversion from uncemented hemiarthroplasty of hip
7K24y00	Other specified prosthetic uncemented hemiarthroplasty hip
7K24z00	Prosthetic uncemented hemiarthroplasty of hip nos
7K25.00	Other prosthetic hemiarthroplasty of hip
7K25000	Primary prosthetic hemiarthroplasty of hip nec
7K25100	Conversion to prosthetic hemiarthroplasty of hip nec
7K25200	Revision of prosthetic hemiarthroplasty of hip nec
7K25300	Attention to prosthetic hemiarthroplasty of hip nec
7K25x00	Conversion from previous hemiarthroplasty of hip nec
7K25y00	Other specified other prosthetic hemiarthroplasty of hip
7K25z00	Other prosthetic hemiarthroplasty of hip nos
7K2y.00	Other specified operations on hip joint
7K2z.00	Hip joint operations nos
7K30.00	Total prosthetic replacement of knee joint using cement
7K30.11	Anametric total replacement of knee joint using cement
7K30.13	Attenborough total replacement of knee joint using cement
7K30.15	Cavendish total replacement of knee joint using cement
7K30.16	Charnley total replacement of knee joint using cement
7K30.17	Deane total replacement of knee joint using cement
7K30.18	Denham total replacement of knee joint using cement
7K30.19	Freeman total replacement of knee joint using cement
7K30.1A	Geomedic total replacement of knee joint using cement
7K30.1B	Geometric total replacement of knee joint using cement
7K30.1C	Guepar hinge replacement of knee joint using cement
7K30.1D	Gunston total replacement of knee joint using cement
7K30.1E	Herbert total replacement of knee joint using cement
7K30.1F	Ilch total replacement of knee joint using cement
7K30.1G	Irving total replacement of knee joint using cement
7K30.1H	Liverpool total replacement of knee joint using cement
7K30.1I	Manchester total replacement of knee joint using cement
7K30.1J	Marmor total replacement of knee joint using cement
7K30.1L	Melbourne total replacement of knee joint using cement
7K30.1N	Polycentric total replacement of knee joint using cement
7K30.1P	Sheehan total replacement of knee joint using cement
7K30.1Q	Shiers total replacement of knee joint using cement
7K30.1R	Stanmore total replacement of knee joint using cement
7K30.1S	Swanson total replacement of knee joint using cement
7K30.1T	Uci total replacement of knee joint using cement

7K30.1V	Tkr -total prosthetic replacement of knee joint using cement
7K30000	Primary cemented total knee replacement
7K30100	Conversion to cemented total knee replacement
7K30200	Revision cemented total knee replacement
7K30x00	Conversion from cemented total knee replacement
7K30x11	Removal previous cemented total prosthetic replacement knee
7K30y00	Total prosthetic replacement of knee joint using cement os
7K30z00	Total prosthetic replacement of knee joint using cement nos
7K31.00	Total prosthetic replacement of knee joint not using cement
7K31.12	Tkr - total prosthetic replacement knee joint without cement
7K31000	Primary uncemented total knee replacement
7K31100	Conversion to uncemented total knee replacement
7K31200	Revision uncemented total knee replacement
7K31x00	Conversion from uncemented total knee replacement
7K31x11	Removal previous uncemented total prosthet replacement knee
7K31y00	Total prosthetic replacement knee joint not using cement os
7K31z00	Total prosthetic replacement knee joint not using cement nos
7K32.00	Other total prosthetic replacement of knee joint
7K32.12	Tkr - other total prosthetic replacement of knee joint
7K32000	Primary total knee replacement nec
7K32011	Primary hybrid total knee replacement nec
7K32100	Conversion to total knee replacement nec
7K32111	Removal of prosthetic knee joint
7K32112	Conversion to hybrid total knee replacement nec
7K32200	Revision of total knee replacement nec
7K32211	Revision hybrid total knee replacement nec
7K32400	Attention to total knee replacement nec
7K32411	Attention to hybrid total knee replacement nec
7K32x00	Conversion from total knee replacement nec
7K32x11	Removal previous total prosthetic replacement knee joint nec
7K32x12	Conversion from hybrid total knee replacement nec
7K32y00	Other total prosthetic replacement of knee joint os
7K32z00	Other total prosthetic replacement of knee joint nos
7K37.00	Cemented unicompartmental knee replacement
7K37000	Primary cemented unicompartmental knee replacement
7K37100	Conversion to cemented unicompartmental knee replacement
7K37200	Revision cemented unicompartmental knee replacement
7K37x00	Conversion from cemented unicompartmental knee replacement
7K38.00	Uncemented unicompartmental knee replacement
7K38000	Primary uncemented unicompartmental knee replacement
7K38100	Conversion to uncemented unicompartmental knee replacement

7K38200	Revision uncemented unicompartmental knee replacement
7K38x00	Conversion from uncemented unicompartmental knee replacement
7K39.00	Hybrid unicompartmental knee replacement
7K39000	Primary hybrid unicompartmental knee replacement
7K39100	Conversion to hybrid unicompartmental knee replacement
7K39200	Revision hybrid unicompartmental knee replacement
7K39x00	Conversion from hybrid unicompartmental knee replacement
8L80.00	Hip replacement planned
7K20.11	Arthroplasty of hip joint using cement
7K20600	Conver from hybrid total prosth hip joint replace nec
7K22.11	Other arthroplasty of hip joint
7K30.12	Arthroplasty of knee joint using cement
7K30.14	Autophor arthroplasty of knee joint using cement
7K30.1K	Mckee arthroplasty of knee joint using cement
7K30.1M	Platt arthroplasty of knee joint using cement
7K30.1O	Pretoria arthroplasty of knee joint using cement
7K30.1U	Wallidus hinge arthroplasty of knee joint using cement
7K31.11	Arthroplasty of knee joint not using cement
7K32.11	Other arthroplasty of knee joint
7K68500	Excision arthroplasty of hip
7L0G200	Secndry arthroplasty hip for correctn congenital deformity
7L0G211	Colonna arthroplasty of hip