KEPPRA® (LEVETIRACETAM)

COMPARING THE INCIDENCE OF ACUTE RENAL FAILURE IN PATIENTS WITH EPILEPSY EXPOSED TO LEVETIRACETAM VERSUS OTHER ANTIEPILEPTIC DRUGS

Title	**Comparing the incidence of acute renal failure in patients with epilepsy exposed to levetiracetam versus other antiepileptic drugs**
Protocol version identifier	V1.0
Date of last version of protocol	V0.4 on 6th February 2018
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Active substance	Levetiracetam, lamotrigine, phenytoin, valproic acid, carbamazepine, gabapentin, topiramate, oxcarbazepine, pregabalin, phenobarbital, zonisamide, lacosamide, ethosuximide
Medicinal product	Levetiracetam, lamotrigine, phenytoin, valproic acid, carbamazepine, gabapentin, topiramate, oxcarbazepine, pregabalin, phenobarbital, zonisamide, lacosamide, ethosuximide
Product reference	N03AX14
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Marketing authorisation holder(s)	UCB Pharma SA
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Research question and objectives	This study is being conducted to compare the incidence of acute renal failure in patients with epilepsy exposed to levetiracetam versus other antiepileptic drugs in order to further review the association between exposure to levetiracetam and acute renal failure using real world data from a claim database in the US
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2 LIST OF ABBREVIATIONS

AED	Antiepileptic drug
AKI	Acute kidney injury
ARF	Acute Renal Failure
CCMC	Commercial Claims and Medicare Database
CI	Confidence Interval
CNS	Central Nervous System
CPT	Current Procedural Technology
EMA	European Medicines Agency
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
HIPPA	Health Insurance Portability and Accountability Act
HCUP	Healthcare Cost and Utilization Project
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	Internal Classification of Diseases, Tenth Revision, Clinical Modification
IPTW	Inverse Probability of Treatment Weights
IR	Incidence Rate
IRR	Incidence Rate Ratio
LEV	Levetiracetam
MDCD	MarketScan Multi-State Medicaid Database
MDCR	MarketScan Medicare Supplemental and Coordination of Benefits (Medicare Supplemental)
MHPD	Market Health Product Directorate
NDC	National Drug Code
PI	Prescribing Information
PRAC	Pharmacovigilance Risk Assessment Committee
US	United States
WHO	World Health Organization

3 RESPONSIBLE PARTIES

This study is being sponsored and conducted by UCB Pharma SA.

4 ABSTRACT

Title: Comparing the incidence of acute renal failure in patients with epilepsy exposed to levetiracetam monotherapy or polytherapy versus other antiepileptic drugs

Rationale and background: UCB identified a published case-report suggesting a link between the occurrence of acute renal failure (ARF) and levetiracetam (LEV) administration. In addition, there was a signal assessment conducted by the World Health Organization (WHO) on impaired renal function, including acute renal failure and interstitial nephritis in association with exposure to LEV. UCB received a request from the Marketed Health Product Directorate (MHPD) of Health Canada to submit a summary of adverse events and serious adverse drug reactions of acute renal failure in patients exposed to LEV. UCB also received another similar request from Medsafe, the New Zealand Medicines and Medical Devices Safety Authority. UCB thus conducted a comprehensive safety signal assessment and confirmed the risk of ARF after exposure to LEV. A signal assessment specific for interstitial nephritis disease was also conducted but the risk was not confirmed. Consequently, the term "acute kidney injury" was added to section 4.8 undesirable effects of the company core data sheet for LEV in the post-marketing experience sub-section and under renal and urinary disorders system organ class. Additionally, following a review of the US PI to add ARF submitted on the 29th of April 2016, the Food and Drug Administration (FDA) requested UCB on the 25 Oct 2016 to update the labeling to include interstitial nephritis in post-marketing experience section 6.2. The UCB Benefit Risk Team decided to conduct the present study to further characterize the risk of acute renal failure in patients exposed to LEV and other antiepileptic drugs (AEDs). Subsequently, UCB received an assessment report, (Procedure No. EMEA/H/C/000277/II/0162) from the European Medicines Agency (EMA) on 23 Aug 2016, with a request to investigate the actual mechanism underlying the development of acute renal failure after use of LEV. The EMA acknowledged that the proposed study would not provide information on the underlying mechanism for developing acute renal failure, but agreed to the study to compare the risk of acute renal failure in patients exposed to LEV versus other AEDs.

Research question and objectives: This study is being conducted to compare the incidence of acute renal failure in patients with epilepsy initiating LEV monotherapy or polytherapy versus other antiepileptic drugs (AEDs) as monotherapy or polytherapy to further review the association between exposure to LEV and ARF using real world data from a claims database in the US

Study design: This will be a retrospective cohort study

Population: The study population will comprise a US population of patients with an epilepsy diagnosis with a new prescription of LEV or comparator AED between 2009 and 2017, identified in the IBM® MarketScan® Databases.(Although the name of the database has changed since last Protocol version, we are referring to the same database as before).

Variables: The exposure variable is treatment with LEV or comparator AED as monotherapy (first time use) or polytherapy (continuing AED use). The outcome variable is acute renal failure.

Covariates include baseline demographic characteristics, comorbidities, medications, and health care resource utilization.

Data source: The analysis will be conducted using the IBM® MarketScan® Databases, a US claims database.

Study size: Each AED treatment cohort will comprise a minimum of 3000 eligible study participants in order to detect an incidence rate ratio ranging from 1.5 to 4.0 between any two AED comparator cohorts with a power of 80% and a 2-sided 99.9995% confidence interval, and also assuming that the incidence of acute renal failure in the comparator cohorts is 0.5%.

Data analysis: A modified Poisson regression model with robust variance estimator will be used to estimate the incidence rates (IRs) and incidence rate ratios (IRR) of acute renal failure. The IR will be calculated as the total number of new cases diagnosed with acute renal failure during the follow-up period divided by the sum of person-years at risk during follow-up. The IRR will be obtained by dividing the IR in the LEV cohort by the IR for each of the comparator cohorts. Crude incidence rate ratios and 95% CI based on unweighted samples will be calculated. To control for confounding, inverse probability of treatment weights (IPTW) using high dimensional propensity score will be constructed. A modified Poisson regression model with robust variance estimator performed based on the stabilized IPTW weighted samples will be used to generate final adjusted effect measure estimates (incidence rate ratios).

Milestones: Registration in EU PAS 10Dec2018; Planned Study results June 30th 2020.

5 AMENDMENTS AND UPDATES

Details of protocol amendments are provided in below Table 5–1

Table 5–1: Protocol amendments

Number	Date	Section of study protocol	Amendment or update	Reason
V0.2	12-Apr-2017	N/A	Update	Initial submission to EMA
V0.3	18-Sep-2017	N/A	Update	1st Response to Questions from EMA
V0.4	12-Feb-2018	N/A	Update	2nd Response to Questions from EMA
V1.0	Mar-2020	N/A	Update and Amendments	See below in Appendix 6 the list of amendments and updates

6 MILESTONES

The planned dates for study milestones will be indicated below in Table 6–1.

Table 6–1: List of study milestones

Milestone	Planned dates
Date of data extraction	April 1st 2020
Date of final analytical data set	April 30th 2020
Registration in the EU PAS registry	December 10th 2018
Final study report (planned)	June 30th 2020

7 RATIONALE AND INTRODUCTION

Epilepsy is a condition characterized by at least two unprovoked (or reflex) seizures occurring greater than 24 hours apart or one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years (Fisher et al, 2014). It is one of the most common neurological disorders of the brain, affecting approximately 70 million people worldwide (Ngugi et al, 2010). The lifetime risk of developing epilepsy is between 3% and 5%, with highest incidence reported in neonates, young children, and the elderly (Barnejee et al, 2009). Epilepsy is associated with increased morbidity and mortality, and can severely impact the quality of life of patients with epilepsy (Quintas et al, 2012).

The goal of epilepsy treatment is to get the patient to be seizure-free and experience no or minimal side effects, with optimal quality of life. Anticonvulsants are the mainstay of epilepsy treatment in addition to other non-pharmacological treatment options including ketogenic diet, vagal nerve stimulation and surgery. There are approximately 20 antiepileptic drugs (AEDs) available on the market with diverse mechanisms of action, and efficacy and safety profiles. The choice of AEDs is primarily based on evidence of efficacy for the patient's seizure type, safety profile of the drug and patient-specific factors including age, sex, childbearing potential, comorbidities, and use of concomitant medications (Perucca et al, 2011). Monotherapy is recommended for patients with newly diagnosed epilepsy. Combination therapy is initiated upon unresponsiveness to monotherapy. Despite available treatment options, seizure control remains a challenge for many patients, particularly those with partial epilepsy. About one-third of treated patients continue to experience seizures, and are thus receiving little benefit from their current therapy (Kwan et al, 2000). Adverse effects of AEDs are common and can have a considerable impact on quality of life and contribute to treatment failure in up to 40% of patients (Perucca, 2005). The adverse effect profiles of AEDs differ greatly and are often a determining factor in drug selection because of the similar efficacy rates shown by most AEDs.

UCB identified a published case-report suggesting a link between the occurrence of Acute Renal Failure (ARF) and LEV administration (Spengler et al, 2014). Following this, the Marketed Health Product Directorate (MHPD) of Health Canada requested UCB to submit a summary of adverse events and serious adverse drug reactions of acute renal injury in patients exposed to LEV. UCB then received another similar request from Medsafe, the New Zealand Medicines and Medical Devices Safety Authority. Both health authority requests appeared to be in response to a signal assessment conducted by the World Health Organization (WHO) on impaired renal function, including acute renal failure and interstitial nephritis in association with LEV exposure

(Choonara and Star 2015). UCB thus conducted a comprehensive safety signal assessment and confirmed the risk of acute renal failure after exposure to LEV. A signal assessment specific for interstitial nephritis was also conducted but the risk was not confirmed. Consequently, the term "acute kidney injury" was added to section 4.8 undesirable effects of the CCDS for LEV in the post-marketing experience sub-section and under renal and urinary disorders system organ class. Acute Kidney Injury (AKI) is another term for Acute Renal Failure (ARF). It is often used interchangeably by the medical field. Additionally, following a review of the US Prescribing Information (PI) to add AKI submitted on the 29th of April 2016, the Food and Drug Administration (FDA) requested UCB on the 25 Oct 2016 to update the labeling to include interstitial nephritis in post-marketing experience section 6.2. The UCB Benefit Risk Team decided to conduct the present study to further characterize the risk of acute renal failure in patients exposed to LEV and other AEDs. Subsequently, UCB received an assessment report (Procedure No. EMEA/H/C/000277/II/0162) from the EMA on 23 Aug 2016 with a request to investigate the actual mechanism underlying the development of acute renal failure after use of LEV. The EMA acknowledged that the proposed study would not provide any information on the underlying mechanism for developing acute renal failure, but agreed to the study This study is being conducted to further review the association between exposure to LEV and acute renal failure using real world data from a claims database in the US in order to further characterize this risk with respect to other AEDs.

8 RESEARCH QUESTION AND OBJECTIVE

The objective of the study is to compare the incidence rate of acute renal failure among patients exposed to LEV versus other AEDs (as monotherapy or polytherapy) to further characterize the risk of renal failure in patients treated with AEDs.

The research question that will be addressed by this project is as follows: Is the incidence rate of acute renal failure higher in patients with epilepsy exposed to LEV treatment compared to patients with epilepsy exposed to other AEDS?

The following hypothesis will be addressed:

- Null hypothesis (H_0): The incidence rate of acute renal failure in patients with epilepsy exposed to LEV (as monotherapy or polytherapy i.e. LEV in combination with other AEDs) is the same as in patient with epilepsy exposed to other AED monotherapy regimens or AED polytherapy regimens excluding LEV.
- Alternative hypothesis (H_1): The incidence rate of acute renal failure in patients with epilepsy exposed to LEV (as monotherapy or polytherapy i.e. LEV in combination with other AEDs) is the different from patients with epilepsy exposed to other AED monotherapy regimens or AED polytherapy regimens excluding LEV.

9 RESEARCH METHODS

9.1 Study design

This will be a retrospective cohort study that will be conducted using the US-based claims database, IBM® MarketScan® Research Databases. Details of the study design and statistical analysis methods are presented below.

9.2 Setting

9.2.1 Study period

The study period is defined based on data availability. The IBM® MarketScan® Research Databases covers the period between 01-Jan-2008 and 31-Dec-2017. The study period will include a baseline period, a patient selection period and a follow-up period.

9.2.1.1 Patient selection period

The patient selection period will be from 01-Jan-2009 to 30-Sept-2017. This will allow for patients to have a 1-year baseline period and to allow for 90 days of follow-up for patients identified at the end of the patient selection period.

The index date (and start of follow-up) will be the date of the first LEV or comparator AED prescription (as monotherapy or polytherapy) claim among patients with a diagnosis of epilepsy during the 1-year-period prior to the index date (the baseline period).

9.2.1.2 Baseline period

The baseline period is the period before the index date, and for this study will be defined as the 1-year period preceding (and not including) the index date. During the baseline period, patients will be required to have continuous insurance enrolment with both medical and pharmacy coverage. This requirement ensures availability of complete claims history for each study patient for services received in hospital, emergency department, outpatient clinics, and prescriptions filled in an outpatient pharmacy. These data permit evaluation of the baseline demographic and clinical characteristics prior to the index date.

9.2.1.3 Follow-up period

The follow–up period will be defined as the period after (and including) the index date. The patients will be censored (end of follow-up) on the date of the first occurrence of any of the following events:

- Discontinuance of insurance coverage (last enrolment after the index date) among patients who were not continuously enrolled through the end of the study period
- End of risk-time window (30 (main analysis), 60 or 90 (sensitivity analysis) days post-index date).
- End of the study period (31st Dec 2017)
- First diagnosis of acute renal failure as defined in Section 9.3.2.

9.2.2 Study population

The study population will comprise a US population of patients with an epilepsy diagnosis as defined in Section 9.2.2.1 , with a new prescription of LEV or comparator AEDs, as monotherapy or polytherapy. The following 12 AED monotherapy comparator cohorts will be evaluated in the study: lamotrigine, phenytoin, valproic acid, carbamazepine, gabapentin, topiramate, oxcarbazepine, pregabalin, phenobarbital, zonisamide, lacosamide and ethosuximide. The “monotherapy” analysis includes patients who are AED naïve for at least one year (baseline) and start a new treatment of LEV or of one of the other AEDs listed above. For polytherapy, two cohorts will be evaluated; patients on a LEV-based polytherapy regimen will be compared with a cohort of patients on all other AED polytherapy regimens that do not include LEV as explained in the "polytherapy" definition (see Section 9.3.3.1). These patients are being treated by any AEDs (one or several, except levetiracetam) during the year preceding the index date when a new treatment of AED (different from those given during baseline) is introduced. Details of the study population are indicated below.

9.2.2.1 Epilepsy diagnosis

Patients will be classified as having an epilepsy diagnosis if they fulfill any of the criteria indicated below:

- The presence of ≥ 2 ICD-9-CM codes of 780.39 (seizure symptoms) during separate medical encounters, specifically different dates of care in any medical care venue that are separated by at least 1 day
- An occurrence of ≥1 ICD-9-CM code of 780.39 AND ≥1 ICD-9-CM code of 345.xx (excluding 345.3) during separate medical encounters, specifically different dates of care in any medical care venue that are at least 1 day apart, when the first code identified during the baseline period is 780.39
- An occurrence of at least one ICD-9-CM code of 345.xx (excluding 345.3)
- Patients with ICD-9-CM code of 345.3 will be required to have
  - an occurrence of ≥2 ICD-9-CM codes of 345.3 separated by at least 30 days
  - or an occurrence of the ICD-9-CM code 780.39 followed by 345.3 code and separated by at least 30 days,
  - or ≥1 ICD-9-CM code 345.3 and ≥1 ICD-9-CM code 345.xxencounters on separated by at least 30 days

The ICD-9-CM codes for epilepsy will be identified in the baseline period and are listed in Appendix 2. The validity of the algorithms that are being used to identify patients with epilepsy have been investigated in multiple studies. The performance of the algorithms was very variable. The positive predictive values varied widely across populations between 21% and 98%, the sensitivity ranged between 86% and 99%, whilst the specificity varied between 85% and 93% (Kee et al, 2012; Reid et al, 2012).

9.2.3 Selection criteria

9.2.3.1 Inclusion criteria

Patients will be eligible for inclusion in the study if they meet all of the following criteria:

1. A diagnosis of epilepsy (as defined in Section 9.2.2.1) during the baseline period
2. Initiation of treatment with either LEV or comparator AED (as monotherapy or polytherapy as defined in Section 9.3.1.1 and Section 9.3.1.2, respectively) within the patient selection period without prior treatment for the specific AED in the 12 months prior.

a) If the patient's index AED prescription occurs after 12 months (baseline) without any AED use, the patient will be included in the monotherapy cohort

b) If the patient's index AED prescription occurs after having already used AEDs during the 12 preceding months (baseline) the patient will be included in the polytherapy/switching cohort.

3. Continuous medical and prescription benefit coverage during the baseline period

9.2.3.2 Exclusion criteria

Patients will be excluded from the study if they meet any of the following criteria:

Monotherapy analyses:

1. Patients with a prescription of any AED during baseline period will be excluded
2. Patients starting 2 or more AEDs on index day will be excluded

Polytherapy analyses:

3. Patients with a prescription of LEV or index AED during baseline will be excluded
4. Patients without any prescription of AED during baseline will be excluded

The rest of the criteria are applicable to both monotherapy and polytherapy:

5. We will exclude patients with preexisting renal disease to identify new cases of acute renal failure after exposure to the index AED. Therefore, patients with a diagnosis claims of renal dysfunction and renal failure (ICD-9-CM 580.xx to 588.xx, 590.xx;) or use of dialysis (ICD-9-CM codes of, V45.1, V56.0, V56.1; or the procedure codes 3995), CPT codes for dialysis services of 90935, 90937,90939, 90940, 90945, 90947, 90997, 90999, 99512, 99559 and HCPCS codes G0257; S9335; S9339 in any field of diagnosis / procedure during the baseline period will be excluded.
6. We will exclude patients with medical conditions or procedures that cause acute renal failure, when these events occur close to the index date. This will ensure that the outcomes that the cases of acute renal failure identified during the follow-up period are attributable to the index AED, not other causal factors proximal to the index date. Therefore, the following patients will be excluded:

- Patients with a claims record of diagnosis of rhabdomylosis (ICD-9-CM 728.88) in the 90 days prior to the index date.
- Patients with a claims record of a diagnosis of status epilepticus (ICD-9-CM 345.3) within 90 days prior to the index date
- Patients with a record of a hospitalization and a claims record indicating the patient had a major surgical procedure within 30 days prior to the index date
- Procedures using radiocontrast agents within 30 days of the index date

While the new user design will control for selection bias, it might reduce the available follow-up time for patients. Additionally, exclusion of patients with a history of status epilepticus might reduce the number of patients in the study population with severe epilepsy symptoms. Furthermore, excluding patients who had a hospitalization and major surgery might reduce the number of patients with other significant comorbid conditions. This will be taken into account when interpreting the final study results as they may not be generalizable to the wider epilepsy population.

9.3 Study variables

9.3.1 Exposure: Treatment assessment

Patients will be considered as having continuous treatment coverage if the gaps between the supply of their consecutive prescriptions are less than 30 days. Patients will be considered exposed to AED treatments 30 days after the date of last prescription + days of supply. Benzodiazepines except for clonazepam and clobazam will be excluded from analyses assessing type of AED treatment). The mode day's supply of the non-missing, non-null, non-negative values will be obtained for each AED prescribed (see Appendix 1) for each patient. This will be used for imputation of prescription records with null, negative, or missing values of the days' supply during the study period. In case only one claim is present, or no mode exists, the mode of the non-missing, non-null, non-negative values for that AED for all patients will be used. Prescriptions with more than 90 days of drug supply will truncated at 90 days.

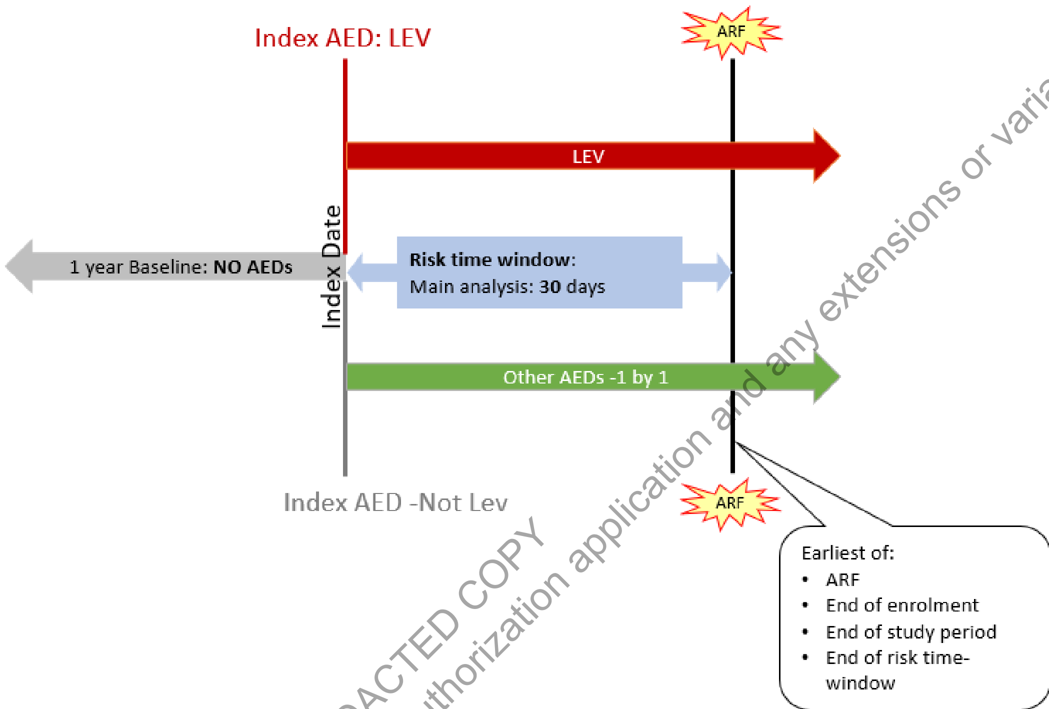
9.3.1.1 Monotherapy

Patients will be classified as having received AED monotherapy treatment if their first registered pharmacy claims records for the index AED are preceded by a 12 months minimum continuous enrolment in the database without any AED claims. Patients receiving two or more AEDs on the same date will be excluded from the analysis.

Exposure to AED will start from index date (first AED prescription registered in the database preceded by a minimum 12 months continuous enrolment period) and will end at the earliest of (Figure 1):

- Discontinuance of insurance coverage
- End of risk time-window (30 (main analysis), 60 or 90 (sensitivity analysis) days post index date)
- End of the study period
- First diagnosis of acute renal failure

Figure 1 Monotherapy design **(Patients starting > 1 AED on index date are excluded)**

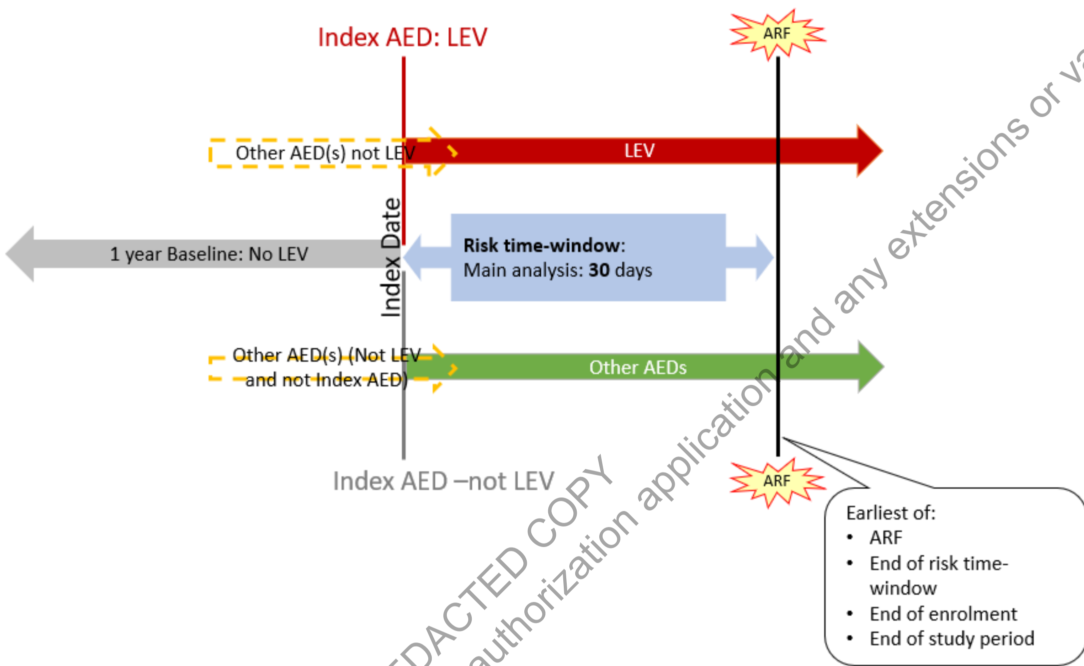


9.3.1.2 Polytherapy: Switchers or patients adding-on a new AED

The "Polytherapy" analysis will include patients adding a new AED to their regimen or switching to the index AED of interest. During the first weeks after the start of a new AED in patients having received previous AED prescriptions, patients are often taking more than one drug as they experience a period so called "cross titration" where they are still on the former AED but start taking the new one. During this "cross titration" period which is also the period of highest risk for acute renal failure (30 days), it is unfortunately not possible to ascertain when patients are taking the drug in monotherapy or concomitantly with other AEDs (polytherapy). Therefore, this analysis will consider all the epilepsy patients already exposed to AED treatment at baseline and receiving a new treatment of AED (different from those given during baseline) as potentially under polytherapy during the risk time window of the study. Exposure to AEDs will start from index date (first new treatment of AED after a minimum period of 12 months continuous enrolment) and will end at the earliest of (Figure 2):

- Discontinuance of insurance coverage
- End of risk time-window (30 (main analysis), 60 or 90 (sensitivity analysis) days post index date)
- End of the study period (31 Dec 2017)
- First diagnosis of acute renal failure

Figure 2 Polytherapy design: Switch and add-on patients continuing AED treatment



9.3.2 Study outcomes

The primary outcome of this study is to compare the incidence rate of acute renal failure among patients exposed to LEV or comparator AEDs (as monotherapy or polytherapy).

Patients will be classified as having acute renal failure if they had a diagnosis claim of at least 1 inpatient or 1 emergency department with the ICD-9-CM diagnoses codes of 584.0 (acute renal failure, unspecified), 584.5 (acute tubular necrosis), 584.6 (cortical acute renal failure), 584.7 (medullary acute renal failure), 584.8 (acute renal failure with other specified pathologic lesion) and 584.9 (acute renal failure, not otherwise specified) or ICD-10-CM diagnoses codes of N17.0 (acute kidney failure with tubular necrosis), N17.1 (acute kidney failure with acute cortical necrosis), N17.2 (acute kidney failure with medullary necrosis), N17.8 (other acute kidney failure), or N17.9 (acute kidney failure, unspecified), as the principal diagnosis (using guidance for previous studies and the FDA sentinel case definition of acute renal failure), during the follow-up period (Patel et al, 2013; Vlasschaert et al, 2011). The validity of the codes that are being used to identify patients with acute renal failure have been investigated in different studies. The positive predictive values varied widely across populations and reference standards between 15% and 96%, the sensitivity ranged between 26.2% and 47.6%, whilst the specificity varies between 97.7% and 99.2% (Waiker et al, 2006; Vlasschaert et al, 2011). Since a new user design will be used for the study consisting of new users of AED medication, it is unlikely that there will be differential misclassification of acute renal failure between treatment groups. Additionally, valid relative effect measures can still be estimated when the specificity of a test is high and that there is non-differential misclassification across treatment groups (Chubak et al, 2012; Greenland and Lash, 2008). For outcomes with ≥ 2 ICD-9-CM or ICD-10-CM codes, the date of the first occurrence will be considered the date of the diagnosis of acute renal failure. For the primary analysis, case identification of acute renal failure has been restricted to the primary diagnosis, as this field usually identifies the primary medical condition for hospital admission.

9.3.3 Other variables

9.3.3.1 Characteristics of patients

The following patient characteristics will be described, defined at the index date: age, gender, region of residence, and payer type of medical coverage. Patients will be stratified by age in years in these categories: 1-<4, 4-17, 18-45, 46-64, 65+years. The region of residence will be classified as Northeast, North Central, South or West regions of the US. Payer type will be classified as Commercial/Medicare and Medicaid.

9.3.3.2 Baseline comorbidities

The prevalence of comorbidities associated with the risk of renal failure (Rewa et al, 2014) in the baseline period will be estimated including hypertension, diabetes mellitus, obesity, cardiovascular disease, peripheral vascular disease, liver disease, chronic obstructive pulmonary disease, cerebrovascular disease, hypovolemia, sepsis, burns, hypotension, heart failure, myoglobinuria, diabetic nephropathy, proteinuria, hemolysis, systemic lupus erythematosus, and other renal disease including renal calculi. A patient will be identified as having comorbidity if they had at least 1 inpatient or 2 outpatient claims (encounters or separate days) with the ICD-9-CM code of interest, as a principal diagnosis, during the baseline period, Appendix 3. Furthermore, the burden of chronic medical conditions in the baseline period will be estimated using the Healthcare Cost and Utilization Project (HCUP) Chronic Condition Indicator which categorizes ICD-9-CM diagnosis codes as chronic or not chronic (HCUP, 2011). Chronic conditions are defined as lasting ≥12 months and either (a) place limitations on self-care, independent living, and social interactions or (b) result in the need for on-going intervention with medical products, services, and special equipment.

These baseline comorbidities will be used to assess the balance in the baseline characteristics between the comparator groups after implementing the high dimensional propensity score model.

9.3.3.3 Baseline medications

The total number of prescriptions during the baseline will be estimated at the generic drug level, and the proportion of patients who had at least one prescription claim of any of the medications in the drug classes listed in Appendix 4. The total number of previous AEDs prior to the index date will also be estimated. These characteristics will be used to assess the balance in the baseline characteristics between the comparator groups after implementing the high dimensional propensity score model.

9.3.3.4 Baseline health care utilization

The overall number of health visits (inpatients, outpatients, emergency department visits) in the baseline period will also be estimated. These characteristics will be used to assess the balance in the baseline characteristics between the comparator groups after implementing the high dimensional propensity score model.

9.4 Data source

The analysis will be performed using the IBM® MarketScan® Commercial Claims and Medicare database (CCMC 20157 v1.0), the IBM® MarketScan® Medicare Supplemental and Coordination of Benefits (Medicare Supplemental) (MDCR 2017 v1.0) database and the IBM® MarketScan® Multi-State Medicaid databases (MDCD 2017 v1.0). This is an US based database. The database contains information of over 125 million covered lives comprising of commercially insured individuals (i.e. working age adults and their dependants), patients aged 65 years and older with Medicare coverage plus employer-paid commercial plans and individuals with limited resources whose insurance is paid by the state respectively. The database captures information on medical (inpatient, outpatient, and emergency care) and pharmacy claims information, as well as enrolment history. The medical service claims record detailed information for inpatient and outpatient healthcare encounters, including date and place of service, provider type, plan- and patient-paid amounts, International Classification of Diseases, 9th and 10th Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) diagnosis and procedure codes, and CPT-4 procedure codes. Pharmacy claims include information on dispensed medications including National Drug Code (NDC), dispense date, quantity, days supplied, and plan- and patient-paid amounts. The enrolment file contains information on age, gender, US census region, health insurance payer type, and monthly enrolment status. These files are linkable based on an encrypted patient identification number.

9.5 Study size and power

A feasibility assessment was conducted in the IBM® MarketScan® Research Databases using the Safety Works software to estimate the number of patients exposed to LEV or other AEDs as monotherapy. Patients were defined as having monotherapy if they had a prescription of an index AED without the prescription of any other AEDs during the follow-up period. Patients were required to have at least one ICD-9-CM code for epilepsy (345) or at least two ICD-9-CM codes for seizures (780.39) in the baseline period of 6 months prior to the index date. The number of patients who had monotherapy are provided in Table 9–1.

Table 9–1: Number of epilepsy patients with AED monotherapy

Description	Total number of patients	Total Outcomes (renal failure)
Levetiracetam	101,424	3,120
Lamotrigine	45,565	501
Phenytoin	38,785	1,152
Valproic acid	33,202	648
Carbamazepine	29,883	406
Gabapentin	29,158	1,218
Topiramate	26,052	296
Oxcarbazepine	20,848	187
Phenobarbital	9,456	204
Pregabalin	7,067	290
Zonisamide	6,397	70
Lacosamide	3,452	63
Ethosuximide	3,334	4
Clobazam	435	2
Felbamate	260	1
Vigabatrin	149	1
Rufinamide	142	2
Tiagabine	101	3
Eslicarbazepine	96	-
Perampanel	27	1
Retigabine	10	-

Based on the number of patients in each AED cohort from the feasibility assessment (Table 9–1), including cohorts with a minimum sample size of 3000, an overall 2-sided 95% confidence interval (and accounting for the multiple comparisons using the Bonferroni test to a confidence interval of 99.995%), a power of 80%, and also assuming the incidence of acute renal failure is 0.5% based on results from a population-based study conducted in the US that estimated the incidence of acute renal failure (Hsu et al, 2007), the minimum difference in the incidence rate ratio of acute renal failure that can be detected ranges from 1.5 to 4.0. There are no published data available estimating the incidence rate of acute renal failure in epilepsy patients in general or in subpopulations of patients exposed to antiepileptic drugs. These estimates for the baseline incidence rates of acute renal failure were obtained from a community-based study and assumed to be the same across all comparator cohorts. The Bonferroni adjustment has been included in the sample size calculation to reduce the chances of obtaining false-positive results (type I errors) as there will be multiple comparisons in this study. Table 9–2 provides further information on the sample size calculations.

For this study the attained power for the minimum sample size required (3000 patients) assuming an acute renal failure incidence of 0.005, a level of significance of 0.05 and varying proportion ratios of 4.0, 2.0 and 1.5 was 99.95, 61.21 and 23.23 for a sample size of 3000. Additional power calculations are reported in Table 9-2. Open Source Epidemiologic Statistics for Public Health (OpenEpi) (Dean 2018), was used to compute the sample size and power calculations for this study.

Table 9–2: Sample size calculations for the study

Reference proportion	Proportion ratio	Power	Alpha	Sample Size
0.005	4.0	0.800	0.05	1,016
0.005	2.0	0.800	0.05	5,148
0.005	1.5	0.800	0.05	16,608
0.005	4.0	0.800	0.01	1,450
0.005	2.0	0.800	0.01	7,469
0.005	1.5	0.800	0.01	24,326
0.005	4.0	0.800	0.005	2,840
0.005	2.0	0.800	0.005	14,928
0.005	1.5	0.800	0.005	49,137

Table 9-3: Attained power for minimum sample size of 3000

Reference proportion	Proportion ratio	Power[1]	Power[2]	Alpha	Sample Size
0.005	4.0	99.95	99.92	0.05	3,000
0.005	2.0	61.21	55.16	0.05	3,000
0.005	1.5	23.23	18.19	0.05	3,000
0.005	4.0	99.61	99.45	0.01	3,000
0.005	2.0	37.01	31.33	0.01	3,000
0.005	1.5	8.77	6.093	0.01	3,000
0.005	4.0	97.4	96.6	0.005	3,000
0.005	2.0	14.75	11.42	0.005	3,000

[1]Normal approximation

[2]Normal approximation with continuity correction

9.6 Data management

The IBM® MarketScan® Research Databases electronic database comprises of fully adjudicated and paid claims records of integrated longitudinal enrollment, inpatient, outpatient and drug data from multiple payors that has been standardized and de-identified prior to use for the analysis. The source data is transferred from MarketScan® Databases via a Secure File Transfer Protocol (FTP) to a UCB internal server with access protection (landing zone). The data is transferred on a quarterly basis to UCB with full year updates at the end of the year. From the landing zone, the data is moved to a destination folder which has been established specifically for storing the IBM® MarketScan® Databases source data on the processing system, where the data are converted into the native format and indexed via SAS software. This process is conducted only by individuals within UCB who have appropriate access rights to the protected storage area of the processing system. Subsequent analysis of the converted data and data extracts are performed using SAS 9.4 software (SAS Institute, Inc., Cary, North Carolina) on the processing system, while creating and storing extracts and results on the same system in separated folders per study.

9.7 Data analysis

The variables that will be examined in this study are comprised of demographics, enrollment information, service provider, diagnoses, procedures, and prescriptions. The demographic variables that will be evaluated include age, gender, enrollment information, region of residence and health plan type. Based on summary data provided by IBM® MarketScan® Databases, there is no missing data for age, gender and enrollment information. For the remaining demographic variables which include region, and health plan type the value “Unknown” will be used for missing records. For variables that will be derived using diagnoses, procedures, and prescriptions codes, patients are assumed to have experienced an event or filled a medication prescription if the relevant code(s) are found among their claim records. Otherwise, it is assumed that the patient did not experience the event or were not prescribed the medication. It is therefore anticipated that the proportion of missing data for all study variables will be very small. In order to confirm this, after the study cohorts have been selected, we will estimate the percentage of missing data for each of the key demographic variable and for each patient in the analysis. However, for the variables that will be derived from diagnoses, procedure and prescription codes, it is expected that there will no missing data because it is assumed that patients that do not have a code did not experience the event or did not receive the prescription. However, for prescription data, in patients who have initial treatment, missing data will be imputed as described in Section 9.3.1.

The analysis will be stratified by type of index AED prescription (monotherapy or polytherapy), and further stratified with respect to age (1-<4, 4-17, 18-45, 46-64, 65+years), gender, and payer type (Commercial/Medicare and Medicaid databases). For monotherapy AED treatment, there will be 12 comparator cohorts with the following AEDs: lamotrigine, phenytoin, valproic acid, carbamazepine, gabapentin, topiramate, oxcarbazepine, pregabalin, phenobarbital, zonisamide, lacosamide and ethosuximide. For polytherapy, all patients on a LEV-based polytherapy regimen will be compared with 1 overall cohort consisting of patients on all other AED polytherapy regimens that do not include LEV.

Means and standard deviations, medians and interquartile range, minimum and maximum values, will be used to describe continuous variables, whereas frequencies and percentages will be used to describe categorical variables.

9.7.1 Adjustment for baseline characteristics

Adjustment for baseline differences between the LEV and comparator AED cohorts to minimize bias due to confounding will be performed using a high-dimensional propensity score which will be generated using a multivariate logistic regression model, in order to balance the cohorts with respect to observed patient characteristics in the baseline period. The high-dimensional propensity score which represents the probability that a specific patient is exposed or non-exposed (prescribed a type of AED) conditional on a set of known baseline confounding factors will be calculated for each patient using all potentially confounding baseline variables. The exposure status will be the dependent variable and the baseline characteristics the independent variables. The high-dimensional propensity score is generated using an automated algorithm that identifies potential confounders or proxies for confounders in longitudinal data sets. Data is obtained from the 5 dimensions of care recorded in the health claims database including pharmacy claims, outpatient diagnoses, outpatient procedures, inpatient diagnoses and inpatient procedure codes. From each data dimension, the most prevalent codes (default n=200) are selected and transformed into binary covariates. Each code is assessed for within-patient occurrence during a predefined period and is divided into three binary variables: once, sporadically, or frequently. Consequently, there are 3,000 possible indicator variables that can be included in the propensity score. The high dimensional propensity score algorithm drops covariates with less than 100 patients (exposed and unexposed combined) per variable, with missing (“zero/undefined”) covariate-exposure association, and with missing (“zero/undefined”) covariate-outcome association. The remaining variables are prioritized by the Bross formula (Schneeweiss et al, 2009; Wyss et al, 2018) after adjusting for demographic covariates. By default, the algorithm includes the top k=500 indicator variables as covariates in the propensity score, in addition to age and gender. A propensity score is estimated for each subject as a predicted probability of exposure conditional on all covariates using multivariate logistic regression (Schneeweiss et al, 2009).

Once the high dimensional propensity scores are estimated, they will be converted into stabilized inverse probability of treatment weights (IPTW) which will be applied to create a pseudo-population where the measured covariates are not associated with the outcome, and both the exposed and unexposed groups are standardized to the overall population (Brookhart et al, 2013). Graphical displays (e.g. boxplots) and descriptive statistics will be used to assess the distribution of the stabilized weights. Generally, a mean of 1 for the weights is often viewed as a necessary condition for correct model specification (Hernán and Robins, 2006; Cole and Hernán, 2008). Conversely, weights with means far from 1 or with extreme values may be symptomatic of violation of the assumptions used in the estimation of the weights. The characteristics of the individuals with outlier weights will be examined and if necessary, the model will be re-specified and the weights re-estimated, or if the outlier weights are not significant the weights will be truncated. After the high dimensional propensity scores have been generated, we will assess for violations of underlying assumptions. Positivity violations will be assessed by plotting the propensity score distributions in an overlay plot for the comparator groups. To evaluate adequate overlap of the propensity scores, we will visually inspect the density distribution of the propensity scores (Rosenbaum and Rubin, 1984). The performance of the model will be evaluated by assessing the covariate balance across the treatment groups. Standardized differences will be used to compare the mean or prevalence of baseline covariates between the comparator treatment groups in the samples weighted by the inverse probability of treatment. Additionally, continuous variables will be compared using graphical methods including boxplots, nonparametric density plots. If covariate imbalances remain, the high dimension propensity score will be refined by either using interaction terms, or modifying the continuous variables (e.g. splines, polynomials or cubic terms). A separate high dimensional propensity score model will be developed for each comparison of LEV and another AED.

After the final high dimensional propensity score has been generated, the stabilized weights will be applied as exposure weights in the analysis to generate final adjusted estimates of the overall effect of each exposure of interest. Advantages of IPTW weighting includes retention all study patients and estimate of an average exposure effect in the whole population of eligible patients

9.7.2 Data analysis for incidence rates and ratios of acute renal failure

The incidence rate (IR) will be calculated as the total number of new cases diagnosed with acute renal failure during the follow-up period divided by the sum of person-years at risk during follow-up. The person time for each patient will be calculated as the total number of days of follow-up from the index date to the censoring date as indicated in Section 9.2.1.3. The incidence rate ratio (IRR) will be obtained by dividing incidence rate in the LEV cohort by the incidence rate for each of the comparator cohorts.

The modified Poisson regression model with robust variance estimator will be used to estimate the IRs and IRRs of acute renal failure (Zou 2004). The crude IR and 95% confidence intervals (CI) will be calculated as the number of new cases per 10,000 person-years of follow-up and reported separately for each AED treatment cohort. Crude incidence rate ratios and 95% CI based on unweighted samples will be computed to compare the incidence rates of acute renal failure between LEV and each comparator AED cohort. Thereafter, to control for confounding, modified Poisson regression model with robust variance estimator will be constructed based on stabilized IPTW weighted samples. The stabilized weights will be applied as exposure weights in the analysis to generate final adjusted effect measure estimates. For each analysis, the comparator cohort will be the reference group. Relevant diagnostics will be used to evaluate compliance with model assumptions.

9.7.3 Sensitivity analysis

Several sensitivity analyses will be conducted. First, sensitivity analyses will be conducted to assess the impact of the parameters used in the case definitions of the treatment exposure and study outcome by using the case definitions indicated below:

- Renal failure definition as defined in Section 9.3.2 but including claims identified in any field of diagnosis.
- Renal failure case definition including the presence of the ICD-9-CM or ICD-10-CM codes of acute renal failure as defined in Section 9.3.2 plus the presence of at least 1 code of renal dialysis, ICD-9-CM codes of, V45.1, V56.0, V56.1; or the procedure codes 3995 , CPT codes for dialysis services of 90935, 90937,90939, 90940, 90945, 90947, 90997, 90999, 99512, 99559 and HCPCS codes G0257; S9335; S9339 in any field of diagnosis / procedure.
- 60 days risk time windows.
- 90 days risk time windows.
- Additional exclusion criterion of a minimum of 30 days continuous enrolment in the database post index date.
- Monotherapy analysis stopping follow-up at the introduction of a new AED instead of 30 days risk time window if the introduction occurred between index date and end of risk time window.
- Analysis using only ICD-9-CM coding, with data selection until October 2015.

Second, quantitative sensitivity analyses will be conducted to evaluate the potential magnitude and direction of bias due to unmeasured confounding on the study effect estimates. The characteristics of the unmeasured confounders including the prevalence of the unmeasured confounder in the study population, the marginal association between the confounder and exposure and the conditional association between confounder and outcome will be varied over a range of values obtained from published literature and applied to the regression model to adjust for the unmeasured confounder using methods described by Schneeweiss et al, 2006.

9.8 Data quality control

The IBM® MarketScan® Research Databases contain information on claims that have been paid and adjudicated. The data is tested for completeness at the client-plan level. In addition, the data is checked for accuracy and completeness by testing selected fields of medical and drug coverage indicators for validity and no-standard values, and quantifying missing fields and records Only MarketScan Annual Files are used in this study which guarantees the highest completeness level and longitudinal integrity. All codes used for each of the study variables are available in the statistical analysis plan. After finalizing the protocol, a statistical analysis plan will be developed that will be used as a guide for conducting analysis. The statistical analysis plan is reviewed and approved by the study team before any analysis is conducted. Double programing will be used in order to validate the analysis.

In October 2015, IBM® MarketScan® Research Databases transitioned from the use of ICD-9-CM to the use of ICD-10-CM. In order to verify the coherence of ICD-9-CM to ICD-10-CM translations, plots of incidence and prevalence of these codes before and after ICD transition in IBM® MarketScan® Research Databases were carried out as described in Panozzo, 2018 for every variable used in the model. For this reason, some ICD-9-CM codelists might be subject to small changes in order to ensure the continuity of our variable definitions with ICD-10-CM. All ICD-9-CM and corresponding translations with ICD-10-CM are available in the statistical analysis plan.

9.9 Limitations of research methods

There are several limitations for this study that arise from the data source. AEDs cause acute renal failure through an idiosyncratic hypersensitivity reaction following exposure to the AED leading to inflammation and interstitial injury (Nast, 2017). This usually occurs within 2 weeks of the drug exposure (Perazella and Markowitz, 2010; Rossert, 2001; Waring, 2006). Second, the study population is limited to patients with commercial, Medicare supplemental or Medicaid insurance coverage, and therefore results may not be representative of the entire US population, as uninsured patients are not included in the database. Risk factors for dose-dependent drug induced ARF have been well described in literature. However, there is very limited data published on idiosyncratic drug-induced ARF; most of the available data is available from case reports (Awdishu and Mehta, 2017). Although there may be differences in the socioeconomic characteristics in the patients included in the database and patients that are excluded due to lack of insurance, it is assumed that the underlying risk factors of idiosyncratic ARF are non-differential and therefore would not have a significant impact on the study estimates. Third, there might be missing information, miscoding or underreporting of disorders in the claims data. Ascertainment of drug exposures, diagnoses, and procedures depends on the precision available in coding systems and the accuracy with which codes are assigned to services. The exposure and outcome variables will be identified using validated algorithms which have been identified to have high specificity. Valid relative effect measures can still be estimated when the specificity of a test is high the under that there is the assumption of non-differential misclassification across treatment groups (Chubak et al, 2012; Greenland and Lash, 2008). Additionally, sensitivity analyses will be conducted to assess the impact of the algorithms on the effect estimates. Fourth, insurance claims are financial records in which the diagnosis is the justification for the medical service. Tentative, rule-out diagnoses can be difficult to distinguish from confirmed diagnoses. When defining the outcomes in the primary analysis, we have limited them to the principal diagnoses has been known to represent the main diagnosis. A sensitivity analysis will also be done to assess the impact of using the main diagnosis only versus all diagnoses. Fifth, patient receipt of a dispensing of an AED is documented in claims data, but there is no record of actual use of drugs. Consequently, there will be some patients who will be misclassified as having been exposed to the index drug even though they did not take the index drug. It is assumed that this will be non-differential across the treatment groups and therefore will have minimal impact on the study results. Sixth, information on potential confounders such as lifestyle, occupational, and environmental factors are missing or at best incomplete in claims data. However, most of the well-known risk factors for acute kidney failure are comorbidities or medications that are well captured in the database. As such it is anticipated that most of the confounders will be adjusted for in the analyses. Additionally, sensitivity analyses will be conducted to assess the impact of the residual confounding on the effect estimates. Finally, the study is not powered to detect moderate changes in the risk of acute renal failure. However, despite these limitations, there are several advantages of using this database. Because of the large sample size, adequate number of patients will be included in the study to assess the risk of renal failure. Additionally, the data represents real-life management of patients with epilepsy.

9.10 Other aspects

Not applicable

10 PROTECTION OF HUMAN SUBJECTS

The data are Health Insurance Portability and Accountability Act (HIPAA) of 1996 compliant. All patient data were de-identified before the data were delivered to UCB. All patient-level and provider-level data within the IBM® MarketScan® Research Databases contain synthetic identifiers to protect the privacy of individuals and data contributors.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Individual case safety reports will not be reported because IBM® MarketScan® Research Databases is a secondary database which consists of fully de-identified data. Therefore, it is not possible to assess the causality of individual cases. Additionally, apart from acute renal failure, no information on adverse events will be collected in the study. The incidence rate of acute renal failure will be provided in the study report in aggregate tables.

12 PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

The final study report will be submitted to the EMA. In addition, data will be disseminated at a scientific congress and will be submitted to a peer-reviewed journal for publication within 6 months after completion of the study report.

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Appendix 1 **LIST OF ANTIEPILEPTIC DRUGS**

[a]Drug Generic Name	[b]Brand Name	Form (MASTFRM RedBook)
Brivaracetam	Briviact	Tablet
Carbamazepine	Carbatrol	Capsule
	Epitol	Tablet
	Equetro	Extended-release capsules
	Tegretol	Chewable tablet, tablet, and oral suspension
	Tegretol®-XR	Extended release tablets
	Teril® Suspension	Suspension, oral
Clobazam	Onfi	Tablet
Clonazepam	Klonopin	Tablet
Eslicarbazepine acetate	Aptiom	Tablet
Ethosuximide	Zarontin	Oral solution
Ezogabine	Potiga	Tablet, film coated
Felbamate	Felbatol	Tablet, oral suspension
Gabapentin	Neurontin	Capsules, tablets, oral solution
Lacosamide	Vimpat	Tablet, film coated; injection; oral solution
Lamotrigine	Lamictal, Lamictal OD, Lamictal CD, Lamictal XR	Tablets, chewable tablets, orally disintegrating tablets
Levetiracetam	Keppra Tablet, oral solution Keppra XR Extended-release tablets	Tablets
Oxcarbazepine	Trileptal, Oxtellar XR	Tablet, film coated; oral suspension
Perampanel	Fycompa	Tablet, oral suspension
Phenobarbital	Luminal, Barbita, Comizial, Gardenale, Fenilcal, Solfoton	Tablet, elixir
Phenytoin	Dilantin, Phenytek	Capsule, tablet
Pregabalin	Lyrica	Capsule, oral solution

[a]Drug Generic Name	[b]Brand Name	Form (MASTFRM RedBook)
Primidone	Mysoline, Desoxyphenobarbital, Primaclone	Tablet
Rufinamide	Banzel	Tablet
Tiagabine	Gabitril	Tablet
Topiramate	Qudexy XR, Topamax, Trokendi XR	Capsule, capsule extended release, tablet
Valproic acid	Depakene	Capsule, oral solution
	Depakote	Tablet, delayed release tablet
	Depakote ER	Tablet, extended release tablet
	Depakote Sprinkle	Capsule
	Stavzor	Capsule, delayed release
	Divalproex sodium	Tablets, delayed release
	Valproate sodium	Injection, intravenous
Vigabatrin	Sabril	Tablets, powder for oral solution
Zonisamide	Zonegran	Capsule

[a] Food and Drug Administration, 2016
[b] MedlinePlus, 2016

Appendix 2 **EPILEPSY CODES**

ICD9-CM Code	Description
345.0	Generalized nonconvulsive epilepsy
345.00	Generalized nonconvulsive epilepsy without mention of intractable epilepsy
345.01	Generalized nonconvulsive epilepsy with intractable epilepsy
345.1	Generalized convulsive epilepsy
345.10	Generalized convulsive epilepsy without mention of intractable epilepsy
345.11	Generalized convulsive epilepsy with intractable epilepsy
345.2	Petit mal status
345.3	Grand mal status
345.4	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures
345.40	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures without mention of intractable epilepsy
345.41	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures with intractable epilepsy
345.5	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures
345.50	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures without mention of intractable epilepsy
345.51	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures with intractable epilepsy
345.6	Infantile spasms
345.60	Infantile spasms without mention of intractable epilepsy
345.61	Infantile spasms with intractable epilepsy
345.7	Epilepsia partialis continua
345.70	Epilepsia partialis continua without mention of intractable epilepsy
345.71	Epilepsia partialis continua with intractable epilepsy
345.8	Other forms of epilepsy and recurrent seizures
345.80	Other forms of epilepsy and recurrent seizures without mention of intractable epilepsy
345.81	Other forms of epilepsy and recurrent seizures with intractable epilepsy
345.9	Epilepsy unspecified
345.90	Epilepsy unspecified without mention of intractable epilepsy

345.91	Epilepsy unspecified with intractable epilepsy
780.39	Other convulsions

APPENDIX 3 ICD-9 CODES FOR BASELINE COMORBIDITIES

Category	ICD-9-CM codes or CCS categories[1]
Heart Failure	CCS 108;
Cardiovascular Disease	CCS 100 ; 101
Proteinuria	791.0
Peripheral Vascular Disease	440, 443, 444, 445, 446, 447
Sepsis	CCS 2
Hypovolaemia	276.5, 958.4, 958.5
Burns	CCS 240
Hypotension	458
Hemolysis	283.11, 283.2, 999.61, 999.62, 999.63, 999.71, 999.72, 999.73, 999.76, 999.77, 999.78, 999.83, 999.84, 999.85, 791.2
Myoglobinuria	791.3
Other renal diseases (hydronephrosis, urinary obstruction)	CCS 161 ; 163
Renal calculi	CCS 160
Diabetic Nephropathy	249.4 ; 250.4
Hypertension	CCS 98 ; 99
Diabetes Mellitus	CCS 49 ; 50
Obesity	278.xx
Liver Disease	570.xx, 571.xx, 572.xx, 573.xx,
Chronic obstructive pulmonary disease	CCS 127
Cerebrovascular Disease	CCS 78 ;109 ;110 ; 111; 112 ; 113 ; 115
Systemic Lupus Erythematosus	710.0
Small kidney of unknown cause	589.xx

[1] To facilitate the translation with ICD-10-CM, the clinical classification software (CCS) from the HCUP, a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality, will be used for some comorbidities as CCS include both validated ICD-9-CM and ICD-10-CM equivalents codelists. A CCS category was therefore linked to some of the

conditions above, the full list of ICD codes included in these categories is available in the statistical analysis plan. ICD codes and corresponding internally validated translations in ICD-10-CM were kept when the conditions were more granular than CCS categories (e.g Obesity).

Appendix 4 **LIST OF MEDICATIONS**

Category	Name of drugs
Antidepressants	Amitriptyline, bupropion, citalopram, clomipramine, desipramine, doxepin, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, protriptyline, fluoxetine, fluvoxaminetrazodone, sertraline
Antimicrobials and antiviral drugs	Albendazole, doxycycline, griseofulvin, indinavir, itraconazole, metronidazole, praziquantel, isoniazid, clarithromycin, erythromycin, fluconazole, ketoconazole, ritonavir, troleandomycin, chloramphenicol, miconazole, imipenem, meropenem, ertapenem, voriconazole, efavirenz, lopinavir, nevirapine, posaconazole, rifampin, saquinavir, sulfamethoxazole-trimethoprim, ciprofloxacin, penicilins, cephalosporins
Antineoplastics	busulfan, cyclophosphamide, etoposide, ifosfamide, irinotecan, methotrexate, lomustine, carmustine, streptozocin, paclitaxel, procarbazine, tamoxifen, teniposide, thiotepa, topotecan, fluorouracil, cisplatin
Antipsychotics	Chlorpromazine, clozapine, haloperidol, mesoridazine (active metabolite of thioridazine), olanzapine, quetiapine, risperidone, ziprasidone
Benzodiazepines	Alprazolam, clobazam, clonazepam, diazepam, midazolam
Cardiovascular drugs	amiodarone, atorvastatin, digoxin, disopyramide, felodipine, metoprolol, mexiletine, nifedipine, nimodipine, nisoldipine, propranolol, quinidine, rosuvastatin, simvastatin, verapamil, warfarin, Apixaban, diltiazem, isradipine, lovastatin, timolol
Immunosuppressants	Cyclosporin A, sirolimus, tacrolimus
Steroids	Cortisol, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone
Analgesics	Buprenorphine, Fentanyl, Methadone, Paracetamol (Acetaminophen), Non-steroidal anti-inflammatory drugs (aspirin, balsalazide, bromfenac, celecoxib, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, , meclofenamate, mefenamic acid, meloxicam, naproxen, nabumetone, nepafenac, oxaprozin, phenylbutazone, piroxicam, tolmetin, sulindac, celecoxib, rofecoxib), Pethidine, (Meperidine), Tramadol
Other drugs	metyrapone, theophylline, thyroxine, vecuronium (and some other nondepolarizing neuromuscular blocking agents), cimetidine, danazol,, allopurinol, omeprazole, esomeprazole, ticlopidine, lithium, lansoprazole

Appendix 5 ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Comparing the incidence of acute renal failure in patients with epilepsy exposed to levetiracetam versus other antiepileptic drugs

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	
1.1.2 End of data collection[3]	☒	☐	☐	
1.1.3 Study progress report(s)	☒	☐	☐	
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] 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.

[3] Date from which the analytical dataset is completely available.

Section 2: Research question	Yes	No	N/A	Section Number
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)	☒	☐	☐	
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?	☐	☐	☒	

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)	☒	☐	☐	
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	
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)	☒	☐	☐	
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)	☒	☐	☐	

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☒	☐	☐	
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)	☒	☐	☐	

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 categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	
5.4 Is exposure classified based on biological mechanism of action and tarfng 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?	☒	☐	☐	

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
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)	☒	☐	☐	
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?	☒	☐	☐	
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)	☒	☐	☐	
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	

Comments:

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)	☒	☐	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	
9.1.3 Covariates?	☒	☐	☐	
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)	☒	☐	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	
9.3.3 Covariates?	☒	☐	☐	
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?	☒	☐	☐	

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.2 Are descriptive analyses included?	☒	☐	☐	
10.3 Are stratified analyses included?	☒	☐	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	
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)	☒	☐	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	
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?	☒	☐	☐	

Section 12: Limitations	Yes	No	N/A	Section Number
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?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	

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?	☒	☐	☐	

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)?	☒	☐	☐	

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	

Comments:

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

Date: 24 F/February/2017

Signature: [redacted]

Appendix 6 AMENDMENTS AND UPDATES

During the elaboration of the Statistical Analysis Plan, several amendments and updates had to be made to the study protocol as follows:

V 1.0 reference and page	Explanation	Type of Change
Page 2: Summary table	Update of version, dates and authors, PAS registration number	Update as required in the 2nd Responses assessment report
Page 6 Abbreviation list	Insertion of ARF, IR and IRR	Update
Page 7 Abstract	Consistent use of the original term Acute Renal Failure (ARF) as both refer to the exact same condition but both terms were previously used in the document.	Update
Page 8 Abstract Population	Update on Dates 2008-2017 and name of Dababase IBM MarketScan which is now called HealthIBM® MarketScan® Research Databases	Update on study dates
Page 8 paragraph 4: Abstract: Data analysis	Change Poisson in "Modified" Poisson and update on statistical analysis, change in IRR baseline IRR LEV/comparator, rewording	Update of the statistical methods in the SAP as advised in the 2nd Responses assessment report
Page 8 paragraph 4. in Milestones	Update of Dates of PAS registration and final study report	Update on dates
Page 8 paragraph 5. Amendments and Updates	Summary of updates of the preliminary version of the protocol.	Update as requested in the 2nd Responses assessment report
Page 9 Paragraph 6: Milestones	Update of study milestones as requested in the last PRAC assessment report	Update
Page 11 Paragraph 9.2.1 Study Period	Update on Study period : 01-Jan2008 and 31-Dec-2017 instead of 2012-2015 in the last version	Update on dates

Page 12 Paragraph 9.2.1.1 Patient selection period	Adapted to the study period: 1-Jan2008 and 31-Dec-2017	Update on dates
Page 14: Paragraph 9.2.1.3 Follow-up period	Necessary adaptation of the methodology, modifying the previous definitions of Mono/Polytherapy in order to include all susceptible cases of ARF in the analysis. Change in the follow-up according to mono or poly definition. The risk window for ARF is now 30 (primary), 60 or 90 days following the Nephrologist expertise explaining that this time represents the realistic time window for ARF.	Necessary adaptation of the methodology
Page 13-14 Paragraph 9.2.3.1 Inclusion criteria	Necessary adaptation of the methodology. Changes due to the new definition of Mono and polytherapy treatments	Amendment
Page 14 Paragraph 9.2.3.2 Exclusion Criteria	Necessary adaptation of the methodology. Changes due to the new definition of Mono and polytherapy treatments and updates on codelists.	Amendment/ Update
Page 15 Paragraph 9.3.1.1 Monotherapy	Necessary adaptation of the methodology. Change of definition due to significant bias of the last definition	Amendment
Page 16 Paragraph 9.3.1.3 Polytherapy	Necessary adaptation of the methodology. Change of definition due to significant bias of the last definition.	Amendment
Paragraph 9.3.2 Study Outcomes	Small correction in the classification of ARF (1 inpatient or ER visit instead of 1 inpatient or 2 outcomes visits separated by 30 days)	Update
Page 18 Paragraph 9.3.3.2 Baseline comorbidities	These were reviewed by the nephrologist which added systematic lupus erythmematosus and reviewed definition of liver disease.	Update
Page 24 Paragraph 9.7. Data analysis	wording	Update
Page 25 Paragraph 9.7.1 Adjustment for baseline covariates	HDPS prioritization method.	Update as advised in the by the 2nd Responses assessment report
Page 26-27 Paragraph 9.7.2 Data analysis for incidence rates	Adaptation to the statistical model. Poisson to Modified Poisson with robust variance estimator.	Update as advised in the by the 2nd Responses assessment report
Page 26-27 Paragraph 9.7.3 Sensitivity analysis	Adaptation to Question 1 of the last report 86.3 where we include sensitivity analyses for 60 and 90 days risk windows, for an analysis with a minimum of 30 days enrolment in the data base post index date and a monotherapy analysis stopping when we include a new AED instead of stopping at the risk window. A last sensitivity analysis will be made using only data before the transistion to ICD-	Amendment /Update

	10 in order to make sure that the translation did not introduce any additional potential bias. Update on codelists	
Page 27 Paragraph 9.8 Data Quality control	Explanation of the process of translations of every variable used in the model checking for consistency of definitions	Update
Page 27 Paragraph 9.9 Limitations	Adaptations to changes of definition	Update
Appendix 3	Update on ICD codelists for comorbidities. Use of the Clinical Classification software (CCS) for some comorbidities to facilitate ICD-10-CM translations.	Update