**Analysis Plan**

This study aims to ascertain whether anti-epileptic drugs (AEDs), including enzyme-inducing AEDs cause an increased risk of cardiovascular events.

**Study Design**

The study is a retrospective cohort study using a previously validated method of identifying people with epilepsy using primary care records (REF).This was used to identify a cohort of people with epilepsy without previous cardiovascular disease and with an identifiable start date for their first AED. These patients were followed to the end of the study timeframe and it was noted whether they suffered from a new major cardiovascular event.

**Data Source**

Within the SAIL Databank the following datasets were used: Annual District Death Extract (ADDE), Patient Episode Database for Wales (PEDW), Welsh Demographic Service Dataset (WDSD) and Welsh Longitudinal General Practice dataset (WLGP).

**Study Population**

Primary care records were used to identify a cohort of people with epilepsy who have not previously suffered from a cardiovascular event. A total of 13,495 patients were identified who had an identifiable start date for their first AED between 01/01/2013 and 31/12/2017 with at least 6 months of available GP data before this. Individuals were only included if they were at least 18 years old at the start of the study period.

It was recorded whether the individuals in the epilepsy cohort were taking non-enzyme inducing AEDs (NIAEDs) or enzyme-inducing AEDs (EIAEDs) and for how long they were taking the AEDs.

The end of the study window for the epilepsy cohort was the end of the study period (31/12/2017), a death, or the date that the individual moved out of Wales or changed to a GP practice without records in the SAIL Databank.

A control cohort was also identified without a diagnosis of epilepsy which was matched on age, gender and date of entry into the study. We aim to have at least a 4:1 matching for the control to epilepsy group. This control cohort will be used to conduct the comparison analysis.

STROBE guidelines for cohort, case-control, and cross-sectional studies will be followed with respect to reporting observational research.

**Assessment of CV Event**

The patients were followed to the end of the study timeframe (31/12/2017), noting whether they have a new major cardiovascular event. A cardiovascular event was defined as cardiovascular death, cardiac arrest, myocardial infarction, stroke, acute coronary syndrome, unstable angina, coronary revascularisation, cardiac arrhythmia or onset of heart failure. Cardiovascular events were those recorded in primary care records, hospital discharge summaries and death certificates.

**Covariates**

In order to adjust the models for potential cofoundingfactors, a number of other details were also recorded, including age, gender, GP-recorded smoking status, BMI, WIMD deprivation quintile, previous diagnosis of hypertension or prescription of anti-hypertensive medication, previous diagnosis of diabetes or prescription of hypoglycaemic drugs.

**Statistical analysis**

Descriptive statistics will be used to analyse the baseline demographic and clinical characteristics of the cohort. A cohort table will be produced to show the baseline characteristics of the epilepsy cohort. A consort diagram of the epilepsy cohort will also be produced to show how this cohort was selected.

Adjusted Cox-proportional hazard models will be used to calculate the hazard ratios for cardiovascular events comparing people with epilepsy not taking AEDs, taking AEDs and EIAEDs with a matched cohort control. This analysis will indicate the relative hazard of developing a cardiovascular event upon exposure to AEDs.

Survival (time-to-event) models will be constructed to compare the time to the cardiovascular event for individuals with epilepsy taking AEDs versus those without epilepsy. Survival models will also be constructed to compare the time to the cardiovascular event for individuals with epilepsy taking enzyme-inducing AEDs versus those with epilepsy taking non-enzyme inducing AEDs. Time-to-event is defined as the time between the start date for their first AED and the first cardiovascular event.