Title: Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: non-interventional study of patients taking Direct Oral Anticoagulants in the EU". Version 2.3 – 23 July 2017, EU PAS Register No: 16014. Main author: Dr. H. Gardarsdottir, Universiteit Utrecht, Utrecht, The Netherlands and University Medical Center Utrecht, The Netherlands

Rationale and background: The protocol has been developed under the Framework service contract (nr. EMA/2015/27/PH) with regard to the re-opening of competition no.3. The objective of this protocol is to describe a pharmacoepidemiological study using longitudinal data collected in 8 electronic health care databases from 6 EU countries to characterize the risk of major bleeding in Direct Oral Anticoagulant (DOAC) users in a real-world setting to help establish the effectiveness of existing and future risk minimization measures. The research undertaken will focus on targeted clinical and demographic subgroups for which variations in plasma concentrations might affect the safety of the products.

Research question and objectives:

Objective 1. The risk of major bleeding, such as gastrointestinal bleeding, intracranial bleeding and haemorrhagic stroke, associated with use of DOACs when compared to other oral anticoagulants (OACs), i.e. vitamin K antagonists (VKAs), in patients with non-valvular atrial fibrillation (NVAF) overall and in relevant clinical and demographical subgroups in a real-life setting.

Objective 2. The utilization of DOACs in the EU for treatment of NVAF, including the characterization of new DOAC users in NVAF patients.

Objective 3. Prescribers' compliance with recommendations included in sections 4.1, 4.3, 4.4, and 4.5 of the SmPC of each DOAC.

Study design: Three studies will be conducted to answer the research questions listed in our aim: one retrospective cohort study (objective 1) and two descriptive studies (objectives 2 & 3).

Population: The study on prescriber compliance with recommendations (objective 3) includes all DOAC users. The study cohort for objective 1 and 2 consists of new users (≥18 years) of DOACs with incident non-valvular atrial fibrillation from the respective data sources.

Variables:

Objective 1: Major bleeding (haemorrhagic stroke/intracranial bleeding, gastrointestinal bleeding, or other extracranial or unclassified bleeding), DOAC exposure, effect modifiers (age, renal function, BMI) and potential confounders (risk factors for bleeding).

Objective 2**:** Patient characteristics, co-morbidities, co-medication use, switching, dose adjustments and treatment duration.

Objective 3: Variables included in SmPC section 4.1 (Therapeutic indications), 4.3 (Contraindications), 4.4 (Special Warnings and precautions for use), and 4.5 (Interaction with other medicinal products and other forms of interaction) of each individual DOAC.

Data sources: These studies will be performed in the following databases: Mondriaan, Danish Registries, Bavarian Claims database, AOK NORDWEST, BIFAP, SIDIAP, CPRD, and EGB.

Study size: This is a large database study.

Data analysis:

Objective 1: Baseline characteristics will be summarized as means and standard deviations or proportions where appropriate. Crude incidence rates of outcomes per 1,000 person years will be estimated, stratified by sex and age groups. Cox proportional hazard regression analysis will be applied to estimate effects (adjusted hazard ratios, HR) of (D)OAC treatment using STATA13 or the SAS 9.2/3/4 PHREG procedure.

Objective 2: The analysis will be descriptive and will be conducted stratified by database, individual DOACs, age group, gender, and calendar year.

Objective 3: The analysis will be descriptive and using information on the index date.