# 1.Title Page

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|---|---|
| **Title** | TARGET-EU: The risk of angiooedema and other safety events in heart failure patients treated with sacubitril/valsartan compared to angiotensin-converting enzyme inhibitors. |
| **Research question & Objectives** | To assess whether treatment with sacubitril/valsartan (SV) increases the risk of angioedema compared to treatment with Angiotensin Converting Enzyme Inhibitors (ACEIs) in patients with Heart Failure (HF). |
| **Protocol version** | V1.0 |
| **Last update date** | 27 February 2026 |
| **Contributors** | **Primary investigators contact information:**<br>Vasiliki Tassopoulou (v.p.tassopoulou@uu.nl) , Dr. Sophie Bots (s.h.bots@uu.nl)<br><br>**Contributor names:**<br>Prof. Olaf Klungel<br>Prof. Ian Douglas<br>Dr. Patrick Souverein<br>Dr. Jetty Overbreek<br>Dr. Daniala Weir |
| **Study registration** | **Site:** https://catalogues.ema.europa.eu/node/4440/administrative-details<br><br>**Identifier:**<br>EUPAS1000000539 |
| **Sponsor** | **Organization:** EU PE&PV research network<br><br>**Contact:** eupepv@uu.nl |
| **Conflict of interest** | None |

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## 2. Abstract


### Background

Sacubitril/valsartan (SV), the first Angiotensin Receptor Neprilysin Inhibitor (ARNI), was found to be superior to enalapril, an Angiotensin Converting Enzyme Inhibitor (ACEI), in delaying the time to the composite outcome of Heart Failure (HF) hospitalization or cardiovascular death in patients with Heart Failure and reduced Ejection Fraction (HFrEF) in the PARADIGM-HF trial. According to these results, SV is now recommended in the 2021 guidelines of the European Society of Cardiology as a replacement of ACEI in patients with HFrEF who remain symptomatic after first line treatment. SV may be considered also as a first-line therapy instead of an ACEI.

Angioedema was a safety outcome of special interest in the PARADIGM-HF trial for both the intervention treatment and the control treatment. The results showed that adjudication committee – confirmed angioedema occurred in 19 of the 4,187 patients of the SV arm (0.45%) and in ten of the 4,212 patients of the enalapril arm (0.24%) with a relative risk of 1.9 (95% CI 0.8-4.5). Nevertheless, the PARADIGM-HF population may not be fully representative of the real-world HF population and angioedema is a rare event, both of which render necessary the assessment of the risk of angioedema with SV on a larger scale and in the general HF population.

### Objectives

The primary objective of this observational study is to estimate the effect of treatment with sacubitril/valsartan versus ACEi on time to first angioedema event in patients with HF while the patients remain alive and while on treatment, i.e. before treatment discontinuation, switching or new add-on of any of the three HF medications (ACEi, ARB, SV).

### Methods

We will perform the observational study using two Electronic Healthcare Record (EHR) databases, the United Kingdom Clinical Practice Research Datalink (CPRD) and the Netherlands PHARMO database, to assess whether treatment with SV increases the risk of angioedema in comparison to treatment with ACEI in patients with HF. Eligible patients will enter the cohort from 01/01/2014 until 31/03/2023 and September 2024 for the PHARMO and the CPRD database respectively. We will apply the Prevalent New User (PNU) active comparator cohort design to match new SV users with ACEI users based on their treatment history before the index date, thereby aligning the start of follow-up between the intervention and the comparator cohort. Our primary aim is to assess the risk of angioedema in SV vs ACEi in patients with HF while the patients remain alive and while on treatment, i.e. before treatment discontinuation, switching or new add-on of any of the three HF medications (ACEi, ARB, SV). We have two secondary aims: 1) to assess the risk of angioedema in SV vs ACEi in patients with HF while the patients remain alive regardless of treatment discontinuation, switching or new add-on of any of the three HF medications (ACEi, ARB, SV); and 2) to assess the difference in Restricted Mean Survival Time (RMST)

to angioedema between SV and ACEi in patients with HF while the patients remain alive and on treatment, i.e. before treatment discontinuation, switching or new add-on of any of the three HF medications (ACEi, ARB, SV).

## 3. Amendments and updates

| Version date | Version number | Section of protocol | Amendment or update | Reason |
|---|---|---|---|---|
| 27 February 2026 | 1.0 | | | |

## 4. Milestones

*Table 1. Milestones*

| Milestone | Date |
|---|---|
| Study protocol for RWD study | 8 August 2025 |
| Preliminary results RWD study | April 2026 |
| Final Study report | 10 June 2026 |

## 5. Background

**What is known about the condition:**

Heart Failure (HF) is a life-threatening cardiovascular syndrome, with mortality rates which reach 42% at five years following hospitalization for HF.[1] HF patients experience burdensome symptoms, such as breathlessness, fatigue, tachycardia and chest pain, significantly affecting their quality of life.[1] HF occurs in 1-3% of the general adult population and is expected to increase in the following years.[2] HF is divided in three subtypes according to the left ventricular ejection fraction (LVEF): i) HF with reduced EF (HFrEF); LVEF < 40%, ii) HF with mid- range EF (HFmrEF); 40% ≤ LVEF < 50% iii) HF with preserved EF (HFpEF); LVEF ≥50%.[3,4] The latest 2021 guidelines by the European Society of Cardiology make specific recommendations for each subtype.[4] In HFrEF, the first-line recommended treatment includes an Angiotensin Converting Enzyme Inhibitor (ACEI), a beta-blocker, a Mineralocorticoid Antagonist (MRA), one of the two Sodium Glucose Transporter 2 inhibitors (SGLT2) dapagliflozin or empagliflozin, and a loop diuretic.

If the patient is intolerant to ACEI, an Angiotensin Receptor Blocker (ARB) is recommended instead. If the patient remains symptomatic after initial treatment, replacement of the ACEI with the Angiotensin Receptor Neprilysin Inhibitor (ARNI), sacubitril/valsartan, is recommended. However, it is stated that SV may be considered also as a first-line therapy instead of an ACEI. In HFmEF and in HFpEF no strong recommendations are made. In HFmEF, it is stated that any of ACEIs, ARBs, beta-blockers, MRAs or SV may be considered to reduce the risk of HF hospitalization and death. In HFpEF, the guideline recommends symptomatic treatment with diuretics and treatment of coexisting comorbidities.

### What is known about the exposure of interest:

ARNI is a therapeutic drug class that acts simultaneously on the Renin-Angiotensin-Aldosterone System (RAAS) and on the neutral endopeptidase system.[5] Sacubitril-valsartan (SV) is the first molecule in this class, and it combines the moieties of valsartan and sacubitril. Valsartan inhibits the Angiotensin II receptor type 1 (AT1) of the Renin Angiotensin Aldosterone System (RAAS) and reduces vasoconstriction, sodium and water retention. Sacubitril inhibits the enzyme neprilysin of the neutral endopeptidase system. Inhibition of neprilysin, inhibits the degradation of natriuretic peptides (NPs) which by binding to the NP receptors stimulate diuresis, natriuresis, myocardial relaxation and anti-remodelling.[6] In addition, NPs inhibit renin and aldosterone secretion. Neprilysin is also responsible for the degradation of bradykinin, adrenomedullin, endothelin-1, substance P and angiotensin II, and therefore inhibition of neprilysin, inhibits the degradation of these substances. The PARADIGM-HF clinical trial compared the effect of 200mg b.i.d. sacubitril/valsartan with that of 10mg b.i.d. enalapril on morbidity and mortality, when added to conventional HF treatment, in patients with symptomatic HFrEF and elevated NP plasma levels.[5,7] Sacubitril/valsartan was superior to enalapril in delaying the time to the composite outcome of HF hospitalization or cardiovascular death and also in delaying the time to all-cause mortality.

Angioedema was a safety outcome of special interest in the trial for both the intervention treatment and the control treatment, considering their mechanism of action.[8] Both treatments inhibit enzymes relevant for the degradation of bradykinin, a vasoactive molecule that can cause angioedema both directly and indirectly. For the intervention treatment (SV), this is the neprilysin enzyme, whereas for the control treatment (enalapril) this is the ACE enzyme. The results showed that adjudication committee – confirmed angioedema occurred in 19 of the 4,187 patients of the SV arm (0,45%) and in ten of the 4,212 patients of the enalapril arm (0.24%) with a relative risk of 1.9 (95% CI 0.8-4.5).[7,8]

With regard to other safety events, SV exhibited a higher rate of symptomatic hypotension compared to enalapril.[7] However, it exhibited a lower rate of cough, elevated creatinine levels and elevated potassium levels in comparison to enalapril. Overall, fewer patients in the SV arm discontinued the medication due to an adverse event than in the enalapril arm.

### Gaps in knowledge:

The PARADIGM-HF trial applied an extensive list of eligibility criteria for the inclusion of patients which may have limited the representativeness of its population for the real-world HF population. In addition, angioedema is a rare event occurring in a total of 29 patients in the trial. For a more reliable assessment of the risk of angioedema with SV, more events would be necessary which could be achieved in a larger sample than the trial's population. Therefore, the knowledge gap identified and addressed here is the risk of angioedema with SV on a larger scale and in the general HF population.

### What is the expected contribution of this study?

We will perform an observational study using two large Electronic Healthcare Record (EHR) databases to assess whether treatment with SV increases the risk of angioedema in comparison to treatment with ACEI in patients with HF, thereby addressing the aforementioned knowledge gap.

## 6. Research questions and objectives

The overall aim is to assess whether SV increases the risk of angioedema compared to ACEIs in patients with HF.

### *6.1 Primary Estimand 1*

### Research question answered by the estimand

**Estimand 1 (primary estimand):** What is the hazard ratio of angioedema associated with SV compared to ACEi in patients with HF while the patients remain alive and while on treatment, i.e. before treatment discontinuation, switching or new add-on of any of the three HF medications (ACEi, ARB, SV)?

*Table 2. Primary estimand (Estimand 1)*

| | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **Population** | Adult patients with Heart Failure | Adult patients with Heart Failure | |

| | | | |
|---|---|---|---|
| **Treatment Conditions** | Treatment with Sacubitril/Valsartan combination vs treatment with ACEi, | Treatment with Sacubitril/Valsartan combination vs treatment with ACEi<br><br>All identified using prescription/dispensing data | Exposure defined based on observed prescribing patterns in the emulation study |
| **Endpoint** | Time to first occurrence of angioedema | Time to first occurrence of angioedema, defined using diagnostic codes in primary and secondary care | Emulated using validated code lists |
| **Summary Measure** | Hazard Ratio | Hazard Ratio | |
| **Intercurrent events and strategies to handle them** | Treatment discontinuation**: while on treatment**<br><br>Treatment switch**: while on treatment**<br><br>Addition of any of the three HF medications (ACEi, ARB, SV) if not the treatment of the group**: while on treatment**<br><br>All-cause death**: while alive** | Intercurrent events handled according to the same prespecified strategies<br><br>Treatment discontinuation is measured using prescribing/dispensing data by identifying gaps of 30 days or more from the end of the estimated duration of the last prescription/dispensation of interest until the next refill.<br><br>Treatment switch and add-on are measured using prescribing/dispensing data by identifying receipt of ACEI, ARB or SV while on study treatment if this is not the treatment of the group.<br><br>All-cause death is identified using the recorded death date in the primary care database. | Identification of time of treatment discontinuation and switch are subject to inaccuracies due to the reliance on recorded prescribing/dispensing data. More specifically, treatment discontinuation is assumed to occur when the expected duration of the prescription/dispensation elapses without a refill. A treatment switch is assumed to occur when a new prescription/dispensation is issued for a different medication. This entails uncertainty and could introduce bias, considering that these are handled with the while on treatment strategy. |

**Rationale for why selected strategies to handle intercurrent events are chosen**

Regarding death from any cause, in all the three estimands we will use the while-alive strategy because although angioedema can be life-threatening in severe cases of airway obstruction, the overall mortality rate due to angioedema is low. [9-14] Therefore, excluding fatal events from the outcome is unlikely to affect the validity of the results. At the same time, patients with HF are at high risk of cardiovascular death rather than due to angioedema, and while all-cause death is usually assessed as an efficacy endpoint in HF trials,[15,16] we did not choose the composite strategy because adding all-cause death to the endpoint would conflate our specific safety outcome with irrelevant events.

Regarding the treatment-modifying intercurrent events, in the primary estimand and in estimand 3 we will use the while-on-treatment strategy because the interest lies in the risk of angioedema when patients are on treatment, considering that the risk of angioedema is increased when patients are on treatment.[17,18]

## *6.2 Supplementary Estimand 2*

**Estimand 2 (supplementary estimand):** What is the hazard ratio of angioedema associated with SV compared to ACEi in patients with HF while the patients remain alive regardless of treatment discontinuation, switching or new add-on of any of the three HF medications (ACEi, ARB, SV)?

*Table 3. Estimand 2*

| | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **Population** | Same as estimand 1 | Same as estimand 1 | |
| **Treatment Conditions** | Same as estimand 1 | Same as estimand 1 | Same as estimand 1 |
| **Endpoint** | Same as estimand 1 | Same as estimand 1 | Same as estimand 1 |
| **Summary Measure** | Same as estimand 1 | Same as estimand 1 | |
| **Intercurrent events and strategies to handle them** | Treatment discontinuation**: treatment policy**<br>Treatment switch**: treatment policy**<br>Addition of any of the three HF medications (ACEi, ARB, SV) if not the treatment of the group**: treatment policy** | Intercurrent events handled according to the same prespecified strategies.<br>Treatment discontinuation is measured using prescribing/dispensing data by identifying gaps of 30 days or more from the end of the estimated duration of the | Identification of time of treatment discontinuation and switch are subject to inaccuracies due to the reliance on recorded prescribing/dispensing data. However, this is of little consequence for a treatment policy approach because we still |

| | | | |
|---|---|---|---|
| | All-cause death**: while alive** | last prescription/dispensation of interest until the next refill.<br><br>Treatment switch and add-on are measured using prescribing/dispensing data by identifying receipt of ACEI, ARB or SV while on study treatment if this is not the treatment of the group.<br><br>All-cause death is identified using the recorded death date in the primary care database. | measure occurrence of the outcome even after the IE. |

**Rationale for why selected strategies to handle intercurrent events are chosen**

In the secondary estimand, considering that certain angioedema events have been reported to occur up to one month (or sometimes more) after ACEi discontinuation,[17] we will use the treatment policy strategy to investigate angioedema risk after initiating treatment with SV/ACEi regardless of treatment-related intercurrent events.

### *6.3 Supplementary Estimand 3*

**Estimand 3 (supplementary estimand):** What is the difference in Restricted Mean Survival Time (RMST) to angioedema between SV and ACEi in patients with HF while the patients remain alive and on treatment, i.e. before treatment discontinuation, switching or new add-on of any of the three HF medications (ACEi, ARB, SV)?

*Table 4. Estimand 3*

| | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| **Population** | Same as estimand 1 | Same as estimand 1 | |
| **Treatment Conditions** | Same as estimand 1 | Same as estimand 1 | Same as estimand 1 |
| **Endpoint** | Same as estimand 1 | Same as estimand 1 | Same as estimand 1 |

| | | | |
|---|---|---|---|
| **Summary Measure** | Difference in Restricted Mean Survival Time | Difference in Restricted Mean Survival Time | |
| **Intercurrent events and strategies to handle them** | Same as estimand 1 | Same as estimand 1 | Same as estimand 1 |

# 7. Research methods

## *7.1. Study design*

**Research design (e.g. cohort, case-control, etc.):**

To emulate the target trial, we will use the prevalent new user (PNU) cohort design. This design includes an active comparator per definition.

**Rationale for study design choice:**

Our hypothetical target trial mimics the real PARADIGM-HF trial, where the new treatment (SV) was compared to an existing treatment for the same indication (ACEI). This set-up reflects the treatment reality of HF patients where a considerable part of the patients who start treatment with SV will already be on previous treatment with an ACEI or an ARB considering the respective recommendations in the guidelines.[3,4] More specifically, SV was approved based on its beneficial effect on HF hospitalization, cardiovascular and all-cause mortality, found in the PARADIGM-HF trial.[7] The trial's population consisted of patients on treatment with an ACEI or an ARB, randomized to either SV or enalapril. Based on this composition of the trial population, the 2016 ESC guidelines recommended it as a replacement for ACEIs (or ARBs in patients intolerant to ACEIs), for patients who remained symptomatic despite optimal treatment with the recommended first-line medications.[3] As mentioned above, the latest 2021 ESC guidelines, still recommend SV as a replacement for ACEI (or ARB), but also state that SV may be considered in the first-line treatment, instead of an ACEI/ARB.[4]

Given these ESC recommendations, we expect a population consisting of incident new SV users (no ACEI, ARB before SV start) and prevalent new SV users (on treatment with ACEI or ARB before SV start). We can in fact consider our study as a set of three sub-studies: i) incident new SV users compared to new ACEI users ii) switchers from ACEIs to SV compared to prevalent ACEI users and iii) switchers from ARBs to SV compared to switchers from ARBs to ACEIs. While the new user design would be appropriate for the sub-study i, this would not be appropriate for sub-studies ii,iii. The prevalent new user (PNU) design was developed specifically to study research questions about switching from an existing therapy (background therapy, ACEI/ARB in our case) to a new treatment (study treatment, SV in our case) and it accommodates both incident new users and prevalent new users .[19,20] It includes an active comparator by design (the existing therapy) and it matches each patient who switches from the active comparator to

the new treatment with a patient with a similar treatment history with the active comparator who instead continues treatment with it. This improves the balance in the baseline measured characteristics between the two treatment groups and reduces the potential of unmeasured confounding.[21] This is because the control patients receive the active comparator for the same indication for which the intervention patients receive the study drug, and have received the comparator for a similar length of time as the intervention patients have, before switching to the new treatment, thereby rendering the two treatment groups more comparable with regard to their clinical profile and disease stage. Balancing the baseline measured characteristics by design is important because even though differences in measured baseline characteristics are accounted for by adjustment for confounding, the active comparator ensures balance in other measured or unmeasured potential confounders before statistical adjustment. This mitigates the risk of confounding by indication and renders statistical adjustment more efficient.

We operationalise the PNU design within the TTE framework using stratified randomisation in the target trial, where patients are stratified based on the treatment they receive at the screening visit: i) none (new users) ii) treatment with ACEi iii) treatment with ARB (both prevalent users).

To emulate the stratified randomisation in our observational study, we will create three strata of eligible patients. All patients must have HF diagnosed before initiation of the treatment of interest, regardless of stratum. The strata are i) stratum 1: patients who are not treated with ACEi, ARB or SV; ii) stratum 2: patients on treatment with ACEi; iii) stratum 3: patients on treatment with ARB. To ensure that patients in the intervention group are at a comparable time-point in their disease trajectory with the patients in the control group, within each stratum we will match patients on their treatment history with ACEI and ARB.

## *7.2. Study design diagram*

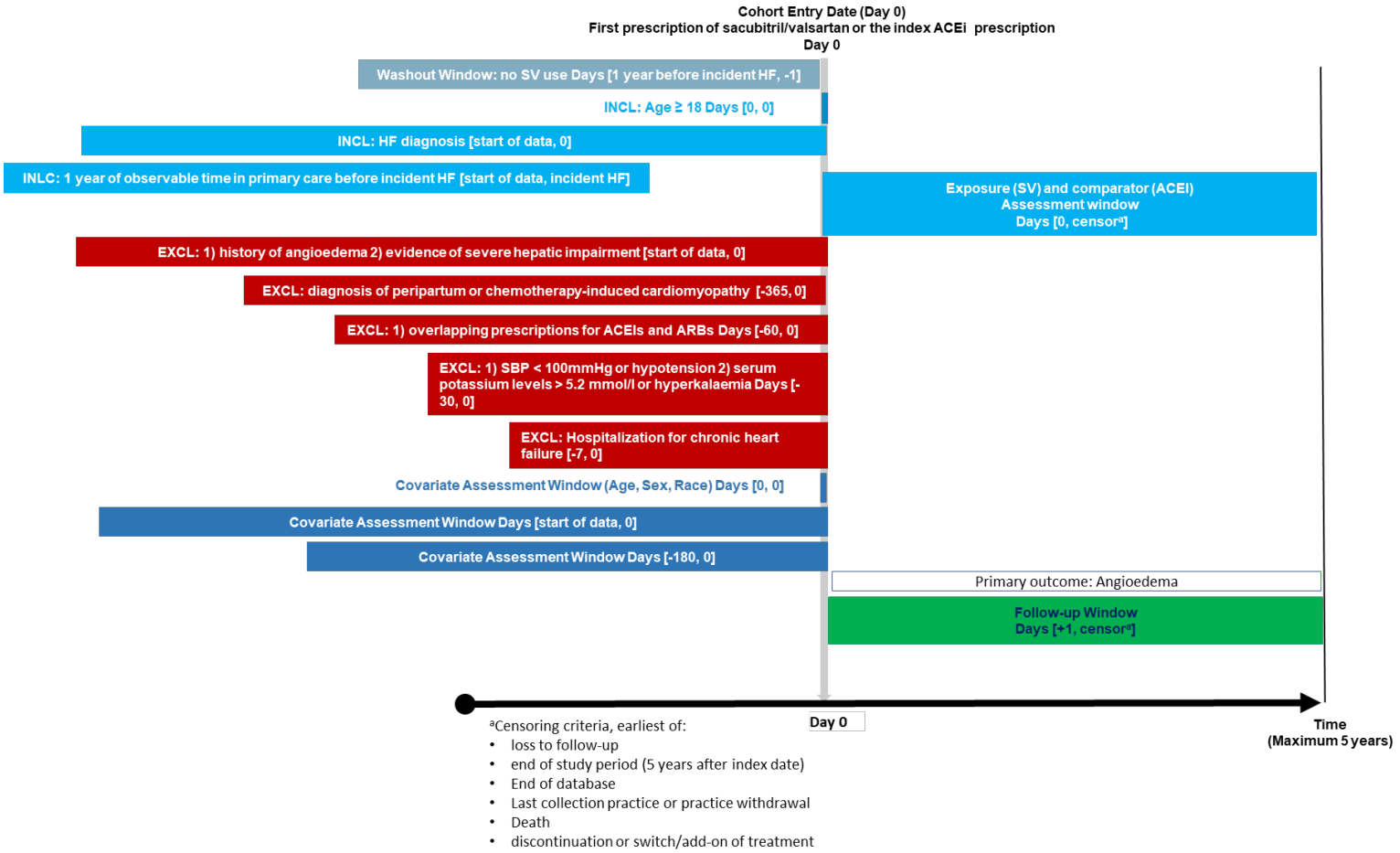



**Figure 1**. Study design diagram. The fourth inclusion criterium (in dashed outline) is stratum – specific: stratum 1: no prior treatment with ACEI or ARB, stratum 2: prior treatment with ACEI and stratum 3: prior treatment with ARB

## *7.3. Setting*

This study is conducted using routinely collected electronic health records from 2014 to 2024, reflecting the period of SV use in routine clinical practice. The study is set primarily in primary care, drawing on longitudinal data from general practices with linkage to hospital data. Data are sourced from two European countries, the United Kingdom (Clinical Practice Research Datalink [CPRD]) and Netherlands (PHARMO), providing population-based and representative coverage of real-world clinical care.

### *7.3.1 Definition of time 0 (and other primary time anchors) for entry to the study population*

**Base cohort and strata formation**

We will sample our three strata from a base cohort of patients with an incident heart failure diagnosis in primary or secondary care between 01/01/2014 and 31/03/2023. Incident HF is defined as the first ever diagnosis of the patient, who must have at least one year of data availability before this diagnosis to ensure that there are no prior diagnoses before. Patients enter the base cohort the date of their incident HF diagnosis. The requirement of one year of data availability before base cohort entry serves the additional purpose of reliably measuring baseline characteristics and treatment history before the incident HF diagnosis.

From the base cohort (e.g., after incident HF diagnosis) we will sample patients to create the following three strata:

- stratum 1: patients are eligible for this stratum if they are not treated with ACEI, ARB
- stratum 2: patients are eligible for this stratum if they are on treatment with ACEI
- stratum 3: patients are eligible for this stratum if they are on treatment with ARB

**Definition of index date (time 0)**

We will emulate our hypothetical trial in which the index date (time 0) is defined as the date of randomisation. Index date will always occur after base cohort entry (e.g., after incident HF diagnosis) and follow-up will start at the index date. The specific definition of index date differs slightly across strata:

stratum 1: the index date is the first prescription of either SV (treatment arm) or ACEI (comparator arm)

stratum 2: the index date for the treatment arm is the first switch from previous therapy (ACEI) to SV. For the comparator arm, every ACEI prescription is a potential index date. The index date is decided when the comparator patient is matched to their respective treatment patient, in other words, the matched ACEi prescription date becomes the comparator's index date.[19]

stratum 3: the index date is the first switch from baseline therapy (ARB) to either SV (treatment arm) or ACEI (comparator arm)

**Matching**

Within each stratum we will match the intervention patients with the control patients in a ratio of 1:1 at index date on the following:

I) Treatment history; following the six trajectories depicted in Figure 2, which were identified in an already performed drug utilisation study. These trajectories will be assessed from one year before the incident HF diagnosis until the index date. For patterns 2 & 3, the matching will be on the total number of prior prescriptions of ACEI or ARB, respectively. For patterns 4-6, we will match on number of prior prescriptions and dominant medication

type (ACEI or ARB). In case of a 50-50 split, we assign a third category (no dominant type) and match on this.

II) Calendar year of the index prescription

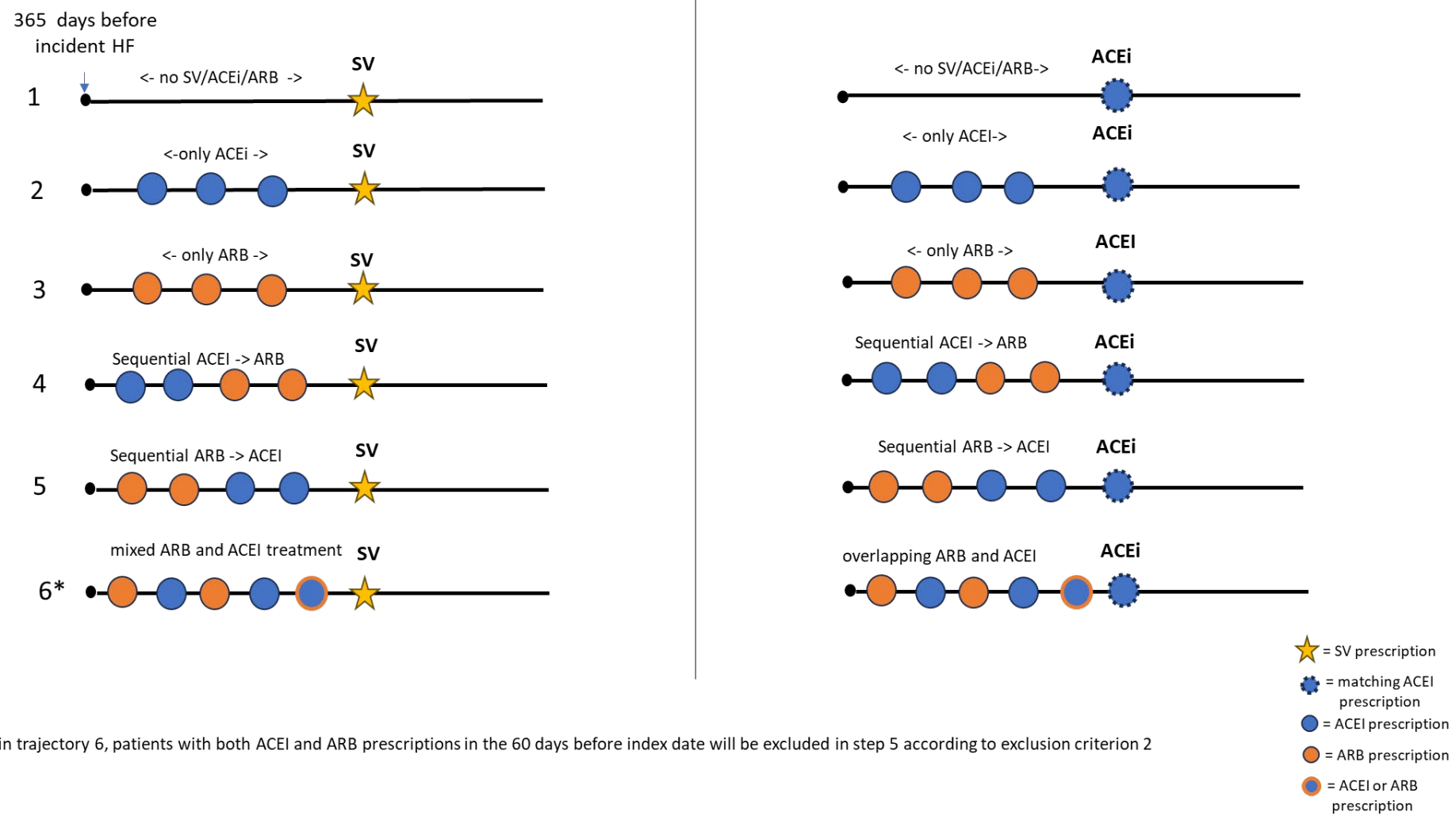
III) Gap (0-60 days, 61 – 180 days, > 180 days) between the last prescription before the index prescription and the index prescription itself

IV) Propensity score, calculated by conditional logistic regression including the confounders of the study measured at the index date. We will use the nearest neighbor method with a caliper of 0.2 of the standard deviation of the logit of the propensity score.

V) .

The intervention and the comparator patients who are matched will not be reused for matching at a different time point of their trajectories (matching without replacement).

For a detailed description of all the steps that will be followed to match each intervention patient with a comparator according to the PNU please see Appendix 1.




*in trajectory 6, patients with both ACEI and ARB prescriptions in the 60 days before index date will be excluded in step 5 according to exclusion criterion 2

**Figure 2.** Trajectories patterns of the SV users identified in the drug utilization study (left) and the required trajectories of ACEI controls for matching (right). Note: the number of circles in the history does not represent the actual number of prescriptions, rather it is indicative of the drug (ACEI/ARB) that patients are on treatment with.

*Table 5. Operational Definition of Time 0 (index date) and other primary time anchors*

| Study population name(s) | Time Anchor Description (e.g. time 0) | Number of entries | Type of entry | Washout window | Care Setting[1] | Code Type[2] | Diagnosis position | Incident with respect to… | Measurement characteristics/ validation | Source of algorithm |
|---|---|---|---|---|---|---|---|---|---|---|
| Intervention cohort: Sacubitril/ valsartan | First prescription of SV | Single | Incident | [1 year before incident HF diagnosis, -1] | Primary care | ATC codes (mapped to DM+D codes) | n/a | Sacubitril/valsartan | No validation study | n/a |
| Control cohort: ACEIs | Matching ACEI prescription | Single | Incident/ prevalent | n/a [1 year before incident HF diagnosis, -1] | Primary care | ATC codes (mapped to DM+D codes) | n/a | Sacubitril/valsartan | No validation study | n/a |

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2]See appendix for listing of clinical codes for each study parameter

### *7.3.2 Study inclusion criteria*

1. Age 18 years or older at index date: We are interested only in adult patients.
2. A diagnosis of HF of any subtype regardless of ejection fraction any time before index date: We are interested in patients receiving the intervention treatment or the control treatment for HF
3. One year of history in primary care before incident HF diagnosis: This criterion is applied to ensure that we will have enough data to assess treatment history with ACEI/ARB – necessary for the matching process within the PNU design and to ensure that the incident HF diagnosis is indeed the first diagnosis.

*Table 6. Operational Definitions of Inclusion Criteria*

| Criterion | Details | Assessment window | Care Settings[1] | Code Type[2] | Diagnosis position[3] | Applied to study populations: | Measurement characteristics/ validation | Source for algorithm |
|---|---|---|---|---|---|---|---|---|
| Age ≥18 yrs | | [0,0] | n/a | n/a | n/a | Intervention cohort: | n/a | n/a |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | sacubitril/ valsartan<br><br>Control cohort: ACEIs | | |
| HF diagnosis | Diagnosis of HF of any subtype regardless of ejection fraction | [start of data, 0] | Primary or secondary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes and ICD-10 codes | any | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | No validation study<br>Clinician's review of the Bellanca – BMC –2023 medcodeId code list | CPRD: Bellanca – BMC – 2023[22]<br><br>PHARMO: no source, search of the clinical term in the ICPC browser |
| Observable time | Start of observation (data) at last 365 days before incident HF | [-365 days before incident HF, incident HF] | n/a | n/a | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | n/a | n/a |

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

### 7.3.3 Study exclusion criteria

1. **Prior history of angioedema**: known history of angioedema (including hereditary or idiopathic angioedema) is a contraindication according to the summary of product characteristics of sacubitril/valsartan
2. **Overlapping prescriptions for ACEIs and ARBs in the 60 days before index date**: the ESC guidelines state that concomitant treatment with both ACEIs and ARBs is generally not recommended because of high risk of side effects.
3. **Hospitalization for chronic heart failure in the 7 days before index date**: following the PARADIGM-HF in which patients with current decompensated heart failure were excluded
4. **Diagnosis of peripartum cardiomyopathy or cardiomyopathy induced by external agents in the 1 year before index date**: following the

PARADIGM-HF trial in which patients with this type of heart failure were excluded

5. **History of severe hepatic impairment**: severe hepatic impairment is a contraindication according to the summary of product characteristics of sacubitril/valsartan
6. **Hyperkalaemia in the 30 days before index date**: potassium levels > 5.4 mmol/l is a contraindication according to the summary of product characteristics of sacubitril/valsartan
7. **Hypotension in the 30 days before index date**: systolic blood pressure < 100mmHg is a contraindication according to the summary of product characteristics of sacubitril/valsartan

We will exclude patients with missing data on necessary variables for the assessment of eligibility criteria (diagnosis date of relevant conditions). This is expected to occur very rarely.

*Table 7. Operational Definitions of Exclusion Criteria*

| Criterion | Details | Assessment window | Care Settings[1] | Code Type[2] | Diagnosis position[3] | Applied to study populations: | Measurement characteristics/ validation | Source for algorithm |
|---|---|---|---|---|---|---|---|---|
| Prior history of angioedema | Includes drug-induced angioedema, hereditary and idiopathic angioedema | [start of data, 0] | Primary and secondary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes and ICD-10 codes | Any | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | CPRD: Williams et al. 2019[23]<br><br>PHARMO: no source, search of the clinical term in the ICPC browser (ICPC code, A12.02 - Angioneurotisch/Quinckes oedeem) |
| Overlapping prescriptions for ACEIs and ARBs | | [-60, 0] | Primary care | ATC codes (mapped to DM+D codes) | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: | No validation study | n/a |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | ACEIs | | |
| Hospitalization for chronic heart failure | | [-7, 0] | Secondary care | ICD-10 codes | any | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | No validation study Clinician's review of the developed ICD-10 codelist | CPRD and PHARMO: ICD-10 code list from Bellanca – BMC – 2023[22] |
| Diagnosis of peripartum cardiomyopathy or cardiomyopathy induced by external agents | | [-365, 0] | Primary and secondary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes and ICD-10 codes | any | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | No validation study | CPRD: no source, search of the clinical term in the Aurum browser<br><br>PHARMO: no source, search of the clinical term in the ICPC browser |
| History of severe hepatic impairment | | [start of data,0] | Primary and secondary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes and ICD-10 codes | any | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | CPRD: Williams et al. 2019[23]<br><br>PHARMO: no source, search of the clinical term in the ICPC browser |
| Hyperkalaemia | diagnosis of hyperkalaemia | [-30, 0] | Primary and secondary care | MedcodeIds (mapped from Read and SNOMED concept IDs), | any | Intervention cohort: sacubitril/ valsartan | | CPRD: Wetmore et al. 2021[24] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | ICPC codes and ICD-10 codes | | Control cohort: ACEIs | | PHARMO: no source, search of the clinical term in the ICPC browser |
| Hypotension | diagnosis of hypotension | [-30, 0] | Primary and secondary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes and ICD-10 codes | | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | CPRD: https://github.com/DynAIRx/Codelists_DynAIRx/blob/main/codelists/Hypotension_syncope.csv<br><br>PHARMO: no source, search of the clinical term in the ICPC browser |

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

## *7.4. Variables*

### *7.4.1. Exposure(s) of interest*

We chose an active comparator design because it is the most appropriate for the observational study, considering also that HF patients are likely already being treated. As mentioned earlier, the 2021 guidelines of European Society of Cardiology recommend ACEIs or SV among the treatments of the first-line therapy of HF with reduced or mildly reduced ejection fraction. SV is also recommended as a replacement of ACEIs in suitable patients who remain symptomatic despite optimal treatment with all the recommended first line treatments. ARBs are considered as an alternative option in patients who are intolerant to ACEIs. Considering this information, ACEIs are the most appropriate comparator in our study.

During the study period all the HF medications apart from ARBs (i.e. beta-blockers, aldosterone antagonists, SGLT-2 inhibitors, ivabradine, vericiguat, digoxin, hydralazine/isosorbide dinitrate) are allowed to be used by the patients.

**Algorithm to define duration of exposure effect:**

For the construction of treatment episodes based on prescription records, the duration of each prescription is first derived using information available in the database. When end date or days supply is recorded, this information is used to directly define the prescription duration along with the date of the prescription. If days supply is not recorded, prescription duration will be estimated based on the quantity prescribed and dosing instructions. If dosing information is missing or incomplete, standard dosing assumptions consistent with routine clinical practice will be used (e.g., one defined daily dose according to WHO ATC classification). Overlapping days between prescriptions are handled by carrying forward any unused supply. Specifically, if a refill occurs before the end of the previous prescription's calculated days' supply, the overlapping days are added to the end of the new prescription's duration. We assume that each dispensed prescription has a lasting effect of up to 90 days. Therefore, a gap of up to 90 days between the end of a prescription's days' supply and the subsequent refill is allowed, without considering the patient as having discontinued treatment. The choice of a 90-day window aligns with common prescribing and dispensing practices for chronic medications such as HF treatments and is consistent with prior pharmacoepidemiologic studies. This grace period accommodates typical variations in refill timing, medication stockpiling, or short treatment interruptions, thereby reducing the risk of misclassifying ongoing therapy as discontinued. Additionally, for the final prescription in a treatment episode, we extend exposure by 90 days beyond the calculated end date to account for any residual pharmacological effect or continued use.

For the PHARMO database the respective dispensations will be used.

### *7.4.2. Outcome(s) of interest*

Angioedema is a safety outcome of particular interest because of the mechanism of action of both the intervention treatment and the control. From a clinical perspective it is important to know the risk of angioedema that treatments are associated with for two reasons. First and foremost, because it may necessitate hospitalization and may be life-threatening when it involves the upper airway. Secondly, because it usually leads to treatment discontinuation, which is the only way it can be addressed, depriving patients of the beneficial effects of HF treatments.[18]

*Table 8. Operational Definitions of Outcome*

| Outcome name | Details | Primary outcome? | Type of outcome | Washout window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to study populations: | Measurement characteristics/ validation | Source of algorithm |
|---|---|---|---|---|---|---|---|---|---|---|
| Angioedema | | yes | Time-to-event | [start of data, 0] | Primary or secondary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes and ICD-10 codes | any | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | CPRD: Williams et al. 2019[23]<br><br>PHARMO: no source, search of the clinical term in the ICPC browser (ICPC code, A12.02 - Angioneurotisch/Quinckes oedeem) |

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

### *7.4.3 Follow up*

Follow-up will start at the day after the index date (see section 7.3.1).

For the primary estimand and estimand 3, we will follow a while-on treatment approach and stop follow-up at treatment discontinuation or treatment switch/add-on.

For the secondary estimand, we will use the treatment policy strategy and ignore treatment-related intercurrent events.

For all estimands, we will use the while-alive approach and stop following patients at death,
Patients will be followed up to a maximum of five years after their index date.

In summary, for estimands 1 and 3, follow-up will end at the earliest occurrence of: the study outcome (first angioedema event), treatment discontinuation, treatment switch/add-on, death due to any cause, five years after index date, end of study period or loss to follow-up.

For estimand 2, follow-up will end at the earliest occurrence of: the study outcome (first angioedema event), death due to any cause, five years after index date, end of study period or loss to follow-up.

*Table 9. Operational Definitions of Follow Up for estimands 1 and 3*

.

| | | |
|---|---|---|
| **Follow up start** | The day after Index date | |
| **Follow up end**[1] | **Select all that apply** | **Specify** |
| **Date of outcome** | yes | First occurrence of angioedema (See table 8) |
| **Date of death** | yes | |
| **End of observation in data** | yes | Transfer out of the database or last collection date of the GP |
| **Day X following index date** *(specify day)* | yes | 5 years after index date |
| **End of study period** (specify date) | yes | CPRD: 31/03/2023 (end of linkage with hospital data)<br>PHARMO (end of linkage with hospital data): September 2024 |
| **End of exposure** *(specify operational details, e.g. stockpiling algorithm, grace period)* | yes | **Stockpiling algorithm:**<br>If refills occur before predicted end of prescription, count overlapping days and add at the end of the treatment episode, s.<br><br>**Grace period**:<br>Bridge gaps ≤ 90 days between end of current prescription and refill. |
| **Date of add to/switch from exposure** *(specify algorithm)* | yes | For the intervention cohort, switch from the SV to ACEI and vice versa for the control cohort. For both cohorts, switch to ARBs |
| **Other date** *(specify)* | n/a | n/a |

*Table 10. Operational Definitions of Follow Up for estimand 2*

| | | |
|---|---|---|
| **Follow up start** | the day after Index date | |
| **Follow up end**[1] | **Select all that apply** | **Specify** |
| **Date of outcome** | yes | First occurrence of angioedema (See table 8) |
| **Date of death** | yes | |
| **End of observation in data** | yes | Transfer out of the database (deregistration or migration) or last collection date of the GP or end of database |
| **Day X following index date** *(specify day)* | yes | 5 years after index date |
| **End of study period** (specify date) | yes | CPRD: 31/03/2023<br>PHARMO: September 2024 |
| **End of exposure** *(specify operational details, e.g. stockpiling algorithm, grace period)* | no | Treatment policy strategy ignores treatment discontinuation |
| **Date of add to/switch from exposure** *(specify algorithm)* | no | Treatment policy strategy ignores treatment switch |
| **Other date** *(specify)* | n/a | n/a |

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

### *7.*4.4 Covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications)

After extensive literature search, we identified the risk factors for angioedema, and we include those as potential confounders in our study. The table below lists the operational definition of these confounders along with the sources from which these were identified.

*Table 11. Operational Definitions of Covariates*

| Characteristic | Source for identification | Details | Type of variable | Assessment window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to study populations: | Measurement characteristics/ validation | Source for algorithm |
|---|---|---|---|---|---|---|---|---|---|---|
| Age | Byrd et al. 2006[17] Rasmussen et al. 2014[25] | | Continuous | [0,0] | n/a | n/a | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | n/a | n/a |
| Sex | Byrd et al. 2006[17] Rasmussen et al. 2014[25] Lacuesta et al. 2024[18] | | Binary | [0,0] | n/a | n/a | n/a | Intervention cohort: sacubitril/ lsartan<br><br>Control cohort: ACEIs | n/a | n/a |
| Smoking status | Byrd et al. 2006[17] Rasmussen et al. 2014[25] Lacuesta et al. 2024[18] | The most recent smoking status | Categorical | [start of data, 0] | Primary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | No validation | CPRD: in-house macro<br><br>PHARMO: no source |
| History of diabetes | Byrd et al. 2006[17] | Diabetes type I or II For PHARMO dispensations of anti- | Binary | [start of data, 0] | Primary care | MedcodeIds (mapped from Read and SNOMED | n/a | Intervention cohort: sacubitril/ valsartan | No validation | CPRD : Carr et al. 2021[26] Conrad et al. 2023[27] |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | diabetic drugs will be used as a proxy | | | | concept IDs), ATC codes | | Control cohort: ACEIs | | PHARMO: Overbeek et al. 2023[28] |
| DPP-4 inhibitors | Rasmussen et al. 2014[25] Lacuesta et al. 2024[18] | | Binary | [-180, 0] | Primary care | ATC codes (mapped to DM+D codes) | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | No validation | n/a |
| History of ACEI-associated cough | Byrd et al. 2006[17] Mahmoudpour et al. 2016[29] | Any diagnosis of cough during ACEI therapy | Binary | [start of data, 0] | Primary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes<br><br>ATC codes (mapped to DM+D codes) | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | Algorithm for CPRD: Mahmoudpour et al. 2016[29]<br><br>PHARMO: no source, search of the clinical term for cough in the ICPC browser |
| History of heart or renal transplant | Byrd et al. 2006[17] Abbosh et al. 1999[30] | | Binary | [start of data, 0] | Primary care or secondary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes and ICD-10 codes | any | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | For both databases: search of the clinical term in the respective browsers |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Seasonal allergies | Byrd et al. 2006[17] Lacuesta et al. 2024[18] Mahmoudpour et al. 2016[29] | | Binary | [start of data, 0] | Primary care | MedcodeIds (mapped from Read and SNOMED concept IDs) | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | For both databases: search of the clinical term in the respective browsers |
| COPD | Mahmoudpour et al. 2016[29] | | Binary | [start of data, 0] | Primary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | CPRD: phenotypes/Medical conditions/COPD_birm_cam/COPD_birm_cam_CPRD_AURUM.csv at main · THINKINGGroup/phenotypes · GitHub<br><br>PHARMO: no source, search of the clinical term for cough in the ICPC browser |
| Antihistamines | Mahmoudpour et al. 2016[29] | | Binary | [-180, 0] | Primary care | ATC codes (mapped to DM+D codes) | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | No validation | n/a |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Corticosteroids | Mahmoudpour et al. 2016[29] | | Binary | [-180, 0] | Primary care | ATC codes (mapped to DM+D codes) | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | No validation | n/a |
| Calcium Channel Blockers | Mahmoudpour et al. 2016[29] | | Binary | [-180, 0] | Primary care | ATC codes (mapped to DM+D codes) | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | No validation | n/a |
| Localized tissue trauma | Lacuesta et al. 2024[18] Rasmussen et al. 2014[25] | | Binary | [-180, 0] | Primary care | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes | | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | For both databases: search of the clinical term in the respective browsers |
| Lymphoproliferative or autoimmune diseases | Lacuesta et al. 2024[18] Mahmoudpour et al. 2016[29] | | Binary | [start of data, 0] | | MedcodeIds (mapped from Read and SNOMED concept IDs), ICPC codes | | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | For both databases: search of the clinical term in the respective browsers |
| estrogen-containing oral | Lacuesta et al. 2024[18] | | Binary | [-180,0] | Primary care | ATC codes (mapped to | n/a | Intervention cohort: | No validation | n/a |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| contraceptives or estrogen replacement therapy | | | | | | DM+D codes) | | sacubitril/ valsartan<br><br>Control cohort: ACEIs | | |
| Infections | Lacuesta et al. 2024[18] | For PHARMO: drug use will be used as a proxy | Binary | [-180, 0] | Primary care | MedcodeIds mapped from Read and SNOMED concept IDs), ATC codes (ICPC codes) | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | | For both databases: search of the clinical term in the respective browsers |
| NSAIDs, acetylsalicylic acid | Lacuesta et al. 2024[18] | | Binary | [-180, 0] | Primary care | ATC codes (mapped to DM+D codes) | n/a | Intervention cohort: sacubitril/ valsartan<br><br>Control cohort: ACEIs | No validation | n/a |

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

## *7.5. Core Emulation Table - Design Summary*

*Table 12. Comparison of Target Trial and Proposed Target Trial Emulation Design Elements, estimands 1 and 3*

Estimands 1 and 3 differ in the summary measure that will be used to estimate the treatment effect (HR and RSM, respectively). Therefore, one common table is used for the design elements of these two estimands.

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| Inclusion criteria | 1. age 18 years or older at the screening visit<br>2. Documented clinical history of Heart Failure of any subtype according to the ejection fraction | 1. age 18 years or older at the index date<br>2. Diagnosis of Heart Failure before index date identified from diagnostic codes<br>3. 1 year of history in primary care before incident HF diagnosis | Eligibility criteria applied using structured EHR<br>The eligible population of the emulation differs from the target trial's eligible population in that in the emulation the eligible study population includes the patients with HF who receive at least one prescription of SV or an ACEI, whereas in the target trial the eligible study population includes all patients with HF.<br>The additional 1-year history in primary care criterion is applied to ensure that we will have enough data to assess treatment history with ACEI/ARB – necessary for the matching process within the PNU design |
| Exclusion criteria | 1.Documented history or diagnosis of angioedema (either ACEI/ARB-induced or hereditary/idiopathic angioedema) any time before the screening visit<br>2.Treatment with both ACEIs and ARBs in the month before or at the screening visit<br>3.Current acute decompensated heart failure, defined as exacerbation of chronic | 1. Prior history of angioedema identified from diagnostic codes<br>2. overlapping prescriptions for ACEIs and ARBs in the 60 days before index date<br>3. Hospitalization for chronic Heart Failure in the 7 days before index date<br>4. diagnosis of peripartum cardiomyopathy or cardiomyopathy induced by external agents in | All criteria will be operationalized using prescription/dispensation and diagnostic codes. Appropriate lookback windows for each criterion will be used for accurate classification.<br>Specific comments for exclusion criteria:<br>2. Relies on strong assumptions about how prescribed/dispensed medication was actually taken |

| | | | |
|---|---|---|---|
| | heart failure manifested by signs and symptoms that may require intravenous therapy at the screening visit<br><br>4.Diagnosis of peripartum- or chemotherapy- induced cardiomyopathy within 1 year before the screening visit.<br><br>5.Diagnosed with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) any time before the screening visit<br><br>6.Patients at their second or third trimester of pregnancy at the screening visit<br><br>7.Potassium levels > 5.4 mmol/l at the screening visit<br><br>8.Systolic Blood Pressure (SBP) < 100 mmHg at the screening visit | the 1 year before index date using diagnostic codes<br><br>5. history of cirrhosis, liver fibrosis, liver sclerosis identified from diagnostic codes<br><br>6. not applied<br><br>7. high potassium levels identified from diagnostic codes for hyperkalaemia in the 30 days before index date<br><br>8.low systolic blood pressure identified from diagnostic codes for hypotension in the 30 days before index date | 4. Chemotherapy-induced and peripartum cardiomyopathy are very specific conditions and we do not expect to reliably capture them in the databases. We do not expect this to be a problem because i) we expect a population of post-menopausal women which is unlikely to include pregnant women ii) according to clinician's advice chemotherapy-induced cardiomyopathies are not treated differently<br><br>6. Linkage to pregnancy data is not included in the license. Nevertheless, we expect a population consisting of post-menopausal patients which is unlikely to include pregnant women.<br><br>7. Given that we expect missingness in lab values, diagnostic codes will be used ensure that the assessment is as complete as possible<br><br>8. same logic as in 7 |
| Setting | Multicentre | Multicentre primary care based clinics represented in electronic healthcare record data sources capturing prescriptions/dispensations, outcomes, and covariates | Real-world data captures care as delivered; supports pragmatic design<br><br>Primary care clinics reflect the setting from which patients are most likely recruited. We will be missing the specialist (cardiologist) setting for recruitment, but eventually all HF patients transition to primary care where they are managed long-term. |
| Study treatment conditions (including | Treatment with SV vs treatment with ACEI | Treatment with SV vs treatment with ACEI identified from prescribing/dispensing records | No dose restrictions for either the intervention or the control. Dose flexibility mirrors routine care. |

| | | | |
|---|---|---|---|
| operational definition) | | | In the emulation, treatment assignment is determined through prescription (CPRD) /dispensation (PHARMO) records. |
| Method of Assignment to Trial Intervention | Stratified randomization in a 1:1 ratio within each of the 3 strata:<br>Stratum 1: no background treatment with ACEI or ARB at screening visit<br>Stratum 2: background treatment with ACEI at screening visit<br>Stratum 3: background treatment with ARB at screening visit | Assignment reflects clinical need as per physician's choice.<br>Patients will be stratified into three strata:<br>Stratum 1: no treatment with SV or ACEI in 365 days prior to HF diagnosis. Assigned trial intervention (SV or ACEI) is their first prescription ("treatment naive/incident new user")<br>Stratum 2: treatment with either ACEI or ARB in 365 days prior to HF diagnosis. Prescription before assigned trial intervention is an ACEI. Assigned trial intervention (SV or ACEI) is at least their second prescription after HF diagnosis ("prevalent new user").<br>Stratum 3: treatment with either ACEI or ARB in 365 days prior to HF diagnosis. Prescription before assigned trial intervention is an ARB. Assigned trial intervention (SV or ACEI) is at least their second prescription after HF diagnosis ("prevalent new user"). | In the statistical analysis 1:1 PS matching will be used to balance confounders in absence of randomization; treatment history matching used to balance disease severity and duration of treatment; design emulates stratified randomisation of the treatment assignment.<br>Patients (except for incident new users of SV) can be part of all strata at different points in their treatment trajectory. Patients are eligible to enter the entire study only once, thereby performing matching of ACEI comparators with the SV treated patients without replacement and not allowing ACEI comparators who later switch to SV to be reused in the intervention cohort. |
| Time *(when follow up begins and ends):* | Start: randomization<br>End: first of<br>1.occurrence of angioedema,<br>2.end of study period | Start:<br>Intervention cohort (all groups): start of SV<br>Control cohort:<br>Stratum 1: first ACEI prescription | Both discontinuation and treatment switch cannot be directly ascertained from the electronic health record and will rely instead on an algorithm based on prescribing/dispensing patterns. As such, the accuracy of discontinuation and switch |

| | | | |
|---|---|---|---|
| | 3.death from any cause<br>4.loss to follow-up<br>5.discontinuation of treatment initiated at index date<br>6.switch to a different treatment from that received on index date<br>7. Study withdrawal | Strata 2&3: matched ACEI prescription<br>End: first of<br>1.occurrence of angioedema,<br>2.end of study period<br>3.death from any cause<br>4.loss to follow-up<br>5.discontinuation of treatment at index date<br>6.switch to a different treatment from that received on index date | ascertainment and dating will be lower in the emulated study than in the target trial. |
| Outcome (including operational definition) | Time to first occurrence of angioedema | Same: time to first occurrence of angioedema, identified using diagnostic codes in primary care and in hospital data | Code lists will be validated by a clinician |
| Intercurrent Events and strategies to handle them. | Treatment discontinuation: while on treatment<br>Treatment switch: while on treatment<br>Addition of any of the three HF medications (ACEi, ARB, SV) if not the treatment of the group: while on treatment<br>All-cause death: while alive | Same strategies implemented based on prescribing/dispensing data, mortality data and using administrative censoring (or lack of for these intercurrent events)<br>Operational definitions:<br>• Treatment discontinuation is measured using prescribing/dispensing data by identifying gaps of 30 days or more between refills.<br>• Treatment switch and add-on are measured using prescribing/dispensing data by | Identification of treatment discontinuation and treatment switch will be a limitation. |

| | | | |
|---|---|---|---|
| | | identifying receipt of ACEI, ARB or SV if this is not the treatment of the group.<br>• All-cause death is identified using the recorded death date in the primary care database. | |
| Loss to follow up | Patients who fail to return for the required study visits and his/her health condition and vital status remains unknown despite multiple attempts to contact them. | Patients with known de-registration date from the database, migration, practice withdrawal or database end. | Loss to follow-up will be defined using real-world proxies, recognizing that in some cases patients may appear to remain under follow-up despite having effectively left (e.g. if they do not formally de-register from their GP). This risk is expected to be low, where unique patient identifiers ensure automatic deregistration upon re-registration at a new practice. |

*Table 13. Comparison of Target Trial and Proposed Target Trial Emulation Design Elements, estimands 2*

Estimand 2 differs from estimands 1 in the handling of intercurrent events, having thereby also a different definition of end of follow-up, while all the other rows remain as in estimand1. Therefore, for estimand 2 we show below only the rows on the definition of end of follow-up and on the intercurrent events and the strategies to handle them, Estimand 3 differs from estimand 1 in the summary measure and all rows remain as in estimand 1. For this reason, we do not show any rows for estimand 3.

| | | | |
|---|---|---|---|
| Time *(when follow up begins and ends):* | Start: randomization<br>End: first of<br>1.occurrence of angioedema,<br>2.end of study period<br>3.death from any cause<br>4.loss to follow-up | Start:<br>Intervention cohort (all groups): start of SV<br>Control cohort:<br>Stratum 1: first ACEI prescription<br>Strata 2&3: matched ACEI prescription<br>End: first of | |

| | | | |
|---|---|---|---|
| | 5. study withdrawal | 1.occurrence of angioedema,<br>2.end of study period<br>3.death from any cause<br>4.loss to follow-up | |
| Intercurrent Events and strategies to handle them | Treatment discontinuation: treatment policy<br>Treatment switch: treatment policy<br>Addition of any of the three HF medications (ACEi, ARB, SV) if not the treatment of the group: treatment policy<br>All-cause death: while alive | Same strategies implemented based on prescribing data, mortality data and using administrative censoring (or lack of for these intercurrent events)<br>Operational definitions:<br>• Treatment discontinuation is measured using prescribing/dispensing data by identifying gaps of 30 days or more between refills.<br>• Treatment switch and add-on are measured using prescribing/dispensing data by identifying receipt of ACEI, ARB or SV if this is not the treatment of the group.<br>• All-cause death is identified using the recorded death date in the primary care database. | Whilst accurate estimation of discontinuation or switch is not assured, this is not a limitation under the treatment policy approach |

## *7.6. Data analysis*

### *7.6.1 Analysis plan*

**Overview**

The analyses are conducted within a target trial emulation framework to estimate the effect of SV compared with ACEIs on the risk of angioedema.

For **Estimand 1**, the main estimand supporting decision making, the primary causal effect summary measure is the hazard ratio for time to first angioedema using a stratified Cox proportional hazards model in the PSM sample. The Cox model will be fitted separately within each data source (CPRD and BIFAP), and the resulting hazard ratios will be combined using a random-effects meta-analysis; potential sources of heterogeneity will be described qualitatively, including structural differences (e.g., coding systems, population coverage) and measurement differences (e.g., recording practices) and their implications (e.g., residual confounding or misclassification).

Sensitivity analyses will assess robustness of the primary findings to key assumptions, including inverse probability of censoring weighting (IPCW), best/worst case scenario, and probabilistic bias analysis for non-differential outcome misclassification (details in Section 7.6.5).

Two supplemental estimands are also defined: **Estimand 2**, applying a treatment policy strategy for intercurrent events, and **Estimand 3**, estimating treatment effects using restricted mean survival time (RMST) derived from a PSM Weibull accelerated failure time (AFT) model. In addition, supplemental analyses (e.g., crude and PS-matching adjusted Kaplan–Meier curves, crude Cox models, event counts and incidence rates, propensity score and weight distributions, covariate balance before and after PSM, censoring and intercurrent event patterns, proportional hazards diagnostics, positivity checks, and multiple-imputation diagnostics) will be conducted to support interpretation of the main analysis.

### *7.6.2 Primary Estimand (1) Analysis*

#### *i. Objective*

This study will estimate the risk of angioedema after exposure to SV relative to ACEIs

#### *ii. Exposure contrast*

SV vs ACEIs

### *iii. Outcome*

Time to first occurrence of angioedema

### *iv. Software*

R software

### *v. Handling of intercurrent events (explaining how follow-up is handled post intercurrent event)*

Treatment modifying intercurrent events (treatment discontinuation, treatment switching): While on treatment

All-cause death: while-alive

### *vi. Outcome Model*

A stratified Cox proportional hazards model in the PSM sample will be used to estimate the effect of treatment with SV versus ACEIs on time to first angioedema.

- **Start of follow-up:** date of initiation of SV or index ACEI prescription
- **Timescale:** time since index
- **Endpoint**: first occurrence of angioedema
- **Censoring**:
  - Non-administrative censoring: loss to follow-up
  - Administrative censoring: end of study follow-up in the absence of angioedema (maximum 5 years)
- **Model covariate**: Treatment group (SV vs ACEI)

**Assumptions of Cox Model**

Proportional Hazards:

- The hazard ratio is assumed to be constant over time.

Non-informative Censoring:

- Censoring is assumed to be independent of the outcome, conditional on the treatment, survival up to the time of censoring and indirectly baseline covariates used to estimate the propensity scores

Times of events and censoring are known and correctly recorded

Independence between observations

Diagnostics for Cox Model

- Proportional hazards assessed using log(-log) survival plots or Schoenfeld residuals.

### *vii. Confounding adjustment*

Following Suissa et al. (2017), we will use conditional logistic regression to estimate the propensity score of receiving SV versus receiving ACEI. The linear predictor of the model will include the following covariates: age, sex, smoking status, history of diabetes, DPP-4 inhibitors, history of ACEI-associated cough, heart/renal transplant, seasonal allergies, localized tissue trauma, lymphoproliferative diseases, estrogen-containing oral contraceptives/estrogen replacement therapy, infections, NSAIDs/acetylsalicylic acid, COPD, anti-histamines, corticosteroids, CBB. We will perform nearest-neighbour propensity score matching, using a caliper of 0.2.

Assumptions Underlying propensity score matching;

- No unmeasured confounding (all relevant baseline confounders are included in the propensity score model).
- Positivity (the propensity score of the SV user should lie within the range of propensity scores of the ACEI comparators with the same treatment history with ACEI/ARB as the SV user who are considered potential comparators for ps matching).
- Correct model specification (the propensity score model is correctly specified [functional form, covariate inclusion]).
- Consistency (each individual's potential outcome under the observed treatment equals their actual outcome).

Diagnostics for propensity score matching:

- Covariate balance: Check that baseline characteristics are balanced across treatment groups after matching
  - Evaluate standardized mean differences (SMDs): SMDs < 0.1 will be considered acceptable.
- Positivity check: Ensure adequate overlap in propensity score distributions between treatment SV users and potential ACEI comparators

### *viii. Missing Data Handling*

We will exclude patients with missing data on necessary variables (diagnosis date of relevant conditions) for the assessment of eligibility criteria. This is expected to occur very rarely.

Missing exposure data

We assume that missing refill or prescription records for SV or ACEIs reflect true treatment discontinuation after 30 days, and not incomplete data capture or prescriptions issued outside the database.

### Missing outcome data

The Cox proportional hazards model implicitly assumes non-informative censoring, meaning that censored participants contribute time at risk up to the time of censoring and their censoring is unrelated to the outcome, conditional on model covariates and survival (i.e. not having experienced angioedema) up to the time of censoring (i.e. outcome data is missing at random under these assumptions)

It is also assumed that participants who do not experience the outcome before censoring are correctly classified as having not had the event—that is, the available data provide complete outcome coverage with respect to the defined endpoint. This assumption concerns the correct classification of the outcome variable, and violations (e.g., missed or delayed event recording) could lead to outcome misclassification.

### Missing covariate data

The absence of a diagnosis code is assumed to indicate the absence of the corresponding condition.

For missing data in the confounder smoking status, we will perform multiple imputation with chained equations (MICE) under the Missing at Random (MAR) assumption using the MICE package in R.

### Assessment of missingness

Before imputation, we will assess the extent and patterns of missingness to ensure that imputation is appropriate. Specifically, we will:

- Quantify the percentage of missing data for smoking status
- Compare the proportion of missing values across treatment groups to assess differential missingness
- If the smoking status has more than 40% missing data, we will consider alternative approaches (exclusion of smoking status or sensitivity analysis) and justify the decision. Thresholds of 40% have been cited because effect estimates begin to be less reliable as the level of missingness increases beyond this threshold [Jakobsen et al. (2017), “When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts”]

### Imputation model

The MICE procedure will include all covariates used in the outcome and treatment models, as well as predictors of missingness. (if there are any additional factors not covered by the covariates in the treatment and outcome models). The treatment and outcomes of interest will also be included.

Key covariates included in the imputation model will be:

- Demographics (age, sex)
- Clinical history and comorbidities (history of diabetes, history of ACEI-associated cough, heart/renal transplant, seasonal allergies,

localized tissue trauma, lymphoproliferative diseases, infections, COPD)

- Smoking status
- Medication use (DPP-4 inhibitors, estrogen-containing oral contraceptives/estrogen replacement therapy, NSAIDs/acetylsalicylic acid, anti-histamines, corticosteroids, CBB)

Full Conditional Distributions

MICE will use the multinomial logistic regression which is the suitable for categorical variables with >2 categories, as the smoking status is (current, former, never)

Number of Imputations and Diagnostics

We will generate at least 10 imputed datasets (to ensure stable estimates given the level of missingness) and pool results across imputations using Rubin's rules. Diagnostics will include:

- Checking whether imputed values are plausible and consistent with observed distributions.
- Evaluating convergence of the chained equations.
- Assessing stability and consistency of results across imputed datasets.

Effect Estimation Under Multiple Imputation

The imputation model will be applied prior to effect estimation. PS matching and outcome models will then be fitted in each imputed dataset, and treatment effect estimates (e.g., hazard ratios) will be pooled across datasets using Rubin's rules.

#### *ix. Subgroup Analyses*

By background treatment at index date: stratum 1 (no background treatment), stratum 2 (background treatment on ACEI), stratum 3 (background treatment on ARB)
Sex
HF diagnosis in primary care vs HF diagnosis in secondary care
Angioedema diagnosis in primary care vs angioedema diagnosis in secondary care

### *7.6.3 Supplemental Estimand (2) Analysis*

Same as primary estimand, but the intercurrent events of treatment discontinuation/switch/add-on are handled using the treatment policy strategy.
Administrative censoring occurs at death from any cause, at 5 years after index date

### *7.6.4 Supplemental Estimand (3) Analysis*

#### *i. Objective*

This study will estimate the risk of angioedema afterexposure to SV relative to ACEIs

#### *ii. Exposure contrast*

SV vs ACEIs

#### *iii. Outcome*

Time to first occurrence of angioedema

#### *iv. Software*

R software

#### *v. Handling of intercurrent events (explaining how follow-up is handled post intercurrent event)*

Same as estimand 1

#### *vi. Outcome Model*

**Outcome model**: accelerated failure time model with Weibull distribution fitted in the propensity score matched population

**Outcome**: time to first angioedema.

**Covariate**: previous treatment (none, ARB, ACEI)
**Main covariate**: treatment group
**Start of follow-up**: the day after start of SV or the day after index ACEI prescription
**Timescale**: time since index
**Endpoint:** time from index date to first occurrence of angioedema
**Censoring**:

- Non-administrative censoring: loss to follow-up

Administrative censoring: end of study follow-up in the absence of angioedema (maximum 5 years) **Model assumptions**:

- Survival times follow a Weibull distribution
- Non-informative censoring (conditional on included covariates and survival up to time t)
- Log-linear relationship between covariates and log survival time

Diagnostics:

- Log(-log(S(t))) vs log(t) should be linearQ-Q plot of residuals

To estimate the RMST at 3 and 5 years from the Weibull AFT model, we first use the model to obtain the predicted survival curve for each treatment group. The RMST is then calculated as the average survival time up to a fixed time point, which corresponds to the area under the survival curve between time zero and the chosen time horizon (3 or 5 years).

- Fit the Weibull AFT model, which gives the shape and scale of the survival curve for each group.
- From this model, generate the predicted survival probability at each time.
- Integrate (i.e., add up) the survival probabilities from time 0 to 3 years and separately from time 0 to 5 years. The result is the expected survival time lived within those windows.
- Compare the RMST values between treatment groups to obtain the difference in average survival time over 3 and 5 years.

To account for uncertainty from both missing data and sampling variability, we will combine multiple imputation with nonparametric bootstrapping. We will use the Boot MI approach proposed by Schomaker & Heumann[7] in which bootstrap resampling is performed first, followed by multiple imputation within each bootstrap sample.

Specifically, we will generate B = 1,000 bootstrap samples of the original dataset (with missing data) and perform M = 10 imputations within each bootstrap sample using the prespecified imputation model. Within each bootstrap sample we will combine the M estimates using Rubin's rules to produce one bootstrap estimate. The empirical distribution of the resulting B bootstrap estimates will be used to construct percentile-based 95% confidence intervals. To obtain final point estimates, we will pool results across M = 40 imputations in the original dataset.

### *vii. Confounding adjustment*

Same as in estimand 1.
The AFT model will be performed in the PS matched sample to obtain estimates of RMST at year 3 and year 5.

### *viii. Missing Data Handling*

Same as in estimand 1.

### *ix. Subgroup Analyses*

Same as in estimand 1.

### *7.6.5 Sensitivity Analyses*

We will perform the following sensitivity analyses in the primary estimand of our study.

*Table 14. Sensitivity analyses - Inverse Probability of Censoring Weighting (IPCW)*

| | |
|---|---|
| **Analysis Methods** | This analysis will examine the impact of varying assumptions about the censoring-at-random condition on the estimated treatment effect. In the primary analysis we assumed censoring independent of the outcome, conditional on treatment group and survival up to the time of censoring. An additional assumption is that propensity score matching indirectly balances covariates between the censored and uncensored (i.e., outcome data is missing at random conditional on observed exposure and outcome). In the IPCW analysis, we use inverse probability of censoring weights in the propensity score matched sample. This analysis assumes censoring is independent of the outcome, with all common causes of both the outcome and censoring being accounted for.<br><br>Follow-up will be divided into equal 30-day intervals. At the start of each interval, we will update the information available on each patient and assess whether they remain followed or have been censored. If they remain under observation, they contribute to the risk set for that interval.<br><br>The weight for each participant at each interval is calculated as: 1/the estimated probability of remaining uncensored, given a set of baseline and time-updated covariates that could affect both censoring and the outcome.<br><br>Characteristics that could affect both censoring and the outcome include:<br><br>1. treatment group (SV vs ACEIs)<br>2. The risk factors for angioedema (see Table 11)<br>3. Risk factors for treatment discontinuation/switch: hypotension, hyperkalaemia<br><br>The weight is calculated separately for each interval, and then multiplied together across all intervals of follow-up to give each participant's cumulative weight.<br><br>The denominator probability will be estimated using pooled logistic regression fit to the person-interval dataset. In this model, the outcome is whether the participant was censored (or not) in that interval. We will truncate weights at prespecified percentiles (1st and 99th). |

| | |
|---|---|
| | • The IPCW will be applied in the propensity score matched population as time-varying weights in the Cox model for time to first angioedema . |
| **Assumptions** | • Censoring is conditionally independent of the outcome given covariates and being angioedema free up to the time of censoring. (i.e. non-informative censoring/censoring at random, conditional on other covariates beyond those in the analysis model)<br>• Correct model specification and positivity.<br>• Positivity (every individual has a non-zero probability of remaining uncensored at each time point given their covariates)<br>• Outcome does not directly influence its own missingness (would imply informative censoring via MNAR mechanism) |
| **What is Being Varied? How?** | • The assumption made in the primary analysis that censoring is non-informative given treatment group and survival up to the time of censoring. A different missing-at-random (MAR) assumption will be tested. |
| **Why? (What do you expect to learn?)** | • To assess the robustness of the treatment effect estimate to changes in the conditions of the missing at random assumption made in the primary analysis. |
| **Strengths Compared to Primary Analysis** | • IPCW makes a different MAR assumption conditioning on more variables, and thus, perhaps more plausible.<br>• IPCW adjusts for common causes (measured) of censoring and the outcome |
| **Limitations Compared to Primary Analysis** | • IPCW is sensitive to model misspecification.<br>• Cannot account for unmeasured factors affecting censoring.<br>• Weighting can increase variance, especially if weights are unstable<br>• Sensitivity analyses rely on varying the assumptions of the primary analysis, but these assumptions cannot be verified from the observed data; their plausibility can be discussed yet ultimately remains unknown |

*Table 15. Sensitivity analyses - Best/worst case scenario*

**Analysis Methods**

• Best/worst case scenario. The goal is to assess the impact on the estimated treatment effect of selected censoring non-at-random assumptions. The assumptions chosen represent the 4 extremes of a tipping point sensitivity analysis.

• For non-administrative censored individuals, repeat the analysis under four scenarios, assuming within each treatment arm that a) all censored individuals had the outcome of interest at the censoring date and b) none of the censored individuals had the outcome of interest by the end of the study. This equates to the following scenarios

| Scenario | Exposed Group (SV) | Unexposed Group (ACEIs) | Interpretation |
|---|---|---|---|
| 1 | Best case (lowest event rate) | Worst case (highest event rate) | Maximally favors SV |
| 2 | Worst case (highest event rate) | Best case (lowest event rate) | Maximally favors ACEIs |

| | | | | |
|---|---|---|---|---|
| | 3 | Best case | Best case | Optimistic for both groups |
| | 4 | Worst case | Worst case | Pessimistic for both groups |
| **Assumptions** | • Censoring not at random assumptions whereby a extreme increase/decrease in the hazard post-censoring is assumed leading to all or none of the censored individuals having the outcome of interest<br>• Correct model specification for the primary analysis. | | | |
| **What is Being Varied? How?** | • The assumption that censoring is non-informative. | | | |
| **Why? (What do you expect to learn?)** | • To assess the robustness of the treatment effect estimate to violations of the non-informative censoring assumption made in the primary analysis.<br>• If the results remain consistent in direction and statistical significance across plausible censoring scenarios, this increases confidence that the primary findings are not sensitive to the assumption made in the primary analysis. | | | |
| **Strengths Compared to Primary Analysis** | • Offers a principled method for exploring alternative assumptions about censoring.<br>• Sets bounds on the extent of maximum possible bias due to informative censoring | | | |
| **Limitations Compared to Primary Analysis** | • Best/worst case scenarios are extreme assumptions | | | |

*Table 16. Sensitivity analyses - Outcome misclassification*

| | |
|---|---|
| **Analysis Methods** | Probabilistic Bias Analysis using Monte Carlo Simulation at the summary level measure (the final risk estimate will be used as the input for this analysis).<br><br>– Plausible probability distributions for the sensitivity and specificity of outcome classification are specified based on available evidence.[31]<br>o Sensitivity range values: 75% - 90%<br>o Specificity range values: 95% - 99%<br>o Each value has the same likelihood of being sampled<br>– Within each Monte Carlo iteration, a hazard ratio will be sampled from a probability distribution informed by the pooled hazard ratio and its variance from the main analysis. This step propagates uncertainty due to sampling variability and multiple imputation into the bias analysis<br>– A new pair of sensitivity and specificity values is sampled, and these are applied to correct the observed HR for outcome misclassification using bias-adjustment formulas.<br>– This process is repeated across many iterations (e.g., 10,000 times), resulting in a distribution of bias-adjusted HR.<br>– This analysis will be conducted after pooling the hazard ratios across imputed datasets. In other words, multiple imputation will first address uncertainty due to missing data, producing a pooled hazard ratio and variance that account for the imputation process. The pooled estimate (and its variance) will then be used as the input for the Monte Carlo simulation in the probabilistic bias |

| | |
|---|---|
| | analysis, which will quantify the additional uncertainty due to outcome misclassification. |
| **Assumptions** | • Misclassification is non-differential considering that angioedema is a known side effect for both the intervention, SV, and the comparator, ACEI thereby ensuring that patients are not monitored differentially with regard to angioedema..<br>• Misclassification is constant over follow-up time<br>• Sensitivity and specificity of outcome classification are known or reasonably estimated from external data or expert opinion.<br>• Misclassification affects only the outcome, not exposure or covariates.<br>• The misclassification process can be simulated accurately. |
| **What is Being Varied?**<br><br>**How?** | Quantitative bias analysis for angioedema assessment, assuming a plausible range of values for angioedema classification<br><br>• The assumption that the outcome is measured without error is relaxed.<br>• Varying values of sensitivity and specificity are drawn from defined distributions in each simulation iteration. |
| **Why? (What do you expect to learn?)** | Even though we will make use of both primary and secondary care data to capture all the angioedema cases, it is likely that certain milder events of angioedema are underreported or misdiagnosed. In addition, the way we assess angioedema is very different from the PARADIGM-HF in which a clinical adjudication committee was employed to confirm the angioedema events.<br><br>Therefore, we will perform the QBA to<br><br>• To assess the robustness of the estimated treatment effect to plausible levels of outcome misclassification.<br>• To determine whether conclusions change under realistic measurement error for outcome. |
| **Strengths Compared to Primary Analysis** | • Explicitly accounts for uncertainty in outcome measurement.<br>• Provides a distribution of adjusted HR rather than a single corrected value.<br>• Can reflect differential or non-differential misclassification.<br>• Enhances transparency around the impact of measurement error. |
| **Limitations Compared to Primary Analysis** | • Requires external data or expert assumptions to specify sensitivity and specificity.<br>• Results are only as reliable as the plausibility of input parameters.<br>• May be computationally intensive.<br>• Does not account for other sources of bias (e.g., unmeasured confounding, exposure misclassification) unless jointly modeled. |

### *7.6.6 Other Supplemental Analyses*

Baseline characteristics will be presented overall and stratified by treatment group. Categorical and binary variables will be summarized as counts (n) and percentages, while continuous variables will be reported using means and standard deviations or medians and interquartile ranges, as appropriate.
Kaplan–Meier methods will be used to compare the time-to-event distribution of angioedema between patients treated with SV and those treated with ACEIs. Crude Kaplan–Meier cumulative incidence curves will be estimated separately for patients treated with SV and for those treated with ACEIs. In patients treated with ACEI, to address the issue of multiple potential index dates before they are matched to SV users, we will use a random sample with the same n as the SV cohort The cumulative incidence (absolute risk) of MACE will be estimated using Kaplan–Meier methods over the entire follow-up period for each treatment group and presented graphically as full cumulative incidence curves. In addition, cumulative incidence will be reported at the pre-specified time points of 3 and 5 years, together with 95% confidence intervals. Values at 3 and 5 years will be obtained by evaluating the Kaplan–Meier step function at those time points. Kaplan–Meier curves in the PSM sample will also be estimated. Time will be measured from the day after treatment initiation (index date) until the first occurrence of angioedema or censoring.

Assumptions of KM

- Non-informative Censoring:
    - For Crude KM curves: Censoring is assumed to be independent of the outcome, conditional on treatment and survival up to the time of censoring.
    - For adjusted KM curves in the PS matched sample; censoring is assumed to be independent of the outcome, conditional on the treatment, survival up to the time of censoring and indirectly baseline covariates used to estimate the propensity scores
- Times of events and censoring are known and correctly recorded
- Independence between observations

We will also conduct descriptive analyses to characterize censoring patterns overall and across treatment groups. This will include median (IQR) time to censoring overall and according to the reason for censoring. This will be estimated separately for the overall study population and by treatment arm (SV vs. ACEIs).

Reasons for censoring will include:

- Administrative censoring: reaching the maximum follow-up period of 5 years or the end of the study period (31 March 2023).
- End of data availability: last recorded healthcare encounter, database end date, or practice withdrawal.
- Loss to follow-up: deregistration from the contributing practice or migration out of the healthcare system.

### *7.6.7 Core Emulation Table – Estimation Summary*

*Table 17. Core Emulation Table: Estimation Summary*

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| Analysis Method | Stratified Cox proportional hazards model to estimate the hazard ratio for time to first angioedema. Randomization ensures balance in measured and unmeasured confounders. | Stratified Cox proportional hazards model in the PS-matched sample to estimate marginal HR, separately in each data source (CPRD and PHARMO); pooled using random-effects meta-analysis. | PS matching used to emulate randomization in observational data<br><br>PS matching represents a departure from the original target trial because it estimates the average treatment effect in the treated (considering that for each patient receiving SV we identify and match with a control patient receiving ACEI). Nevertheless, propensity score matching is the recommended method in the prevalent new user design, and we do not expect effect modification by treatment group. |
| Missing Data Assumptions and Methods to Handle | **Outcome**: Assumes non-informative censoring given treatment group and being angiodedema-free up to the time of censoring; censored participants contribute partial information under Cox models<br><br>**Exposure:** N/A (trial monitoring ensures exposure data completeness)<br><br>**Covariates:** minimized through trial data collection | **Outcome**: Same assumption, covariates included in the condition are different (PS matching included)<br><br>**Exposure**: for missing exposure data, assume absence of refill or prescription/dispensation records for SV or ACEi indicates true treatment discontinuation after 30 days<br><br>**Covariates**: absence of a diagnosis code will be interpreted as absence of the condition, while missing lifestyle variables (i.e. smoking status) will be imputed using multiple | Mechanisms of missing exposure, covariate and outcome data differs between target trial and emulation (e.g., rather than leaving study, patients could be part of GP practice that no longer contributes data). Missing exposure data not possible in target trial but could be as a result of missing or incomplete prescription records in emulation.<br><br>Another deviation from the target trial is that multiple imputation of missing |

| | | | |
|---|---|---|---|
| | | imputation by chained equations (MICE) under the missing at random assumption | covariate data would not be needed in target trial. |
| Statistical Model Assumptions | Proportional hazards assumption for Cox model<br><br>Censoring is non-informative (given assumption re: missing outcome data) | Same: PH assumption tested using Schoenfeld residuals and log(-log) survival plots<br><br>PS matching assumptions: no unmeasured confounding, positivity, correct model specification, consistency | Some assumptions for PS matching are difficult to verify (e.g. unmeasured confounding). Can argue consistency may be violated as a result of allowing variable doses and medications as part of treatment arm.Correct model specification is checked by evaluating SMD in baseline characteristics after ps matching. |
| Sensitivity Analyses | none | **Non-Informative Censoring** conditional on additional baseline and time-varying covariates.<br><br>*Inverse probability of censoring weighting*<br><br>• **Method**: Models the probability of remaining uncensored based on observed baseline and time-varying covariates. The inverse of these probabilities is used to weight observations in the PS matched population to estimate a marginal treatment effect.<br><br>• **Purpose**: Adjusts for potential bias when censoring depends on additional measured baseline and time-varying covariates beyond those included in the primary analysis model. | Motivation for IPCW:<br><br>In the hypothetical target trial we make the assumption of non-informative censoring conditional on the treatment group and on being angioedema-free up to the point of censoring. In the target trial emulation, we make the same assumptions of non-informative censoring, and an additional censoring-at-random assumption conditioning on more covariates implemented through propensity score matching, which indirectly balances covariates between the censored and uncensored. In the IPCW analysis, we relax the assumption of non-informative censoring by conditioning on baseline and time-varying common causes of both the outcome and censoring. |

| | | | |
|---|---|---|---|
| | | • **Key Assumptions**:<br>  ○ Censoring is independent of the outcome conditional on observed covariates.<br>  ○ No unmeasured confounding for censoring.<br>  ○ Correct model specification and sufficient covariate overlap.<br>*Best/worst case scenario under NCAR assumption.*<br>• **Method**: For non-administrative censored individuals, repeat the analysis under four scenarios, assuming a) all censored individuals had the outcome of interest at the censoring date and b) none of the censored individuals had the outcome of interest by the end of the study, separately for each treatment group.<br>• **Purpose**:To assess the robustness of the treatment effect estimate to violations of the non-informative censoring assumption made in the primary analysis.<br>• **Key Assumptions**: | Motivation of QBA: In the obsevational study we will make use of both primary and secondary care data to capture all the angioedema cases, but it is likely that certain milder events of angioedema are underreported or misdiagnosed. In addition, the way we assess angioedema is very different from the PARADIGM-HF in which a clinical adjudication committee was employed to confirm the angioedema events. For this reason, we will perform the QBA to assess the robustness of the estimated treatment effect to plausible levels of outcome misclassification |

| | | | |
|---|---|---|---|
| | | ○ All or none of the censored individuals had the outcome of interest as a consequence of assuming an extreme increase/decrease change in the hazard function post-censoring<br>○ Correct primary analysis model specification<br><br>**Outcome Misclassification**<br>• **Method:** Probabilistic bias analysis using Monte Carlo simulation applied at the summary measure level. In each of 10,000 iterations, plausible values for sensitivity (0.75–0.90) and specificity (0.95–0.99) of outcome classification (based on diagnosis codes) are sampled and used to correct the observed hazard ratio using standard bias adjustment formulas.<br>• **Purpose**: To assess the robustness of the estimated treatment effect to plausible levels of outcome misclassification, acknowledging that diagnoses codes may not always reflect actual diagnoses. | |

| | | | |
|---|---|---|---|
| | | • **Key Assumptions**:<br>  ○ Misclassification is either non-differential or differential (depending on the scenario).<br>  ○ Sensitivity and specificity of outcome classification are known or reasonably estimated from external data or expert opinion.<br>  ○ Misclassification affects only the outcome, not exposure or covariates.<br>  ○ The misclassification process can be simulated accurately. | |

**Estimand 2**: Same as estimand 1, but without sensitivity analysis

*Table 18. Estimation Summary for Estimand 3*

| Attribute | Target Trial | Target Trial Emulation | Comment |
|---|---|---|---|
| Analysis Method | Accelerated failure model assuming Weibull distribution to estimate the restricted mean survival for time to first angioedema | Accelerated failure model in the PS-matched sample to estimate marginal restricted mean survival at years 3 and 5 | Same as table 1 |
| Missing Data Assumptions and Methods to Handle | Same as table 1 | Same as table 1 | Same as table 1 |

| | | | |
|---|---|---|---|
| Statistical Model Assumptions | Survival times follow Weibull distribution<br>Log-linear relationship between covariates and log survival time<br>Correct specification of the model | Same; assessed using diagnostics such as: Plot log(-log(S(t))) vs log(t) for Weibull assumption (Should be linear if Weibull holds) and Q-Q plot for residuals | |
| Sensitivity Analyses | N/A | N/A | |

## *7.7. Data sources*

### *7.7.1 Data sources*

Rationale for selection and feasibility:

CPRD is an English database which collates routinely collected anonymised electronic health record data from general practices who have agreed at a practice level to provide data on a monthly basis. The primary purpose for which these data are collected is to support retrospective and prospective public health studies and interventional research. Centres can join under request by means of a form available online to request joining the network. Specific criteria are not specified/not found. All patients registered with the participating practices are included in the dataset, unless they have individually requested to opt out of data sharing, by asking their GP to amend their registration details on the system to disable the extraction of their data.

The events that trigger a record in the CPRD database are the following:

**Event triggering registration of a person in the data source**: Practice registration

**Event triggering de-registration of a person in the data source**: Death, Practice deregistration

**Event triggering creation of a record in the data source**: Patient has contact with a GP practice

Publications/sources describing CPRD:

- https://www.cprd.com/introduction-cprd
- https://www.cprd.com/join-growing-network-practices-contributing-cprd

- Herret et al. 2015[32]
- Wolf et al.[33]
- https://catalogues.ema.europa.eu/node/1026/data-flows-and-management

The PHARMO Data Network is a population-based network of healthcare databases and combines data from different healthcare settings in the Netherlands. These different settings, including general practitioner, in- and out-patient pharmacy, clinical laboratory, hospitals, cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. All patients registered at the contributing healthcare providers are included, unless the patient requested to opt out.

The events that trigger a record in the PHARMO database are the following:

**Event triggering registration of a person in the data source:** Birth, Disease diagnosis, start of insurance coverage, start of treatment or practice registration

**Event triggering de-registration of a person in the data source:** Death, Emigration, Loss to follow-up, Practice deregistration

**Event triggering creation of a record in the data source:** Multiple prompts depending on healthcare setting (e.g. hospital discharge, specialist visit, medicinal product dispensing etc.)

Publications describing PHARMO:

- https://pharmo.nl/resource-library/,
- https://catalogues.ema.europa.eu/node/997/administrative-details,
- Overbeek et al. 2023[34]
- Kuiper et al. 2020[35]

Considering the aforementioned information regarding the two databases, we selected those for our study because they offer large, high-quality, population-based electronic health records with national coverage in the UK and the Netherlands, respectively. Both data sources provide the required data elements to operationalize the study design, including demographics, diagnoses, prescriptions, dispensations, laboratory test results, hospitalizations, and mortality.

**Strengths of data source(s):**

Our databases have two main strengths. Firstly, they equip us with the ability to assess the critical variables of our study with high completeness and reliability. Secondly, both CPRD and PHARMO, provide us with large datasets, with a long follow-up and representative of the English and Dutch population, respectively.

More specifically, CPRD includes data on demographics (year of birth, sex), diagnoses, which are important to identify our study population (heart failure), to assess our outcome (angioedema), to apply the eligibility criteria (history of angioedema, hypotension, hyperkalaemia etc), and to assess the confounders, and prescriptions, which are important to identify the exposure of interest (sacubitril/valsartan, ACEi), to apply the eligibility criteria and to assess the confounders. For over half of the patients, linkage with secondary care will enhance the range of the available data and our ability to assess the aforementioned variables (e.g. EXLC 3: current acute decompensated heart failure). CPRD covers over 19 million patients in total with a median follow-up of six years. Data are updated frequently (monthly for GOLD and quartertly for Aurum) and numerous checks ensure the quality of the data.

Similarly, PHARMO includes data on all the aforementioned variables and in addition, it includes data on dispensations (both in-patient and out-patient) which increases further our certainty about whether the patients received the medication. It covers over 10 million patients in total with a follow-up of 10 to 30 years. The frequency of the data collection varies across the healthcare providers, but data are collected at least annually. Data acceptance tests ensure the quality of the data.

**Limitations with potential impact in the study results:**

For both of our databases the main limitation is the potential missingness in diagnoses or in lab measurements. Nevertheless, considering a completeness of 70% or more in the critical variables of our study (eligibility criteria, exposure and outcome), as shown in the feasibility analysis, we expect the impact to be minor.

We will not be able to assess and adjust for race, exposure to tissue plasminogen activators and stress in either of the databases. These variables were identified as potential risk factors for angioedema and were included in the initial list of confounders. Omitting these variables from the confounders may have minor impact in the adjustment for angioedema risk.

Smoking will be included as a confounder. In CPRD, it is present in 89,7% of the records, but in PHARMO the completeness of smoking is 40-69%, which may have minor impact in the adjustment for angioedema risk.

In CPRD specifically, there are two additional limitations. Firstly, considering that it has prescription data, it is unknown whether the patient obtained and took the medication. Secondly, given that only the year of birth is available, we may have slight imprecision in estimating the age of patients. For both limitations, we expect their impact to be minor.

### Data quality:

CPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. Data from participating general practices are extracted monthly (GOLD) or quarterly (Aurum) and undergo multi-level validation and quality checks. The CPRD provides data through its secure Trusted Research Environment or via multi-study licenses. Full metadata and Standard Operating Procedures (SOPs) are available at https://www.cprd.com/data-access and https://www.cprd.com/data-quality.

PHARMO is managed by the PHARMO Institute for Drug Outcomes Research in the Netherlands. Data are collected from a network of healthcare providers, including general practitioners, pharmacies, hospitals, and laboratories, and are linked at the patient level through validated algorithms. STIZON, an independent, ISO/IEC 27001 certified foundation, acts as a Trusted Third Party between the data sources and the PHARMO Institute. It performs the data collection, processing, linkage and anonymization, ensuring thereby the privacy of data. Full metadata and SOPs are available in appendix 2.

Databases' suitability and case-study feasibility assessments followed three key steps: (I) characterization of data source systems and processes, using the EMA data quality checklist to evaluate foundational aspects and their maturity; (II) assessment of data quality metrics for each data source (data reliability), based on published research and open-access catalogues; and (III) fitness-for-use evaluation (data relevance), assessing database suitability for each case study based on question-specific determinants. Steps 1 and 2 were database-specific, while step 3 was both database- and case-specific, i.e. it could only be assessed in view of the specific research question to be addressed. From these steps, two tables containing qualitative information (I and III) and one with quantitative metrics (II) were created. The overall feasibility of the case studies using the candidate data sources was determined by critically analysing the collected information. Additional insights were gathered from DEAPs. All of the information was compiled into a report accompanying the generated tables, with our narrative assessment (appendix).

The overall feasibility assessment is summarised in Table 19. Both CPRD and PHARMO were deemed feasible data sources for studying SV and the risk of angioedema, with achievable sample sizes and reasonably up-to-date data. For CPRD, the estimated sample size of ~30,784 participants is supported by its coverage of ~4.4 million inhabitants and frequent exposure to SV/ACEI. The database provides data of good recency and the elements of high criticality (age, diagnosis of HF, eligibility criteria, exposure, all-cause mortality) were deemed to be available and fairly reliable. Nevertheless, some limitations were identified: i) dispensing information is not available ii) discontinuation must be inferred from prescription duration ii) diagnostic coding is incomplete in some emergency room settings. PHARMO also supports the target size by covering 40% of the Dutch population and considering that a large number of Dutch patients were reported to receive SV/ACEI. Elements with high criticality were also deemed available and fairly reliable in the database and the data are of good recency. Completeness is expected from 70% to 100% in most of the variables with no major impact predicted. Overall, while both data sources present minor limitations, these are manageable within the study design and do not prevent the study from being feasible.

*Table 19. Summarized feasibility assessment of case study 6 in CPRD and PHARMO*

| RWD source | Sample size estimation form the hypothetical trial protocol | Feasibility assessment *(yes/yes, with limitations/no)* | Rationale for the feasibility assessment | Limitations identified during the feasibility assessment and categorisation | Description of potential impact of the identified limitations on the study results |
|---|---|---|---|---|---|
| **CPRD** | With an approximate estimated sample size of 30,784 (based on a 1:1 ratio of stopping current ACEi and starting Sacubitril/Valsartan versus continuing on ACEi), and considering that CPRD includes data from approximately 4.4 million inhabitants (as of 2014), the target sample size is anticipated to be reached. Furthermore, experimental exposure is expected to occur frequently. | Yes | Elements with high criticality are available and fairly reliable. Data recency of 3 months before extraction, reasonably enough for the research question. Sample size is achievable. | ·Minor: Dispensing is not available, only prescription.<br>·Minor:Diagnostic codes are available for 86% subjects attending emergency room.<br>·Minor: Treatment discontinuation not directly available but can be assessed using standard adherence calculation methods. | As this database only has prescription data, it is unknown if patients took the prescription, and so, if they discontinued it. However, treatment duration is available, from which this data may be estimated. Diagnostic codes are reported to be available for 86% of subjects in the emergency room; however, the missing cases we expect to capture them from hospitalization records or primary care records, since the severity of this disease may justify an admission and/or the follow-up with the GP, or change of baseline treatment. |
| **PHARMO** | With an approximate estimated sample size of 30,784 (based on a 1:1 ratio of stopping current ACEi and starting Sacubitril/Valsartan versus continuing on ACEi), and considering that Pharmo includes data from 40% of the | Yes | Elements with high criticality are available, and fairly reliable. Sample size is acheivable.<br>Data are available with an approximately 1-year lag depending on the databases required. | ·Minor: 70-100% completness in most of the variables. | No major impact expected. |

| | | | | | |
|---|---|---|---|---|---|
| | Dutch population, the target sample size is anticipated to be reached. Furthermore, experimental exposure is expected to occur frequently (50,102 Sacubitril/Valsartan users and 1,099,000 ACEi users recorded in the Netherlands in 2023). [https://www.gipdatabank.nl/] | | | | |

*Table 20. Metadata about data sources and software*

| | Data 1 | Data 2 |
|---|---|---|
| **Data Source(s):** | CPRD Aurum (Clinical Practice Research Datalink \| HMA-EMA Catalogues of real-world data sources and studies | PHARMO (PHARMO Data Network \| HMA-EMA Catalogues of real-world data sources and studies |
| **Study Period:** | Earliest available data - 31-03-2023 | Earliest available data – September 2024 |
| **Eligible Cohort Entry Period:** | 01-01-2014 – to 31-03-2023 | 01-01-2014 – September 2024 |
| **Data Version (or date of last update):** | CPRD Aurum: September 2024 | Last available version: 2024 extract (annual update) |
| **Data sampling/extraction criteria:** | Patients 18 ≥ years old with Heart Failure, treated with SV or ACEI and 1 year of look back before their incident HF diagnosis | Patients 18 ≥ years old with Heart Failure, treated with SV or ACEI and 1 year of look back before their incident HF diagnosis |
| **Type(s) of data:** | Primary care EHR, linked secondary care data (HES), prescriptions, diagnoses, lab values, demographics, outcomes | Primary care EHR, linked secondary care data, pharmacy dispensation, prescriptions, diagnoses, lab values, demographics, outcomes |
| **Data linkage:** | Yes, deterministic linkages with HES | Yes, deterministic linkage with hospitalization data |
| **Conversion to CDM*:** | Yes, OMOP, CDM, also CONCEPTION CDM | Yes, OMOP, CONCEPTION or bespoke |
| **Software for data management:** | EMIS Web electronic patient record system software for CPRD Aurum<br>Use of own secure Trusted Research Environment for extraction | STIZON (independent, ISO/IEC 27001 certified foundation) performs the collection, processing, linkage and anonymization of data.<br>Data will be decrypted on use with authenticated user accounts.<br>Procedures of data backup, archival and retrieval are defined by PHARMO. |

*CDM = Common Data Model

### *7.8. Data management*

The study will be conducted in a distributed manner using the UMCU, ARS Toscana and VAC4EU tools, procedures, and pipeline. Figure 3 specifies the data sets (D) and transformation processes (T), programming follows this pipeline, with involvement of different types of experts.

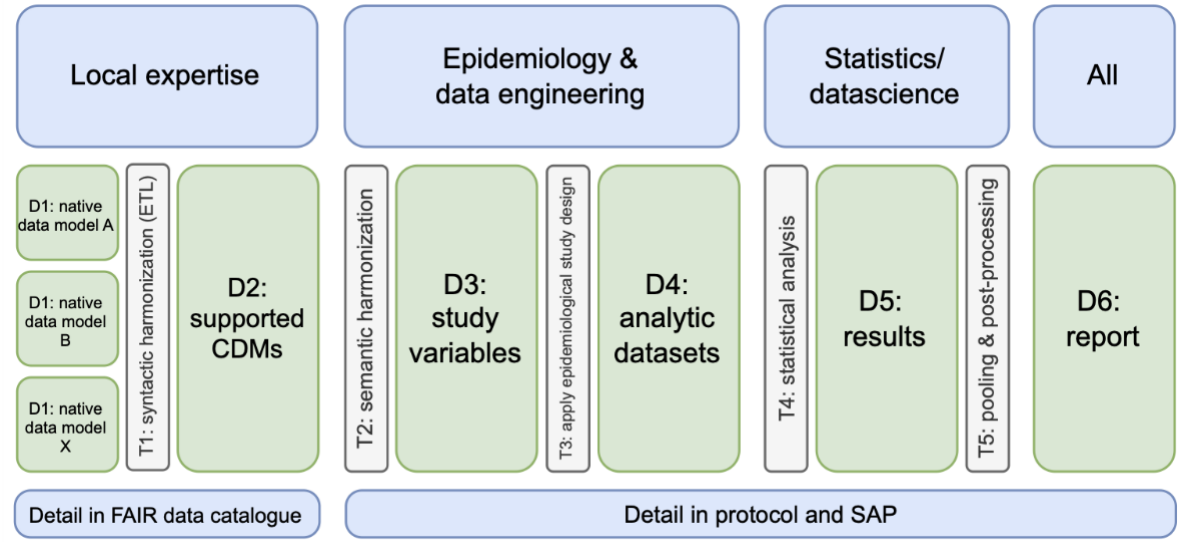



**Figure 3.** Data Management from the data transformation perspective

**D1: Original data can be in any native format**

The RWD-RWE pipeline used by VAC4EU starts with data banks that are controlled by the Data Expert and Access Partner (DEAP) and can be in any format. Data always stays local and never leaves the secure environments of the DEAPs. The ETL (extract, transform, load, see below for more details under 'T1') design is shared in a searchable FAIR VAC4EU catalogue. The VAC4EU FAIR Molgenis data catalogue is a meta-data management tool designed to contain searchable meta-data describing organisations that can provide access to specific data sources.

### T1: Syntactic harmonisation (ETL)

T1: Syntactic harmonisation is conducted through an extraction, transformation, and loading (ETL) process of native data into the ConcePTION common data model (CDM) (see section 'D2: Common data model'). To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation is used. The ETL process has various structured steps as described by Thurin et al (2021)[36]:

- DEAPs are asked to share the data dictionaries of their data banks (selected tables and variable names/structure)
- Metadata (descriptive data about the data sources and databanks) & data dictionaries, are uploaded in FAIR data catalogue (Molgenis).

### D2: Common data model

For this project, the CDM (D2) is the ConcePTION common data model. The CDM version that is used is v2.2, which is available as an open-source CDM. In this CDM, data are represented in a common structure, but the values of the data remain in their original language (e.g. codes will have either ICD9/10/ICPC/SNOMED or MEDCODEID values).

### T2: Semantic harmonisation

During the T2 step, many data transformations occur related to the completion of missing features in the data. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), one or more phenotype algorithms are constructed (typically one sensitive, or broad, algorithm and one specific, or narrow, algorithm) to operationalise the identification and measurement of each event. In this step we conduct time anchoring (observation periods, look back periods), clean the data such as the dose of vaccines, sort on record level, aggregate across multiple records, and combine concepts for implantation of algorithms, and rule-based creation of study variables.

In this phase of the creation of study variables, semantic mapping is conducted. This semantic mapping across different vocabularies is conducted as part of the R-study script using different functionalities. To reconcile differences between different terminologies and native data availability, machine-readable code lists are used that comprise the terminologies that are used in the network (e.g. ICD-9, ICD10, SNOMED, ICPC and DEAP specific adaptations). This is combined with the BRIDGE metadata[37] file that defines risk windows, look-back periods, and algorithms for each study variable.

### D3: Study variables

D3 datasets are interim data sets with information on study variables for each study participant, the unit may be a person, a medicine, or episode of time. The design of these datasets is described in codebooks. Examples of D3 datasets are the outputs of the ConcePTION pregnancy algorithm

(https://github.com/IMI-ConcePTION/ConceptionTools/wiki#conception-pregnancy-algorithm), and outputs of functions that define smoking. Multiple functions/packages exist within the VAC4EU, for different study variables.

### T3: Application of epidemiological design

In the T3 step epidemiological designs are applied such as sampling, matching (on specific variables and/or propensity scores), and selection based on inclusion and exclusion criteria using the study variables in the D3 datasets. The designs will be implemented for the various study objectives using R-scripts, and these may use the existing functions (R-cran) or functions that have been developed in the VAC4EU community (e.g. matching).

### D4: Analytical data set

D4 is an analytical dataset, and multiple D4 data sets may be produced based on the objectives of the study. The format is described initially in a code book for communication between programmers and statisticians.

### T4: Statistical analysis

This step in the data transformation pipeline will produce statistical estimates such as descriptives (counts, percentages), distributions (mean, percentiles), rates (prevalence, incidence), regression coefficients, or other relevant estimates. This will be conducted using R.

### D5: Results

D5 is the set of estimates, tables or aggregate data that is transferred from the DEAPs to the Digital Research Environment (DRE). The aggregated results produced by these scripts at the DEAP's site will be uploaded to the UMCU DRE for post-processing, pooling and visualisation (Figure 3). The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate. The DRE is made available through UMCU. The DRE applies double authentication where researchers can collaborate using data that are stored and organised securely.[38] UMCU is responsible for data processing and data security.

All researchers who need access to the DRE will be granted access to study-specific secure workspaces by UMCU. Access to the workspaces will be possible only after double authentication using an identification code and password together with the user's mobile phone for authentication.

Uploading files will be possible for all researchers with access to the workspace within the DRE. Downloading of files will be possible only after requesting and receiving permission from a workspace member with an "owner" role, who will be a UMCU team member.

### T5: Post-processing/pooling

In this step, the result from different DEAPs is pooled and converted into tables and figures for reporting.

## *7.9. Quality control*

All key study documents such as the hypothetical trial protocol, target trial emulation protocol and study reports will undergo senior scientific and editorial review.

### Data quality

For all data sources and for each data instance we will conduct *INSIGHT* level 1-2 quality checks [39], detailed statistical analysis plans for the indicators are available on the public repositories:

- https://github.com/UMC-Utrecht-RWE/INSIGHT-Level1 Hoxhaj, V. (2023). UMC-Utrecht-RWE/INSIGHT-Level1: https://doi.org/10.5281/zenodo.10035167
- https://github.com/UMC-Utrecht-RWE/INSIGHT-Level2 Hoxhaj, V., & van den Bor, R. (2023). UMC-Utrecht-RWE/INSIGHT-Level2: https://doi.org/10.5281/zenodo.10035169

Briefly, level 1 verifies Data Completeness and level 2 Data Consistency.

### Level 1 – Data Completeness

The purpose of the level 1 check is to verify the completeness of the ETL process and the data in the variables. Examples of tests are:

- Presence of variables in each of the CDM tables in D2
- Checks for misspellings and letter case in variable names in each of the CDM tables
- Verification of vocabularies
- Check date formats
- Check conventions of values
- Missing data analysis
- Frequency tables for categorical variables

### Level 2 – Data Consistency

Real data is not random but follows certain logical constraints that reflect rules governing real-world situations. Examples of indicators generated by level 2 checks are:

- Event dates before date of birth
- Event dates after date of death
- Event dates out of observation periods

- Subjects having an observation but not present in the PERSONS table
- Observations associated with a visit id and occurred before/after the visit start/end date
- Subjects younger than 12 years old reported as parents
- Age at the observation period older than 115 y old Data

### Code Quality

These coding practices define how the TARGET programming team collaborates to write clean, reliable, and reproducible code for the VAC4EU Real-World Evidence (RWE) Analytical Pipeline. They aim to ensure clarity, consistency, and maintainability across all case studies within the project.

### Coding conventions

To ensure clarity, consistency, and maintainability across the project, the following conventions will be applied to all codebases within the project:

- Consistent style: Code follows a consistent and readable style (see the tidyverse style guide for R).
- Meaningful names: Use clear, descriptive names for variables, functions, and files to convey their purpose.
- Modular code: Break down code into small, reusable functions where possible.
- No hardcoded paths: Use configuration files or relative paths to ensure portability.

Following these conventions makes the code easier to understand, test, and reuse across case studies and teams.

### Documenting Code

Code documentation is used to promote good coding practices and ensure our work is understandable, maintainable, and reproducible. To achieve this, we will:

- Use descriptive comments that explain the purpose and rationale behind code sections, focusing on why something is done, not just what.
- Clearly document function inputs, outputs, and side effects, using standardized formats (e.g., roxygen2 in R) where appropriate and supported.
- Write meaningful variable and function names to make the code as self-explanatory as possible.

## Version Control

We use Git and GitHub to manage version control. These tools support good coding practices by enabling collaboration, tracking changes, accessing a project's history, and ensuring code quality through review and documentation.

A dedicated GitHub organisation has been created for the project (https://github.com/target-roc19). Each case study is managed in its own repository within this organisation. Repositories are structured consistently across case studies, to reinforce modularity. Access to repositories is controlled through teams.

During development, all repositories remain private to ensure confidentiality. Once the project is finalised, relevant repositories will be made public and assigned a digital object identifier (DOI) via Zenodo to support transparency, reproducibility, and reuse by the wider research community.

To maintain code quality and clarity, we follow the git and GitHub guidelines below.

- Always use pull requests (PRs): never push directly to the main branch.
- Open an issue before creating a new branch. Ideally, one PR resolves one issue to keep changes focused and reviewable.
- Every PR must be reviewed by at least one other person before merging.
- The PR author merges the PR after it has been reviewed and approved.
- Write clear, descriptive commit messages.
- Write informative PR descriptions, including:
    - A concise title
    - Links to related issues
    - A summary of the changes

## Continuous Integration

Continuous Integration (CI) is set up to automatically check code quality and run tests whenever changes are pushed to the repository or submitted through a pull request (PR). The CI workflow ensures that the package adheres to predefined style guidelines and that all automated tests pass before changes are merged.

## Coding Template

Every case study follows the general coding template used across all code in the TARGET project. The folder structure is organised as follows:

case-study-template

```
|____data
| |____D2_cdm
| |____D3_study_variables
| |____D4_analytic_datasets
| |____D5_results
| |____D6_report
|____docs
|____logs
|____run
|____tests
|____transformations
| |____T2_semantic_harmonization
| |____T3_study_design
| |____T4_statistical_analysis
| |____T5_processing_results
|____CHANGELOG.md
|____LICENSE
|____README.md
```

### Project Data Structure and Storage

The data folder follows the Real-World Evidence pipeline structure. Data conforming to the common data model is stored in the D2_cdm folder.

Results from transformations T2, T3, T4, and T5 are saved in the respective folders:

- D3_study_variables
- D4_analytic_datasets
- D5_results
- D6_report

Each dataset is associated with a codebook, explained in more detail below.

All data remain securely stored on the Data Expert and Access Partners (DEAPs) servers and are never transferred externally. For testing purposes, dummy datasets are created. These fall into two categories:

- Unit test data: Small, predefined input and output pairs used to test individual transformation steps. These are stored in the tests folder, not in data, and can support automated testing.
- Pipeline test data: Larger, more complex dummy datasets used to test whether the full pipeline runs as expected. These may be included in the repository only if they remain below GitHub's 100 MiB file size limit and will otherwise be shared via SharePoint.

### Logging System

When the pipeline is executed, log files are saved in the logs folder. These logs are especially helpful when running the code in the DEAPs environment, as they help trace and diagnose potential errors. We recommend using the logger R package to handle logging throughout the pipeline. A sample logging setup can be found in the logger.R script located at the root of the project directory.

### Executing the Analytical Pipeline

The run folder contains scripts used to execute each transformation step in the pipeline.

- A central script, run_pipeline.R, orchestrates the full pipeline from start to finish.
- Subscripts (e.g., run_T2.R or similar) are available to run individual transformation steps separately.

Typically, the run_pipeline.R script is the main entry point used by a DEAP to execute the full pipeline. Before running it in the DEAP environment, the pipeline may need to be adapted to local settings. This can be done using a configuration file that defines variables required to tailor the pipeline to a specific DEAP. Please note that configuration files should not include sensitive information.

Such a file might include variables like:

- The name of the DEAP
- The path to the local data instance
- The path to any required external resources

### Testing and Quality Assurance

The tests folder contains scripts to test the analytical pipeline. Tests will be used to ensure code behaves as expected and remains stable over time. By systematically checking inputs, outputs, and edge cases, tests help catch errors early and make future changes safer. We use the testthat R package to structure and run unit tests.

Continuous integration (CI) is used to automate testing. With CI, tests are automatically run each time code is pushed to the repository (e.g., via GitHub Actions). This helps identify issues immediately, ensures that new changes do not break existing functionality, and supports better collaboration by enforcing consistent code quality across contributors.

### Modular Data Transformation Workflow

The transformations folder follows the Real-World Evidence pipeline structure. It contains the source code for all transformation steps, which is typically written in R. Each subfolder corresponds to a specific step in the pipeline (e.g., T2_semantic_harmonization, T3_study_design, T4_statistical_analysis, T5_processing_results) and includes the relevant scripts and helper functions for that step.

During the T2 step, a database is usually created (e.g., using DuckDB). This database can be queried using SQL, and it is recommended that all SQL queries be saved as clearly named, standalone SQL script files to ensure readability and reusability.

The purpose of the transformations folder is to structure and modularise the processing logic, making it easier to maintain, test, and reuse across different case studies. By organising code by transformation step, teams can work in parallel, increasing efficiency.

### Changelog

A changelog will be kept for all notable changes in the project. Changelogs help track the evolution of the project over time, making it easier for collaborators to understand what has changed between versions. We follow the structure and best practices outlined in Keep a Changelog.

### Codebooks

Before developing code, codebooks are created to describe each dataset (D) within the pipeline. A codebook is a comprehensive document that outlines the structure, contents, and metadata of a dataset. It serves as a detailed reference guide for anyone working with the data and plays a crucial role in guiding the development of the analytical pipeline by clearly defining both the inputs and expected outputs.

All codebooks are summarized in a central index file, which provides a high-level overview of the pipeline's structure. For each codebook, the index file includes:

- A brief description of its purpose,
- A list of the scripts used to generate the corresponding dataset,
- A description of the input datasets and input parameters required.

The datasets D2, D3, D4, and D5 are typically subdivided into multiple smaller transformation steps, each detailed within their respective codebooks. These smaller transformation steps ensure that each part of the pipeline is clearly scoped and well-documented.

In addition to supporting development, codebooks help ensure quality control by making transformation logic transparent and verifiable, and they enhance reproducibility by documenting exactly how data is structured and used throughout the analytical pipeline.

### Deployment

The analytical pipeline is delivered to DEAPs as a GitHub release, tagged with a version number. Versioning follows the format: vYYYYMMDD.XX, where the date indicates the release date and XX denotes the sub-version or revision number.

Any deployment issues can be reported via the GitHub repository using the issues feature, where the programming team responsible for the R code will collaborate with the local DEAP to resolve them as needed.

### Reproducibility

It is recommended to locally use the renv R package to maintain the R version and version of packages for reproducibility purposes.

At this time, however, using renv reliably across different systems and environments remains challenging. For this reason, we currently recommend its use only in local development setups.

We are actively monitoring developments in the R ecosystem related to cross-platform reproducibility. As soon as a more stable and portable solution becomes available, we will revisit this guidance and promote broader adoption.

### Licensing

The code will be made available under an open source license.

### README Guidelines

Each case study repository includes a README that covers the following points:

- Project Overview: brief summary of the study goals and key research questions.
- Background: context and rationale for the study.
- Repository Structure: Outline of main folders and their contents.
- Data Overview: Description of data sources, formats, and data privacy considerations.
- How to Run: Instructions for running the pipeline and key scripts, plus where outputs are saved.
- Testing: How to run tests to verify code functionality.
- Contributing: Guidelines for code contributions and issue tracking.
- License: Information about the code license.
- Contact: Who to reach out to for help or questions.

## *7.10. Study size*

Sample size estimation from the hypothetical trial protocol:

In the target trial, the sample size was calculated for a hypothesis test as follows: Assuming a two-sided alpha of 0.05, 80% power, a 0.3% risk of angioedema over 3 years, and a 1% loss to follow up, the number of patients required to detect a HR of 1.8 [Risk Ratio of angioedema for SV vs enalapril from PARADIGM-HF] is 30,784 patients (with 91 angioedema events), i.e. 15,392 patients per arm.

Sample size estimation in this NIS protocol:

In this non-interventional study, no hypothesis test will be performed. The focus of the sample size calculation is based on the precision of the estimated treatment effect. Assuming the study size in each RWD source will be similar to the sample size of the target trial, the precision is estimated as described below.

To estimate the level of precision that is achievable with a fixed sample size, we will estimate the expected width of the confidence interval for the effect estimate.

### Estimation of the precision of the HR

To estimate the expected 95% CI for a HR from a Cox proportional hazards model, the standard error (SE) of the log(HR) is derived from the total number of events.

### Assumptions:

- Equal allocation to treatment groups
- Large-sample normal approximation for log(HR)

- Symmetric CI on the log scale

**The confidence interval (CI) width for the Hazard Ratio (HR) can be calculated using the following formula:**

$CI\_width\_HR = exp(\hat{\beta} + 1.96 \times SE) - exp(\hat{\beta} - 1.96 \times SE)$

**Where:**

- $\hat{\beta}$ is the log hazard ratio (log(HR))
- SE is the standard error of the log(HR)
- 1.96 is the z-score for a 95% confidence interval

**Calculation of 95% CI**

1. Assume equal allocation:

Number of events per group: d1 = d2 = d / 2

2. Calculate SE of log(HR):

SE[log(HR)] = sqrt(1/d1 + 1/d2) = sqrt(2/d)

3. Construct the 95% CI on log scale:

log(HR) ± 1.96 × SE[log(HR)]

4. Convert back to HR scale:

CI_HR = exp(log(HR) ± margin)

%precision = (upper limit of the CI/assumed HR) - 1

**Scenario 1**

Calculation based on 91 events, HR=1.8

SE = sqrt(2 / 91) = 0.14825

log(HR) = log(1.8) = 0.5878

Margin = 1.96 × SE = 1.96 × 0.14825 = 0.29057

Lower bound = 0.5878 - 0.29057 = 0.29723

Upper bound = 0.5878 + 0.29057 = 0.8835

Lower CI = exp(0.29723) = 1.3461

Upper CI = exp(0.8835) = 2.4194

CI Width = 2.4194 - 1.3461 = 1.0733

Precision of the estimation: (upper CI/assumed HR - 1)*100 = (2.42/1.8 - 1)*100 = 34%

### Scenario 2

Calculation under assumption that overall event rate for angioedema is 10% lower than expected (82), HR=1.8

SE = sqrt(2 / 82) = 0.1562

log(HR) = log(1.8) = 0.5878

Margin = 1.96 × SE = 1.96 × 0.1562 = 0.3061

Lower bound =0.5878 - 0.3061 = 0.2817

Upper bound = 0.5878 + 0.3061 = 0.8939

Lower CI = exp(0.2817) = 1.3254

Upper CI = exp(0.8939) = 2.4446

CI Width = 2.4446 - 1.3254 = 1.1192

Precision of the estimation: (upper CI/assumed HR - 1)*100 = (2.45/1.8 - 1)*100 = 36%

Scenario 3

Calculation under assumption that overall event rate for angioedema is 30% lower than expected (64), HR=1.8

SE = sqrt(2 / 64) = 0.1777

log(HR) = log(1.8) = 0.5878

Margin = 1.96 × SE = 1.96 × 0.1777 = 0.3465

Lower bound =0.5878 - 0.3465 = 0.2413

Upper bound = 0.5878 + 0.3465 = 0.9343

Lower CI = exp(0.2413) = 1.2729

Upper CI = exp(0.9343) = 2.5454

CI Width = 2.5454 - 1.2729 = 1.2725

Precision of the estimation: (upper CI/assumed HR - 1)*100 = (2.55/1.8 - 1)*100 = 42%

*Table 21. % Precision under different event counts*

| Scenario | Number of Events | Hazard Ratio (HR) | log(HR) | Standard Error (SE) | Margin of Error | Lower CI (HR) | Upper CI (HR) | CI Width | Precision |
|---|---|---|---|---|---|---|---|---|---|
| Scenario 1 | 91 | 1.8 | 0.5878 | 0.14825 | 0.29057 | 1.3461 | 2.4194 | 1.0733 | 34% |
| Scenario 2 | 82 | 1.8 | 0.5878 | 0.1562 | 0.3061 | 1.3254 | 2.4446 | 1.1192 | 36% |
| Scenario 3 | 64 | 1.8 | 0.5878 | 0.1777 | 0.3465 | 1.2729 | 2.5454 | 1.2725 | 42% |

## 8. Limitation of the methods

There are certain limitations of this protocol that should be noted. These derive from the fact that the observational study may not emulate all the aspects specified in the target trial. The emulation departures across the main aspects of the emulation study (estimand, design and estimation) are described below:

### Population, eligibility and setting

Eligibility criteria were operationalised using diagnostic codes, lab measurements and prescriptions within the defined assessment windows relative to index date. Nevertheless, these pragmatic decisions may lead to incomplete ascertainment of conditions compared with trial screening procedures. As a result, some patients included in the emulation may not have met the target trial's eligibility thresholds.

### Treatment conditions and exposure

Treatment initiation/switch/continuation is identified using prescription/dispensation records, which may not fully capture adherence or prescription fill errors. Dose is not restricted, reflecting real-world practice, but also introducing heterogeneity in treatment regimens. In addition, considering that we only include prescriptions issued by a GP, the SV prescriptions issued by the cardiologist will not be captured. These factors represent departures from the controlled dosing and treatment monitoring procedures of a randomised trial.

Exposure is defined based on prescription/dispensation records, which do not capture whether patients actually filled or took their medications. As a result, some individuals categorized as "exposed" may not have received the intended treatment. This limitation is acknowledged as a source of non-differential exposure misclassification, which would bias effect estimates toward the null.

### Treatment assignment and follow-up

Randomisation cannot be emulated. Instead, matching on treatment history with ACEI/ARB and propensity score matching are used to approximate exchangeability. While propensity score matching balances measured baseline covariates, it cannot account for unmeasured confounding. Moreover, even though we intend to match patients as closely as possible on their treatment history before their index date, it is unfeasible to perform exact matching especially for the complex trajectory patterns (patterns 4-6 in figure 2). Therefore, even though we expect the matching rules we specify will result in comparable intervention and cohort control, there is a possibility that there is some imbalance for the complex trajectories. In addition, considering that we expect that the control trajectories which are required for the matching of the patients with patterns 4-6 would be quite uncommon in clinical practice, there is a possibility that few matches are found for these patients restricting thereby the analysis to a subset of patients treated with SV for who the required control patients treated with ACEI exist. This may limit the generalizability of the effects to the entire eligible population.

In the emulation, follow-up begins at the date of first SV prescription or the respective ACEI prescription of the matched control patient rather than randomisation. This aligns the start of follow-up with treatment initiation but differs from the controlled conditions of a trial. In addition, follow-up is based on data availability and practice registration rather than study visits, which may lead to imperfect measurement of loss to follow-up.

### Outcomes and intercurrent events

Angioedema is identified using validated code lists in the real-world data sources. Although this definition is well established, it is not identical to the clinically adjudicated angioedema in the target trial. This means that even though we will make use of both primary and secondary care data to capture all the angioedema cases, it is likely that certain milder events of angioedema are underreported or misdiagnosed. Nevertheless, we expect that under diagnosis/misdiagnosis happens in a non-differential way between the two cohorts, considering that angioedema is an adverse event of both SV and ACEI, thereby not threatening the validity of our study. Besides, one of our sensitivity analyses is the Quantitative bias analysis for angioedema assessment during which we will estimate if there is a systematic error in the result due to imperfect angioedema assessment and its direction, magnitude and uncertainty.

Strategies for handling intercurrent events (treatment discontinuation, switching, or addition of any of SV/ACEI/ARB, if not the assigned drug at index date) are implemented using prescription/dispensation records. While these reflect real-world effectiveness, the accuracy of operational definitions (e.g., gaps of >30 days to define discontinuation) is limited by prescribing and refill practices. For Estimands 1 and 3, in particular, misclassification of discontinuation or switching may bias estimates of while-on-treatment effects.

Loss to follow-up is defined using practice deregistration which is proxy for true loss. Although unique patient identifiers mitigate risks of missed de-registration, there remains potential for misclassification (e.g., patients who stop attending their practice but do not formally deregister).

### Analysis methods and statistical assumptions

Unlike the target trial, which relied on randomisation to achieve balance, the emulation employs PS matching in Cox and AFT models. This approach requires unverifiable assumptions: no unmeasured confounding, correct model specification, and positivity. Departures from these assumptions could bias results.

The Cox proportional hazards model assumes that the relative treatment effect is constant over time, which may not be appropriate. This assumption is explicitly tested using Schoenfeld residuals and log-log survival plots. In addition, a supplemental analysis is conducted using an accelerated failure time (AFT) model with a Weibull distribution to estimate restricted mean survival time (RMST) at fixed time points (3 and 5 years).

With PS matching, for every patient who was treated with SV, we identify a patient with the same propensity score (caliper of 0.2) and the same treatment history with regard to ACEI/ARB who received ACEI instead, and we match the two patients. In this way we are only including patients who are very similar to the patients treated with SV, thereby estimating the Average Treatment effect in the Treated (ATT) and restricting the generalizability of our results to patients treated with ACEIs. The target trial estimates the Average Treatment Effect in the entire population (ATE). Nevertheless, the PS matching is the suggested method to adjust for confounders when applying the PNU design1. In addition, we do not expect effect modification by treatment group.

### Missing data and censoring

Unlike the trial, where exposure and covariates were actively collected, the emulation must rely on real-world data. Missing exposure data may occur through incomplete prescribing/dispensation records, while covariates (e.g., lifestyle factors) are imputed under a missing-at-random assumption. Misclassification is also possible when absence of a diagnostic code is assumed to reflect absence of a condition. These differences from trial data collection procedures may affect validity.

A key limitation of this study is the reliance on assumptions regarding the censoring mechanism. In the primary Cox model, we assume that censoring is non-informative, meaning that the probability of being censored is independent of the outcome, conditional on treatment assignment, baseline covariates, and survival up to the time of censoring. This assumption may not always hold in practice. For example, patients may leave the database or deregister from a practice due to worsening health, which could be directly related to their risk of experiencing the outcome. If this relationship is not fully captured by measured covariates, effect estimates could be biased.

To address this, we perform sensitivity analyses using inverse probability of censoring weights (IPCW), which relax the primary assumption by conditioning not only on baseline confounders but also on time-varying covariates that predict both censoring and the outcome. While IPCW provides a more flexible and potentially more realistic adjustment, it remains dependent on correct model specification and the availability of sufficient data to capture predictors of censoring. If important determinants of loss to follow-up are unmeasured or poorly recorded, residual informative censoring may persist. In addition, a best/worst case sensitivity analysis is conducted to assess the robustness of the treatment effect estimate to violations of the non-informative censoring assumption made in the primary analysis.

### Data source heterogeneity

CPRD and PHARMO differ in population coverage, healthcare systems, coding practices, and linkage availability, which may introduce heterogeneity in effect estimates. Analyses will be performed separately within each data source using harmonized definitions under the Conception CDM framework. If pooled estimates are produced, heterogeneity will be assessed qualitatively

## 9. Protection of human subjects

This is a non-interventional study using secondary data collection and does not pose any risks for individuals. Each data source research partner will apply for an independent ethics committee review according to local regulations. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants. Patient information This study involves data that exists in an anonymized structured format and contains no patient personal information. All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure the protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. Patient personal data will be

stored at DAPs in encrypted electronic form and will be password protected to ensure that only authorised study staff have access. DAPs will implement appropriate technical and organisational
measures to ensure that personal data can be recovered in the event of a disaster. In the event of a potential personal data breach, DAPs shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

### Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from individuals is not required.

## 10. Reporting of adverse events

For studies in which the research team uses only data from automated healthcare databases, according to the International Society for Pharmacoepidemiology Guidelines for GPP. “Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines.” For non-interventional study designs that are based on secondary use of data, such as studies based on
medical chart reviews or electronic health records, systematic reviews, or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarized in the study report, where applicable. According to the EMA Guideline on GVP, Module VI – Management and Reporting of Adverse Reactions to Medicinal Products, “All adverse events/reactions collected as part of [non-interventional postauthorization studies with a design based on secondary use of data], the submission of suspected adverse reactions in the form of [individual case safety reports] is not required. All adverse events/reactions collected for the study should be recorded and summarized in the interim safety analysis and in the final study report.” Module VIII – Post-Authorization Safety Studies echoes this approach. Legislation in the EU further states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health records, it may not be feasible to make a causality assessment at the individual case level.

# 11. References


1. Malik A, Brito D, Vaqar S, Chhabra L. Congestive Heart Failure. *StatPearl*s. StatPearls Publishing
Copyright © 2024, StatPearls Publishing LLC.; 2024.
2. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovascular Research*. 2022;118(17):3272-3287. doi:10.1093/cvr/cvac013
3. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. Jul 14 2016;37(27):2129-2200. doi:10.1093/eurheartj/ehw128
4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. Sep 21 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368
5. McMurray JJ, Packer M, Desai AS, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. Sep 2013;15(9):1062-73. doi:10.1093/eurjhf/hft052
6. Menendez JT. The Mechanism of Action of LCZ696. *Card Fail Rev*. May 2016;2(1):40-46. doi:10.15420/cfr.2016:1:1
7. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. Sep 11 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077
8. Shi V, Senni M, Streefkerk H, Modgill V, Zhou W, Kaplan A. Angioedema in heart failure patients treated with sacubitril/valsartan (LCZ696) or enalapril in the PARADIGM-HF study. *International Journal of Cardiology*. 2018/08/01/ 2018;264:118-123. doi:https://doi.org/10.1016/j.ijcard.2018.03.121
9. Bezalel S, Mahlab-Guri K, Asher I, Werner B, Sthoeger ZM. Angiotensin-converting Enzyme Inhibitor-induced Angioedema. *The American Journal of Medicine*. 2015/02/01/ 2015;128(2):120-125. doi:https://doi.org/10.1016/j.amjmed.2014.07.011
10. Caballero T, Pedrosa M. Angioedema Due to ACE Inhibitors. *Current Treatment Options in Allergy*. 2016/12/01 2016;3(4):401-415. doi:10.1007/s40521-016-0099-8
11. Hoover T, Lippmann M, Grouzmann E, Marceau F, Herscu P. Angiotensin converting enzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors. *Clinical & Experimental Allergy*. 2010;40(1):50-61. doi:https://doi.org/10.1111/j.1365-2222.2009.03323.x
12. Jackevičiūtė J, Pilvinis V, Pilvinienė R. Fatal outcome of late-onset angiotensin-converting enzyme inhibitor induced angioedema. *Medicine*. 2018-08-01 2018;97doi:10.1097/MD.0000000000011695
13. Liau Y, Chua I, Kennedy MA, Maggo S. Pharmacogenetics of angiotensin-converting enzyme inhibitor-induced angioedema. *Clinical & Experimental Allergy*. 2019;49(2):142-154. doi:https://doi.org/10.1111/cea.13326
14. Stauber T, Confino-Cohen R, Goldberg A. Life-Threatening Angioedema Induced by Angiotensin-Converting Enzyme Inhibitors: Characteristics and Risk Factors. *American Journal of Rhinology & Allergy*. 2014;28(1):54-58. doi:10.2500/ajra.2014.28.3989
15. Taylor CJ, Ordóñez-Mena JM, Jones NR, et al. National trends in heart failure mortality in men and women, United Kingdom, 2000–2017. *European Journal of Heart Failure*. 2021;23(1):3-12. doi:https://doi.org/10.1002/ejhf.1996
16. Zannad F, Garcia AA, Anker SD, et al. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. *Eur J Heart Fail*. Oct 2013;15(10):1082-94. doi:10.1093/eurjhf/hft095

17. Byrd JB, Adam A, Brown NJ. Angiotensin-Converting Enzyme Inhibitor-Associated Angioedema. *Immunology and Allergy Clinics of North America*. 2006/11/01/ 2006;26(4):725-737. doi:https://doi.org/10.1016/j.iac.2006.08.001
18. Lacuesta G, Betschel SD, Tsai E, Kim H. Angioedema. *Allergy, Asthma & Clinical Immunology*. 2024/12/09 2024;20(3):65. doi:10.1186/s13223-024-00934-3
19. Suissa S, Moodie EEM, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiology and Drug Safety*. 2017;26(4):459-468. doi:https://doi.org/10.1002/pds.4107
20. Tazare J, Gibbons DC, Bokern M, et al. Prevalent new user designs: A literature review of current implementation practice. *Pharmacoepidemiol Drug Saf*. Nov 2023;32(11):1252-1260. doi:10.1002/pds.5656
21. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. Jul 2015;11(7):437-41. doi:10.1038/nrrheum.2015.30
22. Bellanca L, Linden S, Farmer R. Incidence and prevalence of heart failure in England: a descriptive analysis of linked primary and secondary care data – the PULSE study. *BMC Cardiovascular Disorders*. 2023/07/26 2023;23(1):374. doi:10.1186/s12872-023-03337-1
23. Williams R, Kothny W, Serban C, Lopez-Leon S, de Vries F, Schlienger R. Association between vildagliptin and risk of angioedema, foot ulcers, skin lesions, hepatic toxicity, and serious infections in patients with type 2 diabetes mellitus: A European multidatabase, noninterventional, postauthorization safety study. *Endocrinology, Diabetes & Metabolism*. 2019;2(3):e00084. doi:https://doi.org/10.1002/edm2.84
24. Wetmore JB, Yan H, Horne L, Peng Y, Gilbertson DT. Risk of hyperkalemia from renin–angiotensin–aldosterone system inhibitors and factors associated with treatment discontinuities in a real-world population. *Nephrology Dialysis Transplantation*. 2019;36(5):826-839. doi:10.1093/ndt/gfz263
25. Rasmussen ER, Mey K, Bygum A. Angiotensin-converting enzyme inhibitor-induced angioedema--a dangerous new epidemic. *Acta Derm Venereol*. May 2014;94(3):260-4. doi:10.2340/00015555-1760
26. Carr MJ, Wright AK, Leelarathna L, et al. Impact of COVID-19 on diagnoses, monitoring, and mortality in people with type 2 diabetes in the UK. *Lancet Diabetes Endocrinol*. Jul 2021;9(7):413-415. doi:10.1016/s2213-8587(21)00116-9
27. Conrad N, Misra S, Verbakel JY, et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. *Lancet*. Jun 3 2023;401(10391):1878-1890. doi:10.1016/s0140-6736(23)00457-9
28. Overbeek J, Baak B, Herings R, Swart-Polinder K. RWD144 Coded Diagnoses Versus Proxy-Based Diagnoses in Primary Care: Registration By General Practitioners in the PHARMO GP Data. *Value in Health*. 2023;26(12):S532. doi:10.1016/j.jval.2023.09.2861
29. Mahmoudpour SH, Baranova EV, Souverein PC, et al. Determinants of angiotensin-converting enzyme inhibitor (ACEI) intolerance and angioedema in the UK Clinical Practice Research Datalink. *British Journal of Clinical Pharmacology*. 2016;82(6):1647-1659. doi:https://doi.org/10.1111/bcp.13090
30. Abbosh J, Anderson JA, Levine AB, Kupin WL. Angiotensin converting enzyme inhibitor-induced angioedema more prevalent in transplant patients. *Annals of Allergy, Asthma & Immunology*. 1999/05/01/ 1999;82(5):473-476. doi:https://doi.org/10.1016/S1081-1206(10)62723-8
31. Brouwer ES, Bratton EW, Near AM, Sanders L, Mack CD. Leveraging unstructured data to identify hereditary angioedema patients in electronic medical records. *Allergy, Asthma & Clinical Immunology*. 2021/04/20 2021;17(1):41. doi:10.1186/s13223-021-00541-6
32. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. Jun 2015;44(3):827-36. doi:10.1093/ije/dyv098

33. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol*. Dec 1 2019;48(6):1740-1740g. doi:10.1093/ije/dyz034
34. Overbeek JA, Swart KMA, Houben E, Penning-van Beest FJA, Herings RMC. Completeness and Representativeness of the PHARMO General Practitioner (GP) Data: A Comparison with National Statistics. *Clin Epidemiol*. 2023;15:1-11. doi:10.2147/clep.S389598
35. Kuiper JG, Bakker M, Penning-van Beest FJA, Herings RMC. Existing Data Sources for Clinical Epidemiology: The PHARMO Database Network. *Clin Epidemiol*. 2020;12:415-422. doi:10.2147/clep.S247575
36. Thurin NH, Pajouheshnia R, Roberto G, et al. From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety During Pregnancy and Breastfeeding. *Clin Pharmacol Ther*. Jan 2022;111(1):321-331. doi:10.1002/cpt.2476
37. Royo AC, Elbers Jhj R, Weibel D, et al. Real-World Evidence BRIDGE: A Tool to Connect Protocol With Code Programming. *Pharmacoepidemiol Drug Saf*. Dec 2024;33(12):e70062. doi:10.1002/pds.70062
38. https://andrea-cloud.com/our-story/
39. Hoxhaj V, Andaur Navarro CL, Riera-Arnau J, et al. INSIGHT: A Tool for Fit-for-Purpose Evaluation and Quality Assessment of Standardized Observational Data Sources for Real World Evidence on Medicine and Vaccine Safety. *Pharmacoepidemiol Drug Saf*. Jan 2025;34(1):e70089. doi:10.1002/pds.70089

# 12. Appendices

## Appendix 1.

### Detailed description of the matching process in the PNU:

To identify the matching ACEI prescription, following the prevalent new user design, we will take the following steps:

Step 1: Base cohort formation: We will form the base cohort of all patients with an incident heart failure diagnosis in primary or secondary care between 01/01/2014 and 31/03/2023, one year of history in primary care before their incident heart failure diagnosis and a prescription for ACEI or SV after their incident HF diagnosis. The base cohort entry will be the incident HF diagnosis.

Patients with a same-day prescription of more than one medication (ACEI + SV or ACEI + ARB or ARB + SV or ACEI + ARB + SV) on the base cohort entry will be excluded in a second step from the base cohort.

Step 2: Formation of exposure sets: for every new SV user in the base cohort, we will create an exposure set by identifying from the base cohort every patient with an ACEI prescription and:

A. The same trajectory pattern among the prespecified six distinct trajectory patterns depicted in figure 2, from base cohort entry until that ACEI prescription, as the new SV user's trajectory from base cohort entry until the first SV prescription. The six distinct trajectory patterns in figure 1 were identified in a prior drug utilization study in which the treatment trajectories of patients with HF with regard to ACEIs and ARBs were assessed from one year before their incident HF diagnosis until their first SV prescription

Practically, we stratify patients as follows:

1. Prior history – absent (group 1, pattern 1) or present (group 2&3, patterns 2-6)
2. For patients with prior history - type of prescription before index date: ACEI (group 2, patterns 2, 4, 6) or ARB (group 3, patterns 3, 5, 6)
3. Type of prior history: stable/concordant (patterns 2 & 3; patient only has either ACEI or ARB in treatment history) or sequential discordant (patterns 4&5; patient switches from ACEI to ARB or ARB to ACEI at some point in history, but is consistent before and after switch) or mixed discordant (pattern 6; patient either has both ACEI and ARB or switches between the two multiple times)

B. The same total number of prescriptions of ACEIs/ARBs from base cohort entry until that ACEI prescription as the new SV user had from base cohort entry until the first SV prescription

Practically, we match patients as follows:

For patterns 2 & 3, we match on number of prior prescriptions only. For patterns 4-6, we match on number of prior prescriptions and dominant medication type (ACEI or ARB). In case of a 50-50 split, we assign a third category (no dominant type) and match on this. For all patterns, counting of prior prescription excludes the first prescription before index date.

C. Receiving that ACEI prescription in the same calendar year as the new SV user received their first SV prescription

D. With the same gap, 0-60 days, 61 – 180 days, > 180 days, between the last prior prescription (either ACEI or ARB) and that ACEI prescription, as the new SV user had between the last prior prescription and the first SV prescription.

Step 3: Perform conditional logistic regression: using all the exposure sets we will perform conditional logistic regression analysis to derive the time-conditional propensity scores including the confounders of the study

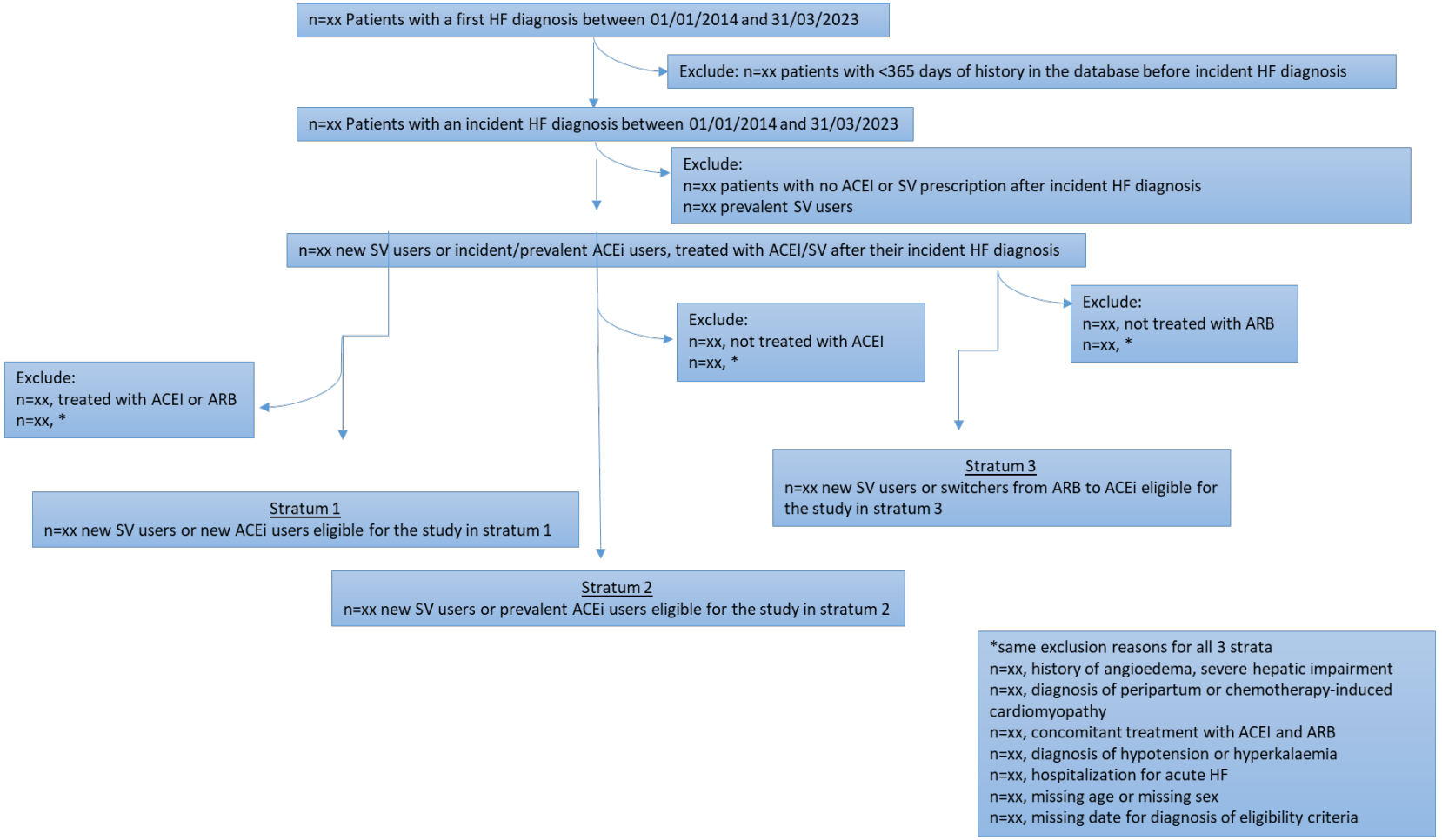
Step 4: Positivity assumption: for each exposure set we will verify that the time-conditional propensity score of the exposed subject lies within the range of the time-conditional propensity scores of the members of the corresponding exposure group. The exposure sets for which the positivity assumption does not hold true will be eliminated.

Step 5: Check eligibility criteria and match the new SV users with the control ACEI users: Starting chronologically with the first new SV user, we will assess the eligibility criteria and whether they have an ACEI prescription on the same day as the first SV prescription. If the SV user is not eligible, they will also be eliminated from all other exposure sets they may belong to as comparators. If the SV user is eligible, then we will select the ACEI user from the exposure set with the closest time-conditional propensity score and assess the eligibility criteria and whether they have an SV prescription on the same day as the ACEI prescription. If the ACEI user is not eligible, they will be excluded from other exposure sets they may belong to, and the ACEI user with the next closest propensity score will be assessed. When an eligible ACEI user is identified, they will be matched with the new SV user, and they will be eliminated from all the other exposure sets. Their matching ACEI prescription will be their index date. This procedure will continue until all new SV users are matched with ACEI users.

## Figures and tables

**Figure 1.** Flow Diagram of Patient Selection and Exclusions

This will be reported separately for each data source (CPRD and PHARMO)



## Appendix 2. Standard Operating Procedures (SOPs) in PHARMO

### SOPs recording

PHARMO conducts studies in accordance with the ENCePP Guide on Methodological Standards in Pharmacoepidemiology and the ENCePP Code of Conduct. Lumanity is ISO 9001:2015 certified. Standard operating procedures, work instructions and checklists are used to guide the conduct of a study. These procedures and documents include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, rules and procedures for execution and quality control of R or SAS programming, standards for writing protocols and reports, and requirements for senior scientific review of key study documents.

Our SOPs include:
0500 Quality policy
0510 Setup quality manual - v2.1
0520 QMS training - v4
0530 QMS checks - v2.3
0531 Compliance assessment - v2.3
0532 Effectiveness assessment - v2.2
0540 QMS adjustment - v2.2
0550 Procedures
P 0511 Information Security Incidents
1000 Research
P 1100 Research and data analysis
I 1101 Request fits PHARMO - v5
I 1101.1 Classifying an opportunity - v4
I 1101.2 SAS feasibility assessment - v5
C 1101.3 Checklist Request fits PHARMO - v3.3
I 1102 Proposal agreed - v5
C 1102.1 Checklist Proposal and Investment - v3.5
I 1103 Contract agreed - v5.1
I 1103.1 Subcontract agreed - v1.4
I 1103.2 Assignment of a project team - v3.4
I 1103.3 Master Service Agreement (MSA) agreed - v1.1
C 1103.4 Checklist (sub)contract/MSA - v5.1
I 1104 Project management - v7
C 1104.1 Checklist Project management prepared - v3.4
I 1105 Protocol/Statistical Analysis Plan agreed - v5.3

C 1105.1 Checklist Protocol/Statistical Analysis Plan - v3.3
I 1106 Programming finalised - v7.1
I 1106.1 Programming execution - v6.1
I 1106.2 Programming execution in multi-country studies - v1.2
I 1106.3 Methodology knowledge base - v3.2
C 1106.4 Checklist Programming - v4.1
I 1107 Report agreed - v6
C 1107.1 Checklist Report - v3.3
I 1108 Dissemination study results - v6
C 1108.1 Checklist Abstract - v3.3
C 1108.2 Checklist Poster presentation - v3.3
C 1108.3 Checklist PowerPoint presentation - v3.3
C 1108.4 Checklist Outline manuscript - v3.3
C 1108.5 Checklist Manuscript - v3.3
I 1109 Research project finalised - v5.1

### How SOPs are implemented and monitored

PHARMO has an established CAPA management process to identify, correct and mitigate deviations, this is described in the CAPA management SOP (Document Number L-SOP-QA-007, v5.0).
Deviations are flagged to Central Compliance team, who investigate and log them, recurring deviations are also monitored for effectiveness and any repeating route causes are escalated to management for further investigation and preventative actions. Re-training is instigated on repeat deviations as necessary. SOP available on request.