SoMoR – UK (Study of Management of RAASi in UK)

A multi-centre, retrospective observational study on renin-angiotensin-aldosterone system inhibitors (RAASi) management in patients treated for chronic kidney disease alongside heart failure and/or type 2 diabetes mellitus

STUDY PROTOCOL

Sponsor Study Reference SoMoR

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Contents

1. List of tables

2. List of abbreviations

Abbreviation	Definition
ACEi	Angiotensin converting enzyme inhibitor
ACR	albumin:creatinine ratio
AE	Adverse event
ADR	Adverse drug reaction
ARB	Angiotensin receptor blocker
CI	Chief Investigator
95% CI	95% confidence interval
CKD	Chronic kidney disease
EDC	Electronic data capture
eDCF	Electronic data collection form
eGFR	Estimated glomerular filtration rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GAfREC	Governance Arrangements for Research Ethics Committees
GCP	Good Clinical Practice
GP	General Practitioner
HF	Heart failure
HRA	Health Research Authority
ISPE	International Society for Pharmacoepidemiology
LVEF	Left ventricular ejection fraction
MHRA	Medicines and Healthcare Products Regulatory Agency
MRA	Mineralocorticoid receptor antagonist
NIHR	National Institute for Health Research
NHS	National Health Service
PAS	Patient Administration System
PCR	protein:creatinine ratio
PI	Principal investigator

Abbreviation	Definition
R&D	Research and Development
RAASi	Renin–angiotensin–aldosterone system inhibitors
REC	Research Ethics Committee
SADR	Serious adverse drug reaction
SDV	Source data verification
STROBE	Strengthening the Reporting of OBservational Studies in Epidemiology
T2DM	Type 2 diabetes mellitus
UK	United Kingdom

3. List of definitions

Baseline: test result in medical records with date closest to and before the index event and within 12 months of the index event, or on the same date as the index event

Chronic Kidney Disease (CKD) stages 3 and 4: estimated glomerular filtration rate (eGFR) >14ml/min/1.73m^2 and <60ml/min/1.73m^2

Enrolment period: the 12 month period between 01 January 2016 and 31 December 2016

Heart failure (HF): presence of reduced ejection fraction and left ventricular ejection fraction (LVEF) <40%

Index event: first prescription of RAASi during the enrolment period

Maximum tolerated dose: highest dose of RAASi (or MRA) recorded in medical records during observation period

Observation period: the 12 month period from index event

Target dose: as stated in medical records, national or international clinical guidelines or Summary of Product Characteristics (SPC) if not recorded in medical records (see Appendices)

Type 2 diabetes (T2DM): Chronic metabolic disorder that results in hyperglycaemia (high blood glucose levels) due to the body's inability to produce enough insulin or lack of ability to utilise the insulin being produced (insulin resistance). Confirmed diagnosis in medical records

4. Study synopsis

Title	SoMoR – UK (Study of Management of RAASi in UK) A multi-centre, retrospective observational study on renin-angiotensin-aldosterone system inhibitors (RAASi) management in patients treated for chronic kidney disease alongside heart failure and/or type 2 diabetes mellitus.
Background and rationale for study	In order to improve renin-angiotensin-aldosterone system inhibitors (RAASi) treatment by increasing the proportion of patients who achieve target doses according to clinical guidelines, the maximum tolerated doses that are currently achieved need to be determined. This study will therefore describe the characteristics and treatment outcomes of patients with CKD and at least one of the following: heart failure (HF) and/or type 2 diabetes mellitus (T2DM) and who receive RAASi in the real world UK NHS setting but do not achieve target dose. The maximum tolerated doses achieved by these patients and the length of time on these doses will be reported.
Objectives	**Primary objective** 1. To describe doses of RAASi prescribed to patients with CKD in the UK NHS setting **Secondary objectives** 1. To describe doses of mineralocorticoid receptor antagonist (MRA) prescribed to patients with CKD and HF 2. To describe other drug types concomitantly prescribed for CKD and/or HF in patients treated with RAASi 3. To describe clinical outcomes associated with RAASi treatment 4. To describe the demographic and clinical characteristics of patients treated with RAASi and do not achieve target dose, at initiation of treatment
Hypothesis statement	This is a descriptive study and therefore an a priori hypothesis will not be tested.
Study design	This is a multi-centre, retrospective observational study to take place in NHS secondary care centres in the UK.
Data source(s)	Patient-level data recorded in primary and secondary care settings will be collected. Patient demographic data, and clinical data on prescribing patterns and patient management, will be collected from each centre. Data will be extracted from the electronic Patient Administration System (PAS), service databases and electronic (or paper) medical

	notes by the NHS clinical care teams or a pH Associates researcher. The extracted data will then be entered into the study database using a web-based, secure data capture and data management tool ('MACRO'). An electronic data collection form (eDCF) will be created to facilitate the entry of data into the database. **Data management** Source data verification (SDV) will be carried out to monitor data quality on a subset of all data submitted (typically 10% of records from each centre).
Number of centres	Based on experiences with similar studies, it is estimated that between five and ten centres will be required to recruit the proposed number of study participants. pH Associates will liaise with Vifor to recruit the optimal number of centres and participants to achieve the study objectives. Centres will be recruited to provide as geographically representative a study sample as possible across the UK.
Number of subjects	The analyses will be descriptive and therefore the required sample size will be estimated based on precision instead of statistical power. It is expected that approximately 100 patients will be sufficient to generate reliable results, as determined by relatively narrow confidence intervals. The number of patients in the study will be allocated as follows: 50% with CKD and HF and 50% with CKD and T2DM. This distribution includes patients with CKD, HF and T2DM.
Study time period	Patients will be eligible for study enrolment if they were initiated on RAASi treatment during the 12 month period from 01 January 2016 to 31 December 2016. The retrospective observation period for each patient will be 12 months from their RAASi initiation date.
Patient selection	This study will investigate the prescribing of RAASi in the real world UK NHS setting in patients with chronic kidney disease (CKD) stage 3 or 4 who do not achieve target RAASi dose during the observation period and have at least one of the following: • heart failure (HF) • type 2 diabetes mellitus (T2DM) Where: • CKD stage 3 or 4 is defined as estimated glomerular filtration rate (eGFR) >14ml/min/1.73m^2 and <60ml/min/1.73m^2 • HF is defined as presence of reduced ejection fraction and left ventricular ejection fraction (LVEF) <40% • T2DM is defined as a confirmed diagnosis in medical records

	The NHS clinical care team will identify eligible patients based on the following: **Inclusion criteria** • Diagnosed with CKD stage 3 or 4 and at least one of the following: HF and/or T2DM • Prescribed a RAASi for the first time at an outpatient CKD and/or HF clinic between 01 January 2016 to 31 December 2016 ('the enrolment period') • Aged ≥18 years when prescribed a RAASi for the first time during the enrolment period • Patients who do not achieve target dose of RAASi during the observation period • With ≥12 months follow up data during the observation period • Consent to researcher access to their medical records for study data extraction (living patients only) **Exclusion criteria** • Received heart or kidney transplant before or during the observation period • Diagnosed with type 1 diabetes mellitus or acute kidney injury • Diagnosed with metastatic, late-stage or end-stage cancer with <12 months life expectancy • Hospital medical records are unavailable for review • Enrolled in a blinded clinical trial of an investigational medicinal product during the observation period
Study endpoints	Endpoints will be analysed by drug type and patient group (CKD and HF, CKD and T2DM, CKD and HF and T2DM), where relevant. **Primary endpoint** 1. Mean maximum tolerated daily dose of RAASi achieved (as percentage of target dose) **Secondary endpoints** 2. Length of time on maximum tolerated daily dose of RAASi 3. Proportion of patients with HF who receive RAASi and MRA 4. Maximum tolerated daily dose of MRA achieved in patients with HF 5. Length of time on maximum tolerated daily dose of MRA in patients with HF 6. Distribution of other drugs concomitantly prescribed for CKD and/or HF to patients treated with RAASi, by drug type 7. Proportion of patients with elevated serum potassium level (>5.1 mmol/L, >5.5 mmol/L or >6.0 mmol/L) during the observation

	period 8. Number of episodes per patient with elevated serum potassium level (>5.1 mmol/L, >5.5 mmol/L or >6.0 mmol/L) 9. Change in mean serum potassium level (from index date to last result during observation period) 10. Change in mean serum creatinine level (from index date to last result during observation period) 11. Change in mean urine protein level (from index date to last result during observation period) 12. Change in mean blood pressure level (from index date to last result during observation period) 13. Proportion of patients who stop RAASi treatment at least once during the observation period 14. Reason(s) for changing RAASi dose or stopping RAASi treatment, where relevant **Other measures** Patient demographic and clinical characteristics at the time of RAASi initiation will also be reported, including age, sex, ethnicity, length of time since diagnosis of CKD (and HF and/or T2DM if relevant), eGFR, LVEF (if diagnosed with HF), and comorbidities.
Statistical considerations	Given the descriptive nature of the study, results will be reported in terms of precision (95% confidence intervals, CIs) and not statistical power. Data from all centres will be pooled for analysis. Categorical data will be described by the number (n) and percentage (%) of patients in each category. Continuous data will be described by number of observations, mean and standard deviation (SD) for normally distributed data or median and interquartile range for non-normally distributed data, and minimum and maximum values where relevant. Missing and invalid observations will be tabulated as a separate category. Rates will be reported with 95% CIs.
Regulatory, ethical and administrative obligations	This is an observational research study where only patients who consent (if living) for their medical records to be accessed for the purpose of the study will be included in the study. For deceased patients study data will be extracted from medical records by a member of the direct care team to preserve patient confidentiality in absence of consent from these patients. There will be no change to the clinical management of patients as a result of taking part in the study. No additional patient investigations or tests will be required. Data collection will be carried out by either the clinical care team at

	each centre or a pH Associates researcher. Therefore, this study will be submitted for NHS Research Ethics Committee (REC) approval in line with the harmonised edition of the Governance Arrangements for Research Ethics Committees (GAfREC). Local management approval will be obtained via the Health Research Authority (HRA) and Trust/Health Board Research and Development (R&D) departments. All electronic data files will be securely stored on a password-protected internal UK-based server at pH Associates and all study-related documents will be kept in a locked cupboard when not in use. Access to the study database will be restricted (by password protection) and only granted to pH Associates staff who are directly involved with the study.

5. Study amendments and protocol deviations

All amendments to the protocol will be documented in Table 1. Protocol deviations will be documented in a Protocol Deviation Log.

Table 1. Study amendments

Amendment number	Date of amendment	Description	Reason for amendment
1	21st March 2018	References to mineralocorticoid receptor antagonists (MRAs) updated in the following sections: 3. List of definitions (page 8), 4. Study synopsis (pages 9 and 11), 6. Background (page 15), 7. Aim and objectives (page 16), 9. Study design and methodology (pages 20 and 23).	Only spironolactone was previously included in the protocol but data on eplerenone will also be collected in the study.
2	21st March 2018	Removal of exclusion criteria for "Received dialysis during the observation period". The following sections have been updated: 4. Study synopsis (page 11) 9. Study design and methodology (page 18).	Although very few patients with CKD stage 3 or 4 (study population of interest) will receive dialysis, excluding these patients may introduce bias and therefore they should not be excluded from the study.
3	21st March 2018	Secton 17. Study timelines updated (page 31).	Updated as timelines for study activities (but not study completion date) have changed since the last version of the protocol in December 2017.

6. Background and rationale

It is estimated that approximately 6% of the population of England aged 16 years or older have (diagnosed or undiagnosed) chronic kidney disease (CKD) stage 3 to 5[1]. Renin–angiotensin–aldosterone system inhibitors (RAASi) are commonly prescribed to patients with CKD, with or without heart failure (HF) and with or without diabetes mellitus. RAASi include the following drug types: angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs).

RAASi are used to delay disease progression (e.g. end-stage renal failure) and to prevent major cardiac events. As such, they can maintain/improve and prolong patients' quality of life. The introduction and maintenance of RAASi treatment is well established as part of recommended treatment pathways for CKD and HF[2–4]. However, patients treated with RAASi are at risk of elevated serum potassium levels (hyperkalaemia), through impaired renal function and/or side effect of the drugs. As hyperkalaemia can be a serious medical emergency, leading to organ failure and resulting in death, patients often do not achieve the target doses that are required for optimal clinical benefit due to clinician concerns about potential, or actual episodes of, hyperkalaemia[5–7]. Patients with HF are typically also treated with a mineralocorticoid receptor antagonist (MRA), such as spironolactone or eplerenone.

Patients with HF are recommended to be treated with a MRA as well, to reduce symptoms of HF such as fluid retention and to lower mortality risk[8]. MRAs add to the risk of hyperkalaemia. As such, patients with CKD and HF who are treated with RAASi may receive a below target dose of MRA or not receive MRA treatment at all, which hampers the management of HF in this patient group[9,10].

6.1 Rationale for study

In order to improve RAASi treatment in terms of increasing the proportion of patients who achieve target doses according to clinical guidelines, the maximum tolerated doses that are currently achieved need to be determined. This study will therefore describe the characteristics of patients with CKD (and at least one of the following: HF and/or T2DM)

who are treated with RAASi but do not achieve target dose. The maximum tolerated doses achieved by these patients and the length of time on these doses will be reported.

7. Aim and objectives

7.1 Aim

To investigate the use of RAASi in the real world UK NHS setting in patients with CKD stage 3 or 4 and who also have HF and/or T2DM.

7.2 Primary objective

1. To describe doses of RAASi prescribed to patients with CKD in the UK NHS setting

7.3 Secondary objectives

1. To describe doses of MRA prescribed to patients with CKD and HF
2. To describe other drug types concomitantly prescribed for CKD and/or HF in patients treated with RAASi
3. To describe clinical outcomes associated with RAASi treatment
4. To describe the demographic and clinical characteristics of patients treated with RAASi who do not achieve target dose, at initiation of treatment

8. Hypothesis

This is a descriptive study and therefore an a priori hypothesis will not be tested.

9. Study design and methodology

The study is designed and will be conducted according to the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and International Society for Pharmacoepidemiology (ISPE) guidance, as appropriate[10,11]. This will be a multi-centre, retrospective non-interventional study of patients with CKD and HF

and/or T2DM. The study will take place in between five and ten NHS secondary care centres in the UK.

9.1 Study time periods

Data will be collected retrospectively over 24 months, from 01 January 2016 to 31 December 2017. Patients who were initiated on RAASi between 01 January 2016 and 31 December 2016 will be retrospectively followed up for 12 months from the date of RAASi initiation (study index date), i.e. their first prescription of RAASi during the enrolment period.

9.2 Study population

The study will include adult patients with CKD stage 3 or 4 who do not achieve target dose of RAASi and have at least one of the following:

- heart failure (HF)
- type 2 diabetes mellitus (T2DM)

Where:

- CKD stage 3 or 4 is defined as estimated glomerular filtration rate (eGFR) >14ml/min/1.73m^2 and <60ml/min/1.73m^2
- HF is defined as presence of reduced ejection fraction and left ventricular ejection fraction (LVEF) <40%
- T2DM is defined as a confirmed diagnosis in medical records
- Target dose is defined as recorded in medical records, or Summary of Product Characteristics (SPC) if not recorded in medical records (see Appendices)

9.2.1 Inclusion criteria

- Diagnosed with CKD stage 3 or 4 and at least one of the following: HF and/or T2DM
- Prescribed a RAASi for the first time at an outpatient CKD and/or HF clinic between 01 January 2016 to 31 December 2016 ('the enrolment period')
- Aged ≥18 years when prescribed a RAASi for the first time during the enrolment period

- Patients who do not achieve target dose of RAASi during the observation period
- With ≥12 months follow up data during the observation period
- Consent to researcher access to their medical records for study data extraction (living patients only)

9.2.2 Exclusion criteria

- Received heart or kidney transplant before or during the observation period
- Diagnosed with type 1 diabetes mellitus or acute kidney injury
- Diagnosed with metastatic, late-stage or end-stage cancer with <12 months life expectancy
- Hospital medical records are unavailable for review
- Enrolled in a blinded clinical trial of an investigational medicinal product during the observation period

9.2.3 Participant recruitment

The NHS clinical care team will identify eligible patients and seek consent from each living patient for their hospital and primary care medical records to be used in the study. Data from patients who are deceased will only be collected by the NHS care team preserve patient confidentiality. The NHS care team will contact living patients by post or face to face at the patients' next hospital appointment. Consecutive patients will be selected by the NHS care team in reverse chronological order of RAASi initiation (index date).

9.3 Data collection

Data from patients' medical records will be collected by members of the NHS care team or external pH Associates researchers using electronic data collection forms (eCRFs) within an electronic data capture (EDC) system called MACRO. This is a web-based, secure data capture and data management tool.

Patients will be identified in all study records by a unique study code to preserve patient confidentiality. Clinical data from secondary care medical records will be collected either by pH Associates or the NHS care team. Information provided by primary care on patients'

RAASi and concomitant drug use for CKD and/or HF, as well as haematology and biochemistry test results, during the observation period will be extracted from patient records within secondary care.

There will be no change to the clinical management of patients as a result of taking part in the study. No additional patient investigations or tests will be required.

9.4 Data sources

Data will be extracted from medical records in secondary care. This will include:

- Patient demographic and clinical data recorded in the electronic Patient Administration System (PAS), service databases and medical notes, prescribing records, laboratory reports and investigation reports.
- CKD/HF prescribing information and haematology and biochemistry test results from primary care (where available within patients' secondary care records).

9.5 Study endpoints and variables

Results will be presented by RAASi drug type, i.e. angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), and patient group (CKD and HF, CKD and T2DM, CKD and HF and T2DM), where appropriate. Patient-level data will be collected from each centre for the following endpoints during the observation period.

9.5.1 Primary endpoint

The primary endpoint of this study is the mean maximum tolerated daily dose of RAASi achieved (as percentage of target dose).

9.5.2 Secondary endpoints

The following endpoints will also be measured:

Prescribing modalities, including concomitant prescribing

- Length of time on maximum tolerated daily dose of RAASi
- Proportion of patients with HF who receive RAASi and MRA

- Maximum tolerated daily dose of MRA achieved in patients with HF
- Length of time on maximum tolerated daily dose of MRA in patients with HF
- Distribution of other drugs concomitantly prescribed for CKD and/or HF in patients treated with RAASi, by drug type

Clinical outcomes

- Proportion of patients with elevated serum potassium level (>5.1 mmol/L, >5.5 mmol/L or >6.0 mmol/L) during the observation period
- Number of episodes per patient with elevated serum potassium level (>5.1 mmol/L, >5.5 mmol/L or >6.0 mmol/L)
- Change in mean serum potassium level (from index date to last result during observation period)
- Change in mean serum creatinine level (from index date to last result during observation period)
- Change in mean urine protein level (from index date to last result during observation period)
- Change in mean blood pressure level (from index date to last result during observation period)
- Proportion of patients who stop RAASi treatment at least once during the observation period
- Reason(s) for changing RAASi dose or stopping RAASi treatment, where relevant

The following patient characteristics will also be included in analyses:

- Age at index event
- Sex
- Ethnicity
- HF status
- Comorbidities documented at baseline
- Length of time since diagnosis of CKD (and HF and/or T2DM, if relevant) at index event
- eGFR at baseline

- LVEF at baseline, if diagnosed with HF

9.5.3 Variables to be collected

The variables to be collected in this study are shown in Table 2.

Table 2 Study variables

Data Item	Required detail	Time point(s)	Data source(s)
Date of birth	MM/YYYY	Index event	Hospital medical record
Gender	F, M	Index event	Hospital medical record
Ethnicity	Based on categories recommended by Office for National Statistics: White, Mixed / Multiple ethnic groups, Asian / Asian British, Black / African / Caribbean / Black British, Other ethnic group	Baseline	Hospital medical record
Date of CKD diagnosis	MM/YYYY	Baseline	Hospital medical record
Date of HF diagnosis, if relevant	MM/YYYY	Baseline	Hospital medical record
Date of T2DM diagnosis, if relevant	MM/YYYY	Baseline	Hospital medical record
Comorbidities	Based on diseases and conditions recorded in medical record	Baseline	Hospital medical record
eGFR	Date of observation, rate	Baseline until end of	Hospital medical records,

		observation period	including primary care correspondence
LVEF	Date of observation, ejection fraction	Baseline until end of observation period	Hospital medical records, including primary care correspondence
Serum potassium	Date of observation, level	Index date until end of observation period	Hospital medical records, including primary care correspondence
Serum creatinine	Date of observation, level	Index date until end of observation period	Hospital medical records, including primary care correspondence
Urine protein (albumin:creatinine ratio, ACR or protein:creatinine ratio, PCR)	Date of observation, level, type of test	Index date until end of observation period	Hospital medical records, including primary care correspondence
Blood pressure	Date of observation, level	Index date until end of observation period	Hospital medical records, including primary care correspondence
RAASi prescriptions	Drug name, dose, start date	Index date until end of observation	Hospital medical records, including

		period	primary care correspondence
MRA prescriptions, if relevant	Drug name, dose, start date	Index date until end of observation period	Hospital medical records, including primary care correspondence
Concomitant medications for CKD and/or HF	Drug name, start date	Index date until end of observation period	Hospital medical records, including primary care correspondence
Change in RAASi treatment	Date of change, reason for dose change/stopping of treatment	Index date until end of observation period	Hospital medical records, including primary care correspondence

10. Data management and quality control

10.1 Database management

pH Associates will be responsible for data management in this study, including quality checking of the data. The eDCF will be developed from a paper draft and then converted to electronic form in MACRO, which is a data management system that has a secure web-based data entry interface and is fully validated and compliant with Food and Drug Administration (FDA) Information Governance standard 21 CFR part 11 and Good Clinical Practice (GCP). The MACRO system has restricted access permissions for data entry and data management and it maintains a visible audit trail of all changes to data and activity in the system in line with 21 CFR part 11. It has been widely used in the UK NHS for complex interventional clinical trials. It is used by pH Associates on a range of real world evidence studies.

All electronic study data will be securely stored on a password-protected internal, UK-based server at the pH Associates office and all study related documents will be kept in a locked cupboard when not in use. Entry to the study database will be restricted (by password protection) to only those pH Associates staff members directly involved with the study. System backups for data stored at pH Associates and records retention for the study data will be consistent with pH Associates standard procedures.

10.2 Data quality checks

Data collection will be completed by trained staff either from pH Associates or the NHS care team at study centres. All data collectors will be provided with Data Collection Guidelines to support consistent completion of eDCFs. Additionally, the same data collector will be used at each centre, wherever possible. Data entered into eDCFs will be validated at the point of entry into MACRO using criteria to be pre-agreed criteria with Vifor Fresenius Medical Care Renal Pharma UK Ltd before the start of data collection. All data received by pH Associates will be checked for participant eligibility, accuracy and completeness using programmed validation checks, in accordance with the agreed data management plan.

Furthermore, the accuracy and quality of data collection will be monitored by the completion of source data verification (SDV) for 10% of eDCFs at each centre by pH Associates staff. SDV will only be possible for secondary care data. SDV will not be conducted for primary care prescribing and test results data as access to source GP records will not be sought. Where data collection is completed by pH Associates staff, the staff member who carries out the SDV will be different to the person responsible for data collection at that specific centre. Remedial training will be given to data collectors if necessary.

Quantitative data collected for laboratory (haematology and biochemistry) parameters will be standardised per centre using laboratory reference ranges entered on the eDCF. This will allow pooling of these study parameters across centres. Data submitted to the study will be checked for completeness and queries will be raised by the pH Associates data management

team. Study centres will be required to co-operate with the data management team in the resolution of these queries. Where data queries are raised by the pH Associates data management team, study centres will be required to cooperate with pH Associates in the resolution of these queries. On completion of the first three eDCFs from at least two centres, a pilot of the data collection process will be completed. This will assess the feasibility of capturing the study dataset using the eDCF, confirm that data collection can be achieved efficiently, and also establish that the data collection method is suitably robust.

11. Study sample size

Given the descriptive nature of this study, a preliminary estimation of the required sample size is expressed in terms of precision and not statistical power. It is expected that approximately 100 patients will be sufficient to generate reliable results, as determined by relatively narrow confidence intervals.

Table 3 Confidence limits for different sample sizes and mean doses of RAASi achieved

Mean dose (as % of target dose)	50 patients		100 patients		150 patients	
	LCL	UCL	LCL	UCL	LCL	UCL
90%	82%	98%	84%	96%	85%	95%
80%	72%	88%	75%	85%	76%	84%
70%	63%	77%	65%	75%	66%	74%
60%	54%	66%	56%	64%	57%	63%
50%	45%	55%	47%	53%	47%	53%
40%	34%	46%	36%	44%	37%	42%
30%	23%	37%	25%	35%	26%	32%

LCL – lower confidence limit

UCL – upper confidence limit

The table shows that the reliability of estimates for the mean dose of RAASi achieved (as a percentage of the target dose) improves when the study sample is increased from 50 to 100

patients. This is applicable for relatively small or large percentages of the target dose achieved. Reliability does not improve much more when the sample size is increased from 100 to 150 patients. Therefore, approximately 100 patients will be sufficient to generate reliable results for the primary endpoint. The number of patients in the study will be allocated as follows: 50% (approximately n=50) with CKD and HF and 50% (approximately n=50) with CKD and T2DM. This distribution includes patients with all three conditions: CKD, HF and T2DM.

12. Statistical analysis

Analyses will be performed by pH Associates. Data from all centres will be pooled for analysis. Distributions and descriptive statistics of central tendency (medians and arithmetic means) and dispersion (standard deviation, interquartile range) will be presented for quantitative variables wherever possible. Categorical variables will be described with frequencies and percentages. Ordinal variables will also have medians and interquartile ranges described. 95% confidence intervals will be presented for estimates of proportions and means of distributions.

Between-group differences (for drug type and patient group) will be evaluated by unpaired t-tests, Wilcoxon rank-sum test or chi-square test, as appropriate. Within-group differences will be assessed by paired sample t-test, Wilcoxon matched-pairs signed-ranks test or McNemar test, as appropriate. 95% confidence intervals will be presented for estimates of proportions and means of distributions, as appropriate. Additional statistical tests may be applied, as appropriate to the data. Statistical analyses will be carried out using Stata version 14 (StataCorp LLC) and Microsoft Excel™ 2010. A technical overview of study reporting will be provided in a statistical analysis plan (SAP) before data collection is completed.

12.1 Missing data

As data will be collected retrospectively, the quality of the study dataset will depend on the accuracy and completeness of information recorded in patients' records in secondary care

and primary care. Data fields that are missing will be left blank. Where data on study variables are not available, fields will be marked as 'not known' rather than left empty. Checks will be made to confirm that data are truly missing and that the data extraction process from patient records was error free.

Where data are missing from the original medical record, the affected analyses will be conducted using only the results of those patients with data available (complete case analysis) and the number of patients included in each analysis will be stated. The percentage of data missing will be reported for each study variable. Missing data in itself will be of interest and should provide insight into the way patients are being managed in the 'real world' UK setting, outside of the methodological constraints of a clinical trial. No statistical methods will be applied to address missing data in the analyses.

13. Review of study results

There are no plans for independent review of the study results by the sponsor, through an independent peer review committee or investigator meeting.

14. Study limitations

To maximise the generalisability of the results, a group of study centres that are as representative of the real world NHS setting as possible will be identified and recruited to the study. Nevertheless, there may be methodological limitations that affect the interpretation of the results, which are described as follows:

- As patient consent is required from living patients for this study, selection bias is possible since patients who provide consent may differ from those who decline participation. This may result in a sample that may not be representative of the wider population of interest and an under- or over-estimate of some endpoints of the study. The consent rate in the study sample will be reported in order to allow assessment of whether such bias in the sample may be significant. However, it is expected that the proportion of deceased patients in this study will be small and

therefore the potential impact of associated biases on the study results will be limited.

- As only patients with 12 months of follow up data will be included in the study, patients who died or were discharged from outpatient care within the follow up period will be excluded. The number of patients affected by this is likely to be small and, consequently, there should be minimal potential bias due to their exclusion from the study.
- Data collected retrospectively will rely on the completeness and quality (including accuracy) of the medical records. The impact of poor quality data has been minimised by robust feasibility testing of the protocol framework during its development and additional evaluation during site selection. Furthermore, training of all data collectors and SDV will ensure consistent data collection and adherence to the study protocol.
- The study sample size may be inadequate to show results with adequate statistical precision, due to differences in patient and/or treatment characteristics in the published studies that were used to guide the choice of sample size.
- There will be inconsistencies in the availability of primary care prescribing data and haematology and biochemistry test results through secondary care computer systems and paper medical records. During study development and set up, study centres with access to the required primary care data will be identified to reduce the potential effects of missing or incomplete data.

15. Pharmacovigilance

15.1 Reporting procedures for adverse events

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, is provided on an aggregate level only; no reporting on an individual case level is required. In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions should be summarised in the study report, i.e. the overall association between an exposure and an outcome. Relevant

findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

15.2 Definitions

15.2.1 Adverse events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an AE includes worsening of a pre-existing medical condition.

15.2.2 Serious adverse events

A serious adverse event (SAE) is any adverse drug reaction as defined above that:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

A serious adverse drug reaction (SADR) is a serious adverse event that is considered related to the medicinal product. A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility. “Other significant medical hazards” refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an

emergency room visit, outpatient surgery, or other events that require other urgent intervention.

16. Ethical and regulatory obligations

16.1 Protection of human subjects

This study will comply with all applicable laws, regulations, and guidance regarding patient protection, including patient privacy. As the study will make use of medical records, compliance with the HIPAA Privacy Rule (46 CFR Part 160; Part 164 (subparts a, e)) is required.

To maintain subject confidentiality, no demographic data that could be used to identify the patient will be collected (e.g. name, date of birth). Only gender and the month and year of birth (to calculate age) will be collected. In order to protect patients' identity, a study-specific unique number (study ID) will be assigned to each patient and related study records. Patients' study ID will only be linked to their name and hospital identification number on a patient recruitment log which will remain in the secure custody of the study team at each centre and will not be disclosed to any person outside the centre study team, not even pH Associates staff involved in the study. This log will not leave the corresponding NHS Trust/Health Board and will be the responsibility of the principal investigator at each study centre.

This study will use data available within secondary care, including patient information from primary care that is provided within medical records in secondary care. Permission will not be sought to directly access primary care medical records. Since this observational study relies only on data collected from medical records in secondary care that are anonymised for study use, no risks or benefits to patients participating in the study are expected. Patients will have no direct involvement in the study with the exception of providing their informed consent for data to be collected from their medical records. There will be no change to the management of patients as a result of taking part in the study.

17. Study timelines

The key milestones of this study are shown in Table 4.

Table 4 study timelines

Study milestone	Expected date(s)/frequency
Start of data collection	March 2018
End of data collection	July 2018
Data analysis	July – August 2018
Study progress reports	By telephone every two weeks
Submit final report of study results	September 2018

18. Administrative and legal obligations

18.1 Study amendments and study termination

Amendments must be made only by prior agreement between Vifor Fresenius Medical Care Renal Pharma UK Ltd, pH Associates and Robin Ray, Chief Investigator. The Research Ethics Committee (REC) must be informed of all amendments and give approval for substantial amendments. The Chief Investigator must send a copy of the approval letter from the REC to Vifor Fresenius Medical Care Renal Pharma UK Ltd.

pH Associates, Vifor Fresenius Medical Care Renal Pharma UK Ltd, and the investigator reserve the right to terminate participation in the study according to the study contract. pH Associates will notify the REC in writing of the study's completion or early termination and send a copy of the notification to Vifor Fresenius Medical Care Renal Pharma UK Ltd and the Chief Investigator.

18.2 Study documentation and archive

All electronic data files will be securely stored on a password-protected internal, UK-based server at pH Associates and all study-related documents will be kept in a locked cupboard when not in use. Access to the study database will be restricted (by password protection)

and only granted to pH Associates staff who are directly involved with the study. Completed eDCFs will be transmitted in real time over a secure internet connection to pH Associates. The principal investigator (PI) at each centre must ensure that information entered onto the eDCF is traceable to the source documents in patients' medical record (paper or electronic). Changes to the eDCF will recorded in the MACRO audit trail, including changes in response to data queries, SDV and data entry errors.

18.3 Ethical and regulatory approvals

Data collection may be carried out by either the NHS clinical care team at each centre or pH Associates. Therefore, this study will be submitted for NHS Research Ethics Committee (REC) approval via the Health Research Authority (HRA), in line with the harmonised edition of the Governance Arrangements for Research Ethics Committees (GAfREC)[11]. NHS management approval for local conduct of the study will be sought through the Research and Development (R&D) department in each participating NHS Trust/Health Board. The study will also be submitted for inclusion in the National Institute for Health Research (NIHR) portfolio of research studies.

18.4 Ethical issues

This is an observational research study where only living patients providing written informed consent will be included in the study and no data collection will take place until written informed consent has been provided (except for deceased patients whose data will be collected by members of the NHS care team to preserve patient confidentiality).

19. Communication of study results

When the study has been completed and the study report is finalised, the results of this observational study may either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with Vifor Fresenius Medical Care Renal Pharma UK Ltd's standards and the STROBE (Strengthening the Reporting of OBservational Studies in Epidemiology) checklist for cohort, case-control, and cross-sectional studies (combined checklist)[12].

Authorship of publications arising from the study will follow the guidelines proposed by the International Committee of Medical Journal Editors (2015)[13].

All authors will have:

- made substantial contributions to conception or design or acquisition of data, or analysis and interpretation of data; AND
- participated in drafting the article or revising it critically for important intellectual content; AND
- approved the final version to be published.

Each author will meet all of these conditions and all individuals meeting these criteria will be authors. Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author will have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Potential conflicts of interest will be disclosed.

20. Study support

Vifor Fresenius Medical Care Renal Pharma UK Ltd, the study sponsor, have commissioned pH Associates Ltd to develop materials for and co-ordinate the conduct of the study, including protocol development, ethical and local approval, retrospective data collection, analysis and presentation of the results. pH Associates is an independent consultancy specialising in the evaluation of healthcare services and interventions in the NHS through observational research, with a focus on the design and implementation of 'Real World Data' projects in order to understand current NHS practices.

21. References

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22. Appendices

Appendix 1 Drugs of interest

Drug name	Drug type	Start dose	Target dose
Captopril	ACEi	6.25 mg three times daily	50 mg three times daily
Enalapril	ACEi	2.5 mg twice daily	10-20 mg twice daily
Lisinopril	ACEi	2.5-5 mg once daily	20-35 mg once daily
Perindopril	ACEi	2-4 mg daily	8 mg daily
Ramipril	ACEi	2.5 mg once daily	10 mg once daily
Trandolapril	ACEi	0.5 mg once daily	4 mg once daily
Candesartan	ARB	4-8 mg once daily	32 mg once daily
Eprosartan	ARB	600 mg once daily	-
Irbesartan	ARB	150 mg once daily	300 mg once daily
Losartan	ARB	12.5-50 mg once daily	150 mg once daily
Sacubitril/Valsartan (Entresto®)	ARB	49/51 mg twice daily	97/103 mg twice daily
Telmisartan	ARB	20–40 mg once daily	80 mg once daily
Valsartan	ARB	40 mg twice daily	160 mg twice daily
Eplerenone	MRA	25 mg daily	50 mg daily
Spironolactone	MRA	25 mg daily	50 mg daily

Sources: European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure, 2016. Available from https://academic.oup.com/eurheartj/article/37/27/2129/1748921 and British National Formulary. Available from https://bnf.nice.org.uk