FULL/LONG TITLE OF THE TRIAL

Patiromer-facilitated, dose-escalation of mineralocorticoid antagonists for the management of worsening congestion in people with heart failure and hyperkalaemia.

A Phase IV, registry-based, randomised, controlled, open-label trial investigating the potential for patiromer-facilitated use of higher doses of mineralocorticoid antagonists in addition to standard care (compared to standard care alone) to improve congestion, well-being, morbidity and mortality.

SHORT (Patient & Public Friendly) TRIAL TITLE

Can patiromer (a substance that binds potassium in the gut) enable use of higher doses of medicines to improve outcomes for people with worsening heart failure?

ACRONYM

RELIEHF: **REL**ieving **I**ncreasing o**E**dema due to **H**eart **F**ailure

PROTOCOL VERSION NUMBER AND DATE

Version 5.0, 22 July 2021

RESEARCH REFERENCE NUMBERS

IRAS number:	253294
EudraCT number:	2018-003662-14
ISRCTN number / Clinical trials.gov number:	NCT04142788
SPONSORS number:	GN17CA082
FUNDERS number:	Ph4Study_0213

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given, and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:  Date: 8th /Nov/2021

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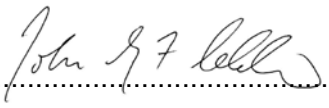
Name: Pamela Sandu

Position: Research Coordinator

Greater Glasgow & Clyde NHS Board

Chief Investigator:

Signature:  Date: 5th / Nov. / 2021

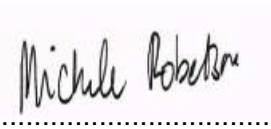
.....

Name: John GF Cleland

Position: Director - Robertson Centre for Biostatistics & Glasgow CTU
& Honorary Consultant Cardiologist

University of Glasgow / Greater Glasgow & Clyde NHS Board

Statistician:

Signature:  Date: 9th November 2021

.....

Name: Michele Robertson

Position: Assistant Director Commercial Biostatistics

Robertson Centre for Biostatistics & Glasgow CTU

University of Glasgow

KEY TRIAL CONTACTS:

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Clinical Trials Unit	Glasgow Clinical Trials Unit Robertson Centre for Biostatistics, 11th Floor Boyd Orr Building University of Glasgow Glasgow G12 8QQ Tel: 0141 330 4744 Fax: 0141 357 5588
Statistician	Michele Robertson Glasgow Clinical Trials Unit Robertson Centre for Biostatistics, 11th Floor, Boyd Orr Building University of Glasgow Glasgow G12 8QQ Tel: 0141 330 4744
Trials Pharmacist	Dr Elizabeth Douglas Senior Clinical Trials Pharmacist R&D Clinical Research and Development NHS Greater Glasgow & Clyde Ward 11, Dykebar Hospital Grahamston Road Paisley PA2 7DE Tel: 0141 314 4073 E-mail: elizabeth.douglas@ggc.scot.nhs.uk
Committees	Trial Steering Committee TBC Trial Management Group TBC Trial Endpoints Committee TBC Independent Data Monitoring & Ethics Committee TBC

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CEC	Clinical Endpoints Committee
CI	Chief Investigator
CRT-D	Cardiac Resynchronisation Therapy Defibrillator
CRT-P	Cardiac Resynchronisation Therapy Pacemaker
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigator Brochure
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mineralocorticoid antagonist
NHS R&D	National Health Service Research & Development
NYHA	New York Heart Association
PGA	Patient Global Assessment
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure

SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY

Trial Title	**REL**ieving **I**ncreasing o**E**dema due to **H**eart **F**ailure	
Internal ref. no. (short title)	RELIEHF	
Clinical Phase	Phase IV	
Trial Design	A registry-based, randomised (two equal-sized groups),open-label trial	
Trial Participants	People with heart failure, worsening symptoms and signs of congestion and serum potassium >5.0mmol/L (participants may or may not already be receiving a mineralocorticoid antagonist)	
Planned Sample Size	Phase A: 400 participants completing 60 days follow-up Phase B: 2,000 participants	
Treatment duration	Up to 5 years	
Follow up duration	Trial follow-up will continue until a minimum of 750 patients has incurred a primary outcome event. It is anticipated that this will occur approximately 5 years after recruitment of the first patient. Patients will be followed by linkage to their electronic medical records for hospitalisation and death for up to 5 years after trial completion.	
Planned Trial Period	Up to 5 years	
	Objectives	**Outcome Measures**
Primary for the Randomised Trial (long-term follow-up)	• To reduce morbidity and mortality	• Composite of time to need for parenteral diuretic therapy (subsequent to initial discharge) for worsening or recalcitrant heart failure, (re-)hospitalisation for worsening heart failure or non-cancer deaths.
Other Primary	**Registry:** • To assess morbidity and mortality **Randomised Trial –to Day 60:** • To improve congestion	**Registry:** • Composite of time to (re-)hospitalisation or death **Randomised Trial –to Day 60:** • "Congestion Index" on Day 60
Key Secondary	**Registry:** • To describe participants characteristics and assess morbidity and mortality *(Note that the registry also includes all patients in the randomised trial.)*	**Registry** • Time to cardiovascular (re-)hospitalisation or non-cancer death • Time to heart failure (re-)hospitalisation or non-cancer death

		• Incidence rate for hospitalisation (all-causes, cardiovascular causes, heart failure causes, cancer causes – separately) • Time to death (all-causes, cardiovascular causes, heart failure causes, cancer causes, and other)
Key Secondary	**Randomised Trial – to Day 60:** • Dose of MRA achieved • Further evidence of improved congestion	**Randomised Trial – to Day 60:** • Dose of MRA (Days 7 & 60) • Congestion Index (Days 7& 60) • Days dead or hospitalised during the first 60 days • Individual Components of the Congestion Index (Days 7 &60) • Quality of Life at (Days 7 &60) • NYHA class (Days 7 &60) • Patient Global Assessment (PGA) (Days 7 &60)
Key Secondary	**Randomised Trial (long-term follow-up):** • To reduce mortality • To reduce morbidity, increase longevity and increase quality-adjusted life-years.	**Randomised Trial (long-term follow-up):** • Mortality – All-Cause – Non-Cancer – Cardiovascular • Days lost to hospitalisation for heart failure or non-cancer deaths over 12 months • Days lost to any hospitalisation or any death over 12 months • Quality adjusted life-years for the duration of the trial • Proportion alive & well at 12 months (well-being defined by quality of life score) • Dose of MRA at 6 & 12 months • Dose of oral diuretics other than MRA at 6 & 12 months • NYHA class at 6 & 12 months • Patient Global Assessment (PGA) at 6 & 12 months
Investigational Medicinal Product(s)	• Patiromer *(compared to no patiromer)* • Spironolactone/Eplerenone *(dose should differ between those assigned to patiromer or not)*	

Formulation, Dose, Route of Administration	**Patiromer:** initially 8.4g/day as a powder dissolved in water or apple juice taken orally. Should be titrated, with the patient's agreement, to 16.8g/day or 25.2g/day depending on serum potassium. **Spironolactone:** oral tablets in doses ranging from 25mg once or more per week up to 200mg/day guided by serum potassium concentrations. *(Licensed dose is up to 200mg/day for oedema and 400mg/day for ascites – many patients in this trial will have both conditions).* **Eplerenone:** oral tablets in doses ranging from 25mg once per week to 50mg/day guided by serum potassium concentrations for patients who have developed troublesome gynaecomastia or other troubling feminising side-effects from spironolactone. *(Licensed dose is up to 50mg/day; note that 50mg of eplerenone probably equates only to 30-40mg/day of spironolactone)* Patients taking Eplerenone who have no contraindications to spironolactone should switch to spironolactone at baseline or during the run-in phase.

FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
VIFOR Pharma Management AG Fabio Dorigotti Flughofstrasse 61 Postfach CH-8152 Glattbrugg Switzerland Tel: +41 58 851 80 00 Email: fabio.dorigotti@viforpharma.com	According the outstanding contract: Financial support for the clinical trial and provision and distribution of patiromer (Veltassa).

ROLE OF TRIAL SPONSOR AND FUNDER

NHS Greater Glasgow & Clyde and The University of Glasgow will be Co-sponsors of the trial. Prior to trial initiation, a non-commercially funded clinical trial co-sponsorship agreement will be put in place between NHS Greater Glasgow & Clyde and The University of Glasgow. The roles and liabilities each organisation will take under The Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2001:1031 are laid out in this agreement signed by both organisations. The University of Glasgow shall be responsible for carrying out the obligations and responsibilities set out in the aforementioned agreement, and shall be deemed "sponsor" for the purposes of, Part 3 of the regulations in relation to the trial. NHS Greater Glasgow & Clyde shall be responsible for carrying out the responsibilities set out in the agreement, and shall be deemed "sponsor" for the purposes of, Parts 4, 5, 6 and 7 of the Regulations in relation to the trial.

The Co-Sponsors will delegate specific roles to the Chief Investigator, Glasgow CTU and other third parties. These arrangements will be clearly documented in agreements and/or the Sponsor Delegated Roles and Responsibilities Matrix.

This is an investigator-initiated trial. Vifor Pharma will supply and deliver Patiromer free of charge and fund the trial (including the cost of acquiring generic spironolactone and eplerenone at standard NHS prices and any cost for labelling and dispensing for trial purposes). Vifor Pharma does not have a designated role or responsibility in trial design, conduct, data analysis and interpretation, manuscript writing, or dissemination of results. Two representatives from Vifor Pharma will be invited to attend TSC meetings as observers. Support from Vifor Pharma will be acknowledged in any publications related to the trial.

The Funder has the opportunity to comment on any aspect of the trial and open minutes of the Trial Steering and Independent Data Monitoring Committees but will not have access to individual patient de-identified data until after the trial is completed and the primary result has been accepted for publication. Access to data obtained from linkage to electronic medical records will be subject to national regulations. The Funder may withdraw funding subject to contract conditions and this may influence the Sponsors' decision on whether to continue with the trial.

Glasgow Clinical Trials Unit will manage the trial, which will be conducted in up to 100 centres in the UK, including designing the case report form, providing randomisation, managing data and statistical analyses.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

- **Trial Steering Committee (TSC)**
  The TSC will provide overall supervision of the trial, ensure that it is conducted in accordance with the principles of GCP and relevant regulations and be responsible for interpretation, manuscript writing and dissemination of the primary results

  The TSC will include the chief investigator, clinical experts, a statistician, a non-clinical representative of the trial management group, at least two patient or carer representatives, up to two VIFOR Pharma representatives (non-voting) and a sponsor's representative. The TSC may invite other attendees from the trial team to present or participate in discussions on particular topics. These attendees will be non-voting members.

  The TSC will have its own charter outlining the role and responsibilities of its members, as well as meeting and reporting formats. Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the TSC who will advise the sponsor and the funder. The TSC will meet at the start of the trial, and regularly thereafter. Meetings can also be requested by co-sponsors and/or funder.

- **Independent Data Monitoring Committee (IDMC)**
  The IDMC will comprise at least two independent medical experts (covering the domains of renal and cardiovascular disease one of whom will act as chair) and an independent biostatistician. The Glasgow CTU will provide regular reports on participant safety, trial progress and serious adverse events. The IDMC will have a formal charter; this will outline the responsibilities of the IDMC members, Glasgow CTU and the co-sponsors.

  Responsibilities include:
  - ensuring the safety of trial participants
  - reviewing information (in full knowledge of treatment allocation and treatment actually received) provided by the Glasgow CTU including trial recruitment, adverse events and outcomes
  - advising the TSC if it is safe and appropriate for the trial to continue.

  The IDMC may recommend to the TSC that the trial should stop prematurely because of concerns about patient safety or conclusive evidence of overwhelming benefit. The IDMC will meet after 100,

200, 400, 1,000, 1,500 and 2,000 patients have completed 60-day follow-up and at other times as decided by the committee/requested by Co-sponsors.

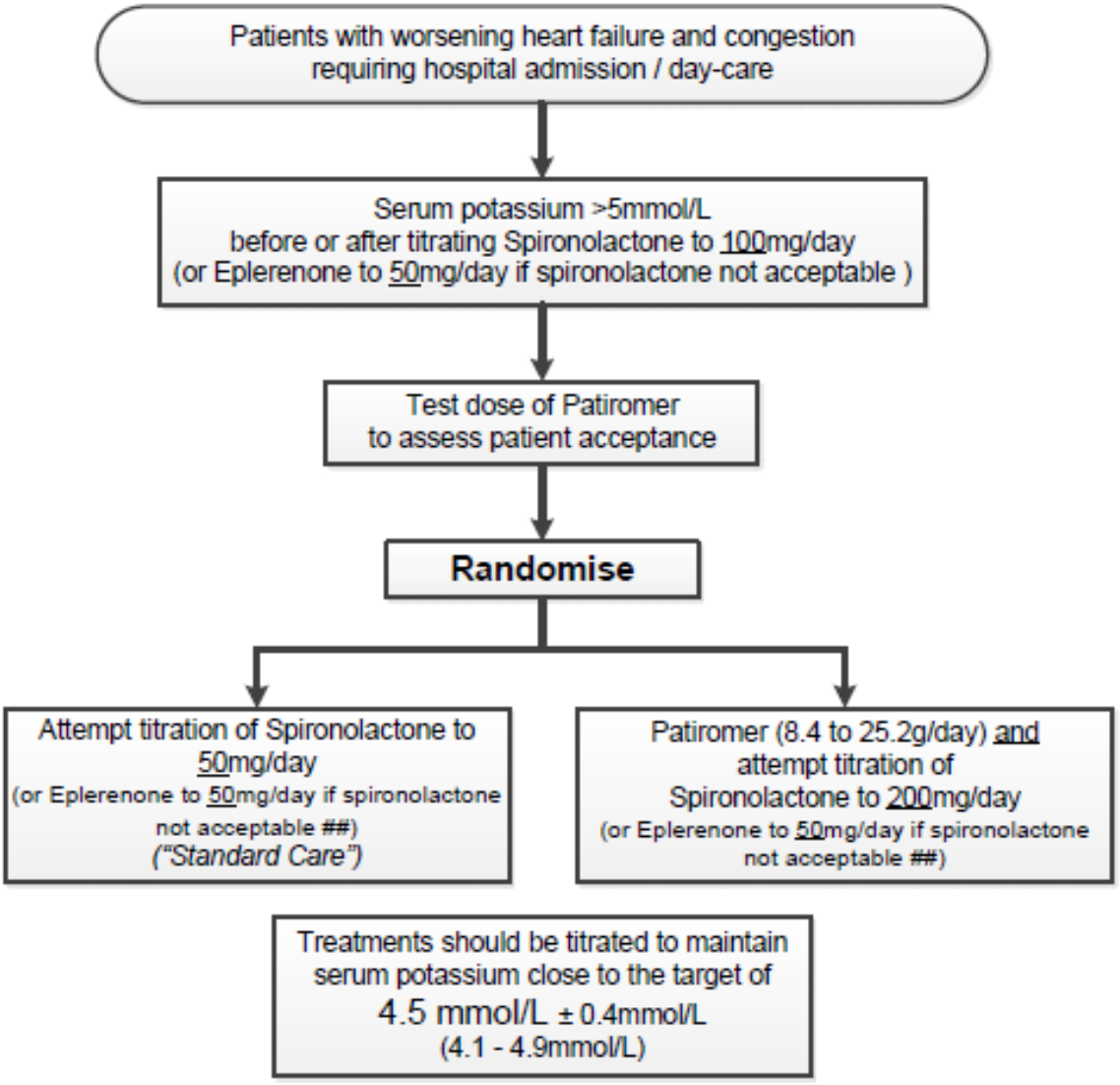
- **Trial Management Group (TMG)**
  The TMG will consist of the chief investigator, one or more nominated delegates from the trial team, a project manager and representatives from the Glasgow CTU, NHS Greater Glasgow & Clyde (NHS GG&C) and the University of Glasgow. The TMG will monitor practical aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

- **Clinical Endpoints Committee (CEC)**
  The CEC will use a charter developed within the Glasgow CTU to adjudicate cardiovascular and heart failure events. The CEC will be chaired by an independent consultant cardiologist who will provide guidance and training to a group of physicians under their direction.

KEY WORDS: Heart Failure, Congestion, Oedema, Mineralocorticoid Antagonist, Aldosterone Antagonist, Spironolactone, Eplerenone, Potassium, Patiromer, Randomised Trial

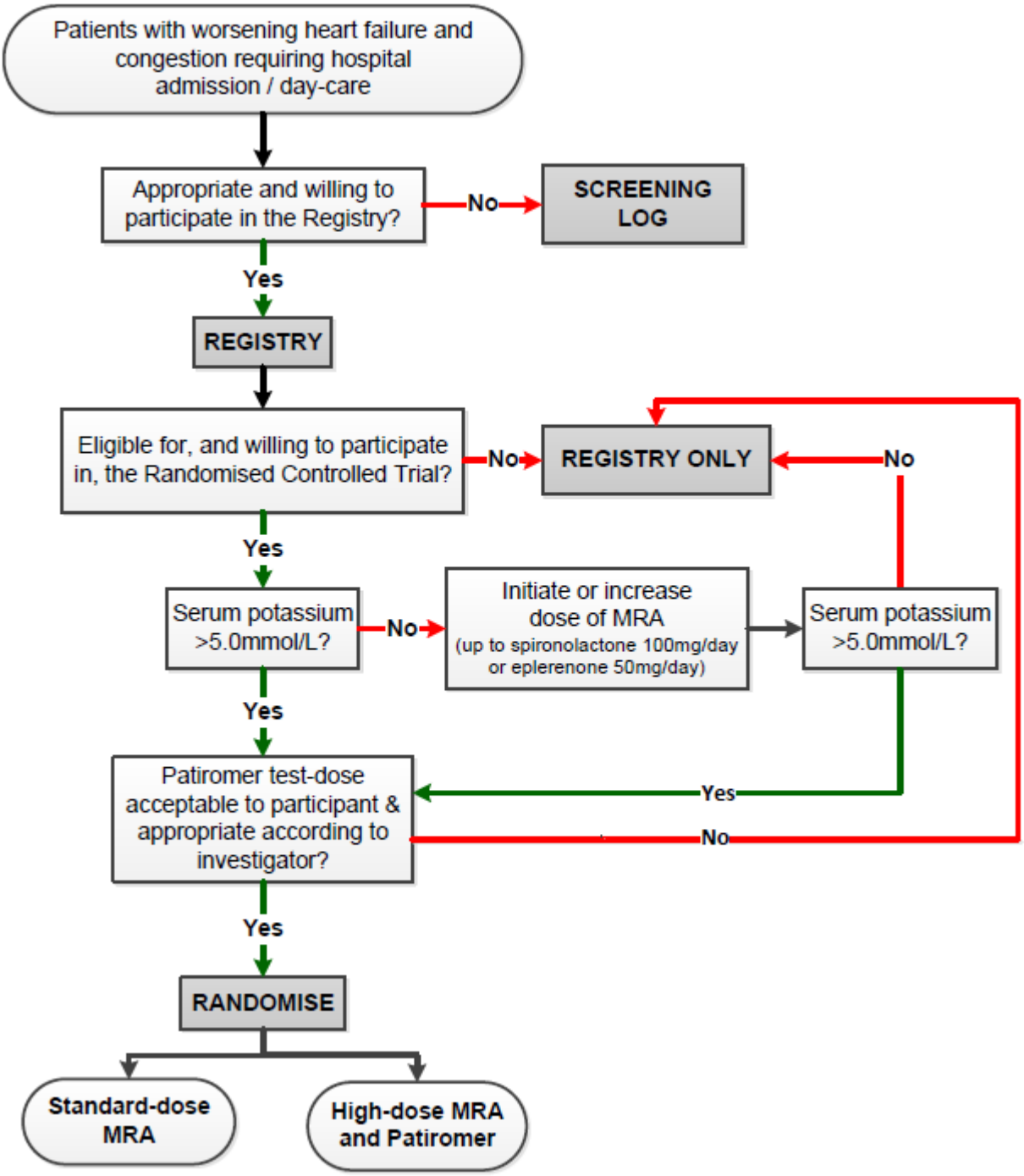
TRIAL FLOW CHART

(i) Simplified flow chart



According to the British National Formulary the maximum permitted dose of spironolactone is 400mg/day but of eplerenone only 50mg/day with a starting dose for the management of oedema (including heart failure) of 100mg/day and 25mg/day respectively. Spironolactone is the predominant MRA used in the UK and, we anticipate, in this trial. Most patients are currently treated with spironolactone or eplerenone in doses of 25mg/day or less. Eplerenone 50mg/day probably has similar MRA activity to ~35mg/day of spironolactone.

(ii) Full flow chart including screening log and registry



1. BACKGROUND

Poor control of congestion is one of the most important unmet needs for patients with heart failure (1). Congestion is an important cause of symptoms, disability and recurrent hospitalisation that commonly results in death due to heart failure, respiratory infection or multiple organ failure.

About half of all hospital admissions with a primary diagnosis of heart failure present with peripheral oedema (>50,000 per year in the UK) (2), usually associated with orthopnoea and dyspnoea on minimal exertion (although often not at rest when sitting upright). The underlying pathophysiology in these cases is fluid retention that has developed over days or weeks (3, 4). It is perhaps misleading to use the term “acute” heart failure in such cases, which implies a medical emergency requiring a response within minutes. The term “subacute” heart failure may better convey the status of such patients, for whom a response time measured in days or weeks is appropriate. Indeed, there is growing interest in managing such patients with home-based subcutaneous furosemide or day-care ‘furosemide lounges’ (5). Although the presentation of “sub-acute” heart failure is less dramatic than for acute pulmonary oedema, patients with sub-acute congestion typically have longer hospital stays (in excess of 10 days) and a poorer prognosis, perhaps reflecting more advanced “right heart” dysfunction and organ congestion (1, 6). Hepatic congestion, which impairs the degradation of aldosterone, and renal congestion both exacerbate sodium retention and congestion.

Although many studies of acute heart failure have been conducted, these have focussed on emergency treatment of breathless patients rather than the management of subacute worsening of congestion. ***Few substantial studies focussing on patients with worsening congestion and peripheral oedema have been published.*** The CARRESS study of ultrafiltration conducted in the USA is perhaps the closest precedent. It failed to show that ultrafiltration was superior to high-dose intra-venous furosemide. By 60 days, almost 40% of patients had died or been re-hospitalised for heart failure (mortality was 15%) (7). A sub-group analysis of the RELAX-AHF trial (6) suggested that 15% of those with moderate/severe oedema would die or be re-admitted for heart failure by 60 days (mortality was about 6%).

Spironolactone, a mineralocorticoid antagonist (MRA), is on the World Health Organization's List of Essential Medicines. It has been used to treat congestive heart failure for >50 years. Until the advent of angiotensin converting-enzyme (ACE) inhibitors, doses of 100-200mg/day were commonly used (8). With the advent of ACE inhibitors in the late 1980s, use and doses of MRA declined. However, in 1999, the RALES trial showed that, for patients receiving ACE inhibitors, spironolactone, titrated up to 50mg/day, markedly reduced re-hospitalisation and mortality in advanced heart failure (9). Pilot-trials suggested that higher doses of spironolactone (75mg/day) were limited by hyperkalaemia (10). Subsequently, two large trials of eplerenone (up to 50mg/day) and several smaller trials of other MRA demonstrated reductions in morbidity and mortality in a broad range of patients with left ventricular dysfunction after myocardial infarction or heart failure.

MRA increase urinary sodium excretion, helping relieve congestion, and cause potassium retention. Some also believe that MRA have effects on sympathetic activation and fibrosis that may be beneficial (11). Whether higher doses of MRA are more effective at improving congestion or reducing fibrosis is uncertain. However, several factors limit the use and dose of MRA for patients with heart failure, particularly hyperkalaemia (12).

Patients with heart failure and severe congestion usually have moderate to severe renal impairment and are therefore at high risk of hyperkalaemia when treated with MRA. MRA may worsen renal function in patients who are not severely congested. However, congestion may be one of the causes of renal dysfunction in this population due to high renal vein pressures. Reduction in severe congestion by MRA might improve renal function (13). MRA may also reduce arterial pressure in patients who are not severely congested but this may be due to excessive reduction in left ventricular

filling pressures. This may not occur until overt clinical congestion is corrected and might then be managed by reducing doses of loop diuretics.

There is a wealth of evidence to show that MRA improve outcome when added to ACE inhibitors. However, the incremental value and safety of using higher doses (as in the pre-ACE inhibitor era) for patients with hepatic congestion and renal dysfunction at high risk of hyperkalaemia is unknown. Higher doses might be highly effective, no more effective than conventional management or might be unsafe unless closely monitored.

Patiromer is an oral potassium-binding agent that reduces serum potassium concentrations in patients with heart failure and renal dysfunction taking contemporary therapy for heart failure including MRA (14, 15). Routine administration of patiromer should allow more patients to be treated with MRA and at higher doses, which may help treat and control congestion more effectively, leading to improved symptoms and reduced morbidity and mortality. Hypotension and renal dysfunction may also limit the use of MRA but can be managed by using lower doses of conventional diuretics or of other medications that don't have important dose-related benefits in severe heart failure (e.g. ACE inhibitors (16, 17)) or in atrial fibrillation (e.g. beta-blockers (17, 18), which is likely to affect >50% of patients in this trial. Moreover, controlling congestion might reduce renal venous pressure and improve renal function (13). Thus, patiromer-facilitated use of higher doses of MRA might manage congestion more effectively. Although patiromer is not absorbed and has a favourable benefit-risk profile, there are concerns about adherence to medication; if a patient stops taking an MRA but continues on patiromer then they are at risk of hypokalaemia; if they stop taking patiromer but continue with an MRA then they are at risk of hyperkalaemia. Educating participants and investigators to ensure adherence and to seek medical advice before adjusting the dose/intake of either is essential.

Accordingly, we plan to conduct a randomised controlled trial to investigate the potential of patiromer to facilitate the use of higher doses of MRA for patients with heart failure, worsening congestion and hyperkalaemia to find out whether this strategy improves the control of congestion and patient well-being and reduces morbidity and mortality.

2. RATIONALE & DESIGN

Rationale: People with worsening congestive heart failure may benefit from treatment with higher doses of MRA if they are administered patiromer to treat or prevent hyperkalaemia.

Design: We will identify potential participants with worsening heart failure identified by their care-teams. Those considered eligible will be asked to provide consent for participation in a registry and give permission for collection of further medical information and personal identifiers to enable long-term follow-up through electronic medical records. Patients who are not approached (*e.g.* those with severe cognitive dysfunction) or who decline to participate will have only a small amount of (de-identified) data collected from their medical records in a screening log, as recommended by the Health Research Authority.

The **consented registry** has several functions:

1. The registry has no exclusion criteria (other than the need for consent) and therefore should be similar to the population requiring management of congestion in clinical practice. This will identify the proportion of people in clinical practice who are potentially eligible for patiromer.
2. We believe that the registry will boost trial recruitment, as it will be relatively easy to enrol a large number of potential participants and to randomise trial participants from this pool. This will address low levels of investigator engagement often caused by demanding protocols that create a vicious downward spiral of low recruitment leading to low research resource allocation.

3. The registry will provide an opportunity to investigate why potential participants are not enrolled in trials.
4. Participants will be asked if they are willing to be approached about future research.

The **randomised trial** will investigate whether patiromer allows patients with worsening heart failure to be titrated to higher doses of MRA (predominantly spironolactone). Participants who are not assigned to patiromer should have titration to guideline-recommended doses of MRA attempted, although many are anticipated not to achieve this. Patients assigned to patiromer may be titrated to 200mg/day of spironolactone (highest licensed dose 400mg/day) or the highest licensed dose of eplerenone (50mg/day). (Eplerenone 50mg/day has similar MRA potency to about 35mg/day of spironolactone; accordingly, spironolactone is the preferred MRA. We expect that the median dose of spironolactone (or eplerenone) in the control group will be 25mg/day and that up to 25% will not tolerate any dose of MRA due to hyperkalaemia or other reasons.) We expect that the median dose of spironolactone in the patiromer-facilitated arm will be about 100mg/day because hypotension and renal dysfunction will prevent many patients from being titrated to 200mg/day and that almost all randomised patients will tolerate some dose of MRA.

The trial is **open-label**, which reduces complexity for participants (those assigned to the control group are not required to take a placebo), increases participant-safety (participants taking patiromer know that if they stop taking either patiromer or MRA this may cause problems), helps investigators and other health professionals manage clinical problems and reduces the logistic complexity of pharmacy trial-supply.

There are **two phases** to the randomised trial: during the first 60 days, the main aim is to control congestion, thereby improving well-being and reducing the need for hospital care; the long-term aim is to reduce morbidity and mortality. Good control of congestion might reduce the risk of death not only from heart failure but also from arrhythmias (including atrial fibrillation and therefore stroke), bronchopneumonia and end-stage renal disease but is unlikely to alter mortality due to cancer within the time-frame of this trial and consequently cancer deaths will not comprise part of the primary endpoint, although they will be recorded. Potentially spironolactone could have a favourable effect on some cancers (e.g. prostate cancer (19)). Evidence for a detrimental effect on sex-hormone sensitive cancers is lacking (20, 21).

This research will determine whether patiromer allows more patients to be treated with higher doses of an MRA, thereby potentially improving the management of congestive heart failure, shortening hospital stay, improving patient well-being, reducing re-interventions and readmissions for worsening heart failure and reducing non-cancer deaths (we do not anticipate an effect on cancer deaths). Both clinicians and patient-advisers believe these goals of treatment are worthwhile.

3. ASSESSMENT AND MANAGEMENT OF RISK

The independent data monitoring committee (IDMC) will review all serious adverse events with particular attention to interventions for and serious consequences of hypo- and hyperkalaemia, symptomatic hypotension and renal dysfunction and may recommend changes to the protocol during the course of the trial.

Patiromer binds potassium in the gut and is not absorbed. It has no direct cardiovascular action. The initial dose is 8.4g/day suspended in water or apple juice and it may be increased to 16.8g or 25.2g/day, either by taking multiple sachets or a higher-dose sachet. Patiromer suspension has a slightly gritty texture that some patients may be unwilling to take regularly. A test dose will be given prior to randomisation to ensure that the patient understands how to prepare patiromer and is willing to take patiromer long-term. Due to the potential for patiromer to bind to co-administered oral medicines in the gastrointestinal tract, administration of patiromer should be separated by at least 3 hours from other oral medicinal products. However, at investigator-discretion, patiromer may be co-administered with other medicines if data are available to indicate bioavailability is unlikely to be affected, based on

in vivo (in healthy volunteers) and *in vitro* studies (22, 23). A list of medicines that may be co-administered with patiromer is provided in section 9.8.

Patiromer may cause constipation in some people. This may be managed by diet, treatments for constipation or by reducing the dose of patiromer.

Patiromer may cause hypokalaemia and hypomagnesaemia (defined in this protocol as serum magnesium <0.75mmol/L) if insufficient doses of MRA are given (this may apply to participants in either arm of this trial). If the dose of MRA cannot be increased due to hypotension or renal dysfunction, this may be corrected by magnesium supplements or by reducing the dose of patiromer.

For patients who do not already have a serum potassium >5.0mmol/L, the initial dose of spironolactone will be 25mg/day for those who are spironolactone naïve and 50mg/day for those already receiving spironolactone or eplerenone at doses <50mg/day. Spironolactone may be increased to 100mg/day if serum potassium remains ≤5.0mmol/L despite 50mg/day of spironolactone or eplerenone. Only if serum potassium rises to >5.0mmol/L is the patient eligible for randomisation. If eGFR falls below 30ml/min/1.73m^2 or systolic blood pressure <90mmHg (and this cannot be corrected by altering the dose of other medications), then the patient is not eligible for the randomised trial and will return to standard care. The clinicians caring for the patient should then decide on the most appropriate dose of MRA.

Participants who have or develop a serum potassium >5.0mmol/L can be randomised directly into the trial provided they do not require intravenous treatment or a potassium binding agent for the treatment of severe hyperkalaemia in the investigator's opinion. Severe hyperkalaemia should be managed according to the UK Renal Association guidelines of 2020 (https://renal.org/sites/renal.org/files/RENAL%20ASSOCIATION%20HYPERKALAEMIA%20GUIDELINE%202020.pdf). Participants may be reconsidered for the trial once such interventions are no longer considered necessary. For patients assigned to patiromer, the dose of MRA should not be increased until serum potassium drops below 5.0mmol/L (see titration schedule). The dose of patiromer may be increased to achieve a serum potassium in the target range. For patients assigned to the standard care control group, the dose of MRA should be reduced to allow serum potassium to fall into the target range.

MRA (spironolactone or eplerenone) may cause hyperkalaemia, hypotension or renal dysfunction. Hyperkalaemia can be corrected by patiromer, which forms part of the rationale for this trial. If hypotension is symptomatic or renal function deteriorates, this can often be managed by adjusting doses of concomitant medications, including conventional diuretics and non-steroidal anti-inflammatory drugs or, failing that, the dose of MRA may be reduced.

In the RALES trial that enrolled patients with advanced heart failure and eGFR >30mls/minute and a serum potassium ≤5.0mmol/L, the target dose of spironolactone was 50mg/day and the mean daily dose achieved at two years was 26mg/day (compared to 31mg/day of the corresponding placebo). The median increase in serum potassium was 0.3mmol/L in those assigned to spironolactone compared to placebo. Of 1,663 patient randomised, 5.6% of those assigned to placebo developed a serum potassium >5.5mmol/L compared to 19.0% of those assigned to spironolactone. The treatment benefit of spironolactone was "maintained at least until serum potassium exceeded 5.5mmol/L" (24) Few patients developed severe hyperkalaemia (serum potassium >6.0mmol/L) in either arm of the trial (1.2% versus 3.9%). No change in average blood pressure occurred and the median increase in serum creatinine was <10umol/L. Worsening renal function, defined as a fall in eGFR by >30% occurred in 7% of those assigned to placebo and 17% of those assigned to spironolactone and appeared unrelated to changes in blood pressure. However, the greatest benefit of spironolactone on morbidity and mortality was observed amongst those with the worst renal function (25). The RALES pilot trial, 5% of patients developed a serum potassium >5.5mmol/L compared to 20% of those assigned to 50mg/day of spironolactone and 24% of those assigned to 75mg/day after 12 weeks of

therapy (26). The mean reduction in systolic blood pressure was 6mmHg.and rise in serum creatinine was 22umol/L. In the recent ATHENA trial (27), patients with acute heart failure were assigned to three days of at least partially-blinded treatment with a standard dose of spironolactone or 100mg/day followed subsequently by standard care. No difference in outcome at 30 days was noted. Serum potassium increased by 0.31mmol/L with 100mg/day of spironolactone compared to 0.15mmol/L in the control group (between group difference p=0.08). eGFR declined by about 5ml/minute/1.73m^2 in both groups. No patient in the higher dose group developed a serum potassium >5.5mmol/L.
A dose-adjustment algorithm for spironolactone is provided in this protocol (Section 9). Spironolactone (tablets of 25mg, 50mg or 100mg) will be supplied (open-label) in appropriately labelled containers for trial purposes. For patients who develop gynaecomastia or other feminising side effects on spironolactone, eplerenone (tablets of 25 or 50mg) will be supplied as an alternative. We assume that 10% of patients assigned to higher doses of spironolactone will develop gynaecomastia requiring a switch to eplerenone on average about 6 months into the trial. This is anticipated to apply to fewer than 200 patients. Switching patients to eplerenone may lead to a reduction in the effective MRA dose, which may then also require a reduction in the dose of patiromer. Investigators will be alerted to this possibility and monitor serum potassium accordingly (Appendix 3).

Currently, there is no evidence that facilitating the use of or higher-doses of MRA by using patiromer improves outcomes for people with heart failure. Currently, patients with hyperkalaemia would usually be managed by reducing the dose of, or stopping, the MRA.

An important risk is the discontinuation of one agent (either patiromer or MRA) but not the other. Participants will be educated accordingly by investigators and provided educational material, and reminders on the labelling of the relevant IMP. Participants will also be provided with a trial safety-card which they will be asked to carry with them at all times and show the card to any doctors or healthcare professionals who are involved in their care. Investigators will be educated by the protocol, site initiation visits, webinars and regular teleconferences. Participants' primary care physicians will be sent information by letter. Patients will receive supplies of both patiromer and MRA as appropriately labelled trial medications. They should be taken approximately three hours apart as indicated in patiromer's license. Treatment will be open-label, which will reduce confusion and uncertainty and avoid the needs and complexity of emergency un-blinding.

Patients will be closely monitored in this trial, with regular measurements of potassium, magnesium, renal function and blood pressure.

Women with childbearing potential will be excluded as the risks of patiromer in pregnancy are unknown (although unlikely to be a problem) and spironolactone poses risks to the developing foetus. Moreover, few women of childbearing potential are likely to be eligible for this trial. Most patients will be aged >60 years. Patiromer is not absorbed and therefore poses no risk to female partners of men who take patiromer.

This trial is categorised as Type B = somewhat higher than the risk of standard medical care.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Hypothesis: Compared to standard care, administering patiromer to patients who have worsening congestion due to heart failure and hyperkalaemia (defined as a serum potassium >5.0mmol/L) allows use of higher doses of mineralocorticoid receptor antagonists (MRA) thereby improving congestion and reducing cardiovascular morbidity and mortality.

4.1 Primary Objective

To find out whether patients with worsening congestion due to heart failure and hyperkalaemia who are randomised to patiromer (thus enabling the use of higher doses of MRA) have a lower rate of

worsening heart failure [defined as a composite of need for parenteral diuretic therapy (either intravenous [IV] or subcutaneous [SC]) for worsening or recalcitrant heart failure (subsequent to discharge from index episode of care), re-hospitalisation for worsening heart failure or non-cancer mortality] compared to patients assigned to a control group that does not receive patiromer.

4.2 Other Primary Objectives

For the Registry

To investigate the willingness of patients with worsening heart failure who require higher doses of diuretics to control worsening symptoms and signs of congestion to participate in a research registry and/or, in principle, a randomised trial (not necessarily this particular trial). Participants may or may not satisfy the criteria for enrolment in the RELIEHF randomised trial. Registry participants will be followed up only through their electronic health records to assess mortality and morbidity. No further research visits are required.

For the Randomised Trial until Day 60

To find out whether administering patiromer and higher-dose MRA improves evidence of congestion on Day 60 (±10 days) compared to standard care.

4.3 Secondary Objectives

For the Registry

To describe the characteristics and outcome of patients with worsening heart failure who require higher doses of diuretics to control worsening symptoms and signs of congestion.

For the Randomised Trial until Day 60

To find out whether patients with worsening congestion due to heart failure and hyperkalaemia who are randomised to patiromer receive higher doses of MRA and have less severe symptoms and signs of congestion, quality of life and hospital length of stay compared to patients assigned to those who are randomised to standard care.

Randomised Trial (long-term follow-up)

To find out whether patients with worsening congestion due to heart failure and hyperkalaemia who are randomised to patiromer receive higher doses of MRA, have improved long-term quality of life, spend less time in hospital and have lower all-cause mortality compared to patients assigned to standard care.

4.4 Outcome Measures/Endpoints

Endpoints have been chosen to reflect the clinical aims of managing patients with worsening congestion due to heart failure. The ‘narrative’ is that better management of congestion by patiromer-facilitated, dose-escalation of MRA will improve symptoms and signs of congestion, leading to a shorter hospital stay, improved quality of life, less need for intravenous and intensified oral diuretic therapy, fewer readmissions for worsening heart failure and increased longevity.

4.5 Primary Endpoint

Composite of time to need for IV or SC diuretics for worsening or recalcitrant heart failure (subsequent to discharge from index episode of care), (re-)hospitalisation for worsening heart failure or non-cancer

deaths. The trial is powered on time-to-first event but analysis will include first and recurrent events for the primary endpoint.

4.6 Other Primary Endpoints

For The Registry

Time to first (re-)hospitalisation or death

Randomised Trial until Day 60

- Congestion Index on Day 60, comprising changes from baseline in
  i. Weight
  ii. Severity of peripheral pitting oedema
  iii. Breathlessness symptom score
  iv. Dose of loop and thiazide diuretics
  v. Walk Test Time (will be considered zero at baseline if not available)
  vi. Plasma concentration of NT-proBNP
  vii. Plasma concentration of CA125

4.7 Secondary Endpoints

Registry

- Time to first cardiovascular (re-)hospitalisation or non-cancer death as judged by primary and secondary ICD-10 codes
- Time to first heart failure (re-)hospitalisation or non-cancer death as judged by primary and secondary ICD-10 codes
- Incidence-rate for hospitalisation, all-causes and due separately to cardiovascular causes, heart failure or cancer, and other as judged by primary and secondary ICD-10 codes
- Time to death
  - All-cause and due to cardiovascular, heart failure, cancer and other based on hospitalisation data and death certificates.

The data for all registry outcome events will be obtained solely by linkage to electronic medical records.

Randomised Trial until Day 60

- Dose of MRA (Days 7 & 60)
- Congestion Index (Days 7& 60)
- Days dead or hospitalised during the first 60 days
- Individual Components of the Congestion Index (Days 7 &60)
- Quality of Life at (Days 7 &60)
- NYHA class (Days 7 &60)
- Patient Global Assessment (PGA) (Days 7 &60)

Randomised Trial (long-term follow-up)

- Mortality
  - All-Cause
  - Non-Cancer

  - Cardiovascular
- Days lost to hospitalisation for heart failure or non-cancer mortality over 12 months
- Days lost to any hospitalisation or death over 12 months
- Quality adjusted life-years for the duration of the trial using EQ5D
- Proportion alive & well at 12 months (well-being defined by KCCQ quality of life score)
- Dose of MRA taken at the time of the 6 and 12 month visits
- Dose of oral diuretics other than MRA taken at the time of the 6 and 12 month visits
- NYHA class at 6 and 12 months
- Patient Global Assessment (PGA) at 6 and 12 months

4.8 Safety Endpoints

- During scheduled follow-up assessments the percentage of patients in each arm of the trial with:
    - Hypokalaemia defined at various thresholds of serum potassium
        - <4.0mmol/L or<3.5mmol/L or <3.0mmol/L
    - Hyperkalaemia defined at various thresholds of serum potassium
        - >5.5mmol/L or >6.0mmol/L or >6.5mmol/L
    - Hypomagnesemia defined as <0.75mmol/L (<1.5mEq/L or <1.8mg/dL).
    - eGFR
        - <30mL/min/1.73m^2 or <20mL/min/1.73m^2 or <10mL/min/1.73m^2
    - Systolic blood pressure
        - <100mmHg or <90mmHg or<80mmHg
    - Heart rhythm
        - Sinus rhythm / atrial fibrillation / other rhythm
    - Doses of MRA, ACE inhibitors, Angiotensin Receptor Blocker and angiotensin-neprilysin inhibitors, diuretics and beta-blockers
    - Heart rate at each scheduled visit according to heart rhythm

- Adverse reactions and Serious Adverse events related to
    - Hyper- or hypo-kalaemia or hypo-magnesaemia – any record defined according to serum concentrations above
    - Renal failure – defined as renal dialysis or death preceded by an eGFR <10ml/min/1.73m^2 (last measurement before death)
    - A decline in eGFR by >30% from baseline [24]
    - A doubling in serum creatinine from baseline
    - Symptomatic Hypotension

4.9 Table of Endpoints/Outcomes

Objectives	Endpoint	Time-point(s) of evaluation of this outcome measure (if applicable)
Primary		
Overall (long-term)	Composite of time to need for IV diuretics for worsening or recalcitrant heart failure (subsequent to discharge from index episode of care), (re-)hospitalisation for worsening heart failure or non-cancer deaths.	End of trial
Other Primary		
For Registry	Composite of time to (re-)hospitalisation or death	Periodically up to 10 years
Until Day 60	Congestion Index at Day 60	After 400 patients have been evaluated at 60 days
Secondary		
Randomised Trial (long-term follow-up)	• Mortality – All-Cause – Non-Cancer – Cardiovascular	End of trial
	• Days lost to hospitalisation for heart failure or non-cancer mortality	12 months
	• Days lost to any hospitalisation or death	12 months
	• Proportion alive & well (defined by KCCQ)	12 months
	• Quality adjusted life-years using EQ5D	End of trial
	• Dose of MRA	6 and 12 months
	• Dose of oral diuretics other than MRA	6 and 12 months
	• NYHA	6 and 12 months
	• Patient Global Assessment (PGA)	6 and 12 months
Until Day 60		
	• Dose of MRA	Days 7 and 60
	• Congestion Index	Days 7 and 60
	• Individual Components of Congestion Index	Days 7 and 60
	• Days dead or hospitalised	Day 60
	• Quality of Life (EQ5D & KCCQ)	Days 7 and 60
	• NYHA	Days 7 and 60
	• Patient Global Assessment (PGA)	Days 7 and 60
Registry		
	• Composite of time to cardiovascular (re-)hospitalisation or non-cancer death • Composite of time to heart failure (re-)hospitalisation or non-cancer death • Incidence rate for hospitalisation (all-causes, cardiovascular causes, heart failure causes, cancer causes – separately) • Time to death (all-causes, cardiovascular causes, heart failure causes, cancer causes, and other)	Periodically up to 10 years

5. TRIAL DESIGN

A Phase IV, registry-based, randomised (1:1), open-label trial investigating whether administration of patiromer enables use of higher doses of mineralocorticoid antagonists and thereby improves the severity of congestion and patients' well-being, morbidity and mortality for patients with heart failure, worsening congestion and hyperkalaemia.

Hospitalisations and mortality will be adjudicated independently blind to treatment allocation.

6. TRIAL SETTING

This is a multi-centre trial that will be conducted in approximately 100 UK NHS Trusts/Boards responsible for managing patients with heart failure who have sufficiently severe manifestations of congestion that they are being considered for intravenous diuretic therapy.

Principal investigators will be experts in the management of heart failure and may either be a) doctors or b) nurses/pharmacists working under the supervision of a doctor with expertise in the management of heart failure. The TSC will review the curricula vitae of all proposed principal investigators to ensure they are suitably qualified and experienced to conduct the trial with adequate support. Either a principal investigator who is medically qualified or a designated medical practitioner on the delegation log will verify that all inclusion/exclusion criteria have been met. Doctors and appropriately qualified non-medical prescribers who have been delegated this task by the local principal investigator may prescribe MRA and patiromer as described in this protocol and as randomly assigned, provided this is in accordance with local policies and procedures.

Participants are typically 'known' to heart failure services and are hospitalised or require intensive management either as day-cases or by community heart failure services.

Participants will be identified from primary or secondary care services, including hospital wards and clinics and community heart failure services. The precise set-up of heart failure services/pathways will vary according to locality. If a patient moves away from their original trial site and they can attend visits at an alternative trial site they may continue with their randomised treatment allocation. Otherwise, patients will be withdrawn from trial follow-up visits and those assigned to receive patiromer will revert to standard care. These patients will continue to be followed for hospitalisations and deaths by the investigators until the end of the trial or by record linkage in the extended follow-up phase.

7. PARTICIPANT ELIGIBILITY CRITERIA

7.1 Inclusion Criteria

For the Screening Log (no follow-up envisaged nor linkage to electronic medical records)

1. ≥18 years
2. Heart failure in the investigators opinion (new onset or decompensated chronic heart failure)
3. Planned to receive ≥80mg/day of furosemide or equivalent* (IV, SC, or oral) in the next 24 hours.
4. Worsening symptoms & signs of congestion in the prior10 days requiring at least **one** of the following:
   a) hospitalisation
   b) administration of intravenous diuretics
   c) an increase in the dose of loop diuretic by at least 40mg/day of furosemide (or equivalent**) to a total of at least 80mg/day of furosemide (or equivalent*)
   d) addition of a thiazide diuretic to treatment with a loop diuretic

** a dose of 80mg/day of furosemide is considered equivalent to 2mg/day of bumetanide or 20mg/day of torasemide.*

*** a dose of 40mg/day of furosemide is considered equivalent to 1mg/day of bumetanide or 10 mg/day of torasemide.*

For the Consented Registry (with linkage to electronic medical records)

1. Fulfils the criteria for the screening log
2. Able and willing to provide written informed consent for registry participation

For Randomised Trial Run-in

1. Fulfils criteria for the consented registry
2. Clinical diagnosis of heart failure for at least 4 weeks
3. Congestion as shown by at least one of the following:
   a) Peripheral oedema
   b) Raised venous pressure
   c) Inferior vena cava diameter >20mm
4. Cardiac dysfunction documented by at least **one** of the following in the previous three years:
   a) A LVEF<50%or a report of moderate or severe left ventricular dysfunction
   b) Left atrial diameter >3.0cm/m2 (body surface area)
   c) Elevated BNP or NT-proBNP
      i. BNP >150ng/L if in sinus rhythm or >450ng/L if not in sinus rhythm
      ii. NT-proBNP >500ng/L if in sinus rhythm and >1500ng/L if not in sinus rhythm
5. Able and willing to provide written informed consent for the randomised trial

For Randomisation

1. Serum potassium >5.0mmol/L
   - Patients with a serum potassium >5.0mmol/L may be randomised immediately unless they have severe hyperkalaemia requiring, in the investigators opinion, intravenous treatment or a potassium binding agent.
   - Severe hyperkalaemia should be managed according to the UK Renal Association guidelines of 2014 (https://renal.org/wp-content/uploads/2017/06/hyperkalaemia-guideline-1.pdf). Participants may be reconsidered for the trial once such interventions are no longer considered necessary.
   - Patients with a serum potassium ≤5.0mmol/L should be initiated on spironolactone or have the dose increased up to 100mg/day and randomised only if serum potassium exceeds 5.0mmol/L. Those intolerant of or unwilling to take spironolactone should be offered eplerenone titrated to a maximum dose of 50mg/day.
   - A run-in period of up to 35 days is permitted (the run-in period will usually occur during hospitalisation or a course of day-care or intense management).
2. After ingestion of a test-dose of patiromer,
   a) the patient is willing to continue in the trial
   b) the investigator considers the patient can follow instructions on preparing patiromer

7.2 Exclusion criteria

For the Screening Log & Registry

- None

For the Randomised Trial

1. eGFR <30ml/minute/1.73m^2 (if clinically appropriate, the dose of other agents such as loop diuretics, ACE inhibitors, angiotensin receptor blockers, beta-blockers and sacubitril-valsartan may be adjusted to allow eGFR to increase)
2. Systolic BP <90mmHg
3. Uncorrected valve disease as the main cause of heart failure in the investigators opinion

4. Hepatic encephalopathy or known severe liver disease
5. Infection currently requiring intravenous antibiotics or temperature >38oC
6. Myocardial ischaemia currently requiring intravenous therapy or coronary intervention in the previous 7 days
7. Arrhythmia requiring urgent cardioversion or intravenous therapy
8. Severe hyperkalaemia requiring, in the investigator's opinion, intravenous treatment or a potassium-binding agent
9. The patient is already receiving a potassium-binding agent (this includes patiromer) or the treating physician has already decided to use one
10. Known hypersensitivity to patiromer or any of the excipients
11. Known intolerance to both spironolactone and eplerenone (not including hyperkalaemia)
12. Known hypersensitivity to the active substance or excipients of spironolactone and eplerenone as per the current Summary of Product Characteristics (Note: actual medicine supplied to participants will vary depending on local arrangements)
13. Women of childbearing potential. For the purposes of this trial this means any woman aged <60 years unless they have had a hysterectomy or bilateral tubal ligation or are aged >50 years and have undergone the menopause and had amenorrhea for at least 3 years
14. Patients taking the following systemic medicines:
    - strong inhibitors of CYP 3A4 (e.g. itraconazole, ketoconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazodone)
    - Lithium
    - Tacrolimus or Cyclosporin
15. The combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB)
16. Rare hereditary problems of galactose or fructose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
17. Known amyloid heart disease
18. Cancer likely to cause death or major disability within the next three years
19. Patients requiring mechanical circulatory support, and
20. Patients who do not develop a serum potassium >5.0mmol/L despite receiving up to 100mg/day of spironolactone or 50mg/day of eplerenone during the run in phase.

Potentially suitable patients may be considered for the randomised controlled trial as soon as arrhythmia, infection, renal dysfunction, hypotension etc. have been corrected to the satisfaction of the investigator and the above noted exclusion criteria no longer exist.

Serum magnesium will be measured during the trial and magnesium supplements given if serum magnesium drops below 0.75mmol/L (1.5mEq/L or 1.8mg/dL). Accordingly, hypo-magnesaemia is not an exclusion criterion for participation. Potassium sparing diuretics (amiloride or triamterene) other than MRA and potassium supplements should be withdrawn unless the patient is hypokalaemic and as soon as hypokalaemia resolves to allow higher doses of MRA to be used.

Co-enrolment in observational studies of routine clinical practice is permitted. Sponsors and CIs must be contacted to discuss in advance.
Co-enrolment in interventional observational studies or randomised trials requires agreement between the Chief Investigators, Trial Steering Committees and Sponsors for the respective studies/trials. The following issues will be taken into account when making this decision:

- Participant burden: does participation in both studies increase the number of participant visits, pill-burden or other activity and if so, by how much?
- Potential interactions between investigational medicinal products that might affect participant safety
- Study design: co-enrolment into double-blind trials should generally be avoided
- Endpoints: could participation in both studies influence the outcome of either study?

8. TRIAL PROCEDURES

Patients with worsening heart failure, either in hospital or in the community, will be identified. Limited information (as advised by the HRA) will be retained in a screening log for those who do not consent or who are not approached for the registry. Patients who consent to participate in the registry will have personal identifiers and further medical information collected and will be followed-up, long-term, through linkage to their electronic medical records. Registry participants will be asked to take part in the randomised trial if they fulfil all of the eligibility criteria. Consenting patients who have a serum potassium >5.0mmol/L will be randomised (after an 8.4g test-dose of patiromer to ensure participant acceptance; note - there is no requirement for the participant to consume the full dose and failure to do so will not constitute a protocol deviation) either to patiromer or not (open-label). If serum potassium is ≤5.0mmol/L, MRA will be initiated or increased to target doses for a “run-in” period of up to 35 days. If serum potassium increases to >5.0mmol/L, the participant may be randomised. Those who do not develop hyperkalaemia despite receiving the run-in target dose of MRA within 35 days of enrolment are not eligible for randomisation and will return to standard care.

8.1 Schedules of Procedures

8.1.1 Schedule of Procedures for Screening Log (-00), the Registry (-0) and Randomised Trial (up to 60 days)

	Mostly in hospital / day-care								Majority of care at follow-up in clinic		
Visit	-00	-0	0	RI	R	T1	T2	T3	T4	T5	T6
Days				***-X***	***1***	***3***	***5***	***7****	***14***	***30***	***60***
Window +/- days			NA	35	1	1	2	3	5	10	14
Consent		X	X								
History	X	X									
Frailty Scale	X	(X)									
Symptoms/NYHA		X			X	X	X	X	X	X	X
PGA						X	X	X	X	X	X
CV Therapy	X	X			X	X	X	X	X	X	X
Non-CV Med♦		X			X			X			X
Height	X	X			X			X			X
Weight	X	X		X	X	X	X	X	X	X	X
Vital Signs	X	X*		X	X*	X	X	X*	X	X	X*
Physical Exam		X			X			X			X
Oedema Grade		X			X	X	X	X	X	X	X
Orthopnoea Test		X			X			X			X
ECG trace		X									
Electronic ECG		Opt			X			X			X
Echocardiogram	X	Opt									Opt
Haematology		X			X			X			X
Biochem Safety	X			X		X	X		X	X	
Biochem+		X			X			X			X
Spot Urine		X			X			X			X
Biomarkers		Opt			X			X			X
KCCQ/EQ5D		Opt			X			X			X
Walk Test @		Opt			X			X			X
Titration/Compliance						X	X	X	X	X	X
AE					X	X	X	X	X	X	X
SAE				X	X	X	X	X	X	X	X
Dispensing				X	X			X			X

-00 = screening log; -0 = consented registry; 0 = consent for trial; RI = run-in phase awaiting rise in potassium. R = randomisation.
T = titration visit. Day 7* = day 7 or discharge if sooner. EOS = end of trial. CV = cardiovascular. X* vital signs measured during orthopnoea (orthop) test. Opt = optional
Local Haematology = Haemoglobin, Haematocrit, White Cell Count, Neutrophils, Lymphocytes.
Local Biochemistry = Sodium, Potassium, Urea, Creatinine.
Local Biochemistry+ = Sodium, Potassium, Magnesium, Bicarbonate, Calcium, Phosphate, Urea, Creatinine, Bilirubin, Transaminases, Alkaline Phosphate, Albumin.
KCCQ = Kansas City Cardiomyopathy Questionnaire. EQ5D = EuroQol 5-dimension questionnaire. NYHA = New York Heart Association functional class. PGA = patient global assessment on a 7-point scale ranging from much worse to much better.
@ for patients who feel unable to do these tests, the reason will be recorded. AE / SAE = adverse / serious adverse events.
♦ includes vaccine history

8.1.2 Schedule of Procedures for the Randomised Trial (long-term follow-up)

	Majority of care at follow-up in clinic									
Visit	T7	T8	T9	T10	T11	T12	T13	T14	TX	EOS
Months	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**+3**	
Window +/- days	14	14	14	14	14	14	14	14	14	NA
Consent										
History										
Symptoms/NYHA	X	X	X	X	X	X	X	X	X	X
PGA	X	X	X	X	X	X	X	X	X	X
CV Therapy	X	X	X	X	X	X	X	X	X	X
Non-CV Med		X		X				X		
Height										
Weight	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X*	X	X*	X	X	X	X*	X	X
Physical Exam										
Oedema Grade	X	X	X	X	X	X	X	X	X	X
Orthopnoea Test		X		X				X		
ECG trace										
Electronic ECG		X		X				X		
Echocardiogram		Opt		Opt				Opt		
Haematology		X		X				X		
Biochem Safety	X		X		X	X	X		X	X
Biochem+		X		X				X		
Spot Urine		X		X				X		
Biomarkers		X		X				X		
KCCQ/EQ5D		X		X				X		
Walk Test @		X		X				X		
Titration/Compliance	X	X	X	X	X	X	X	X	X	X
AE/ SAE	X	X	X	X	X	X	X	X	X	X
Dispensing	X	X	X	X	X	X	X	X	X	

T = titration visit. TX = repeat visits every 3 months for dispensing and titration. EOS = end of trial. CV = cardiovascular. X* vital signs measured during orthopnoea (orthop) test. Opt = optional
Local Haematology = Haemoglobin, Haematocrit, White Cell Count, Neutrophils, Lymphocytes.
Local Biochemistry = Sodium, Potassium, Urea, Creatinine.
Local Biochemistry+ = Sodium, Potassium, Magnesium, Bicarbonate, Calcium, Phosphate, Urea, Creatinine, Bilirubin, Transaminases, Alkaline Phosphate, Albumin.
KCCQ = Kansas City Cardiomyopathy Questionnaire. EQ5D = EuroQol 5-dimension questionnaire. NYHA = New York Heart Association functional class. PGA = patient global assessment on a 7-point scale ranging from much worse to much better.
@ for patients who feel unable to do these tests, the reason will be recorded. AE / SAE = adverse / serious adverse events.

Key visits for the assessment of clinical efficacy and endpoints are

- Day 7 (+/-3 days or discharge from hospital or day-care)
- Day 60 (+/-14 days)
- And at 6 months (+/-14 days) months,12 months (+/- one month) and 24 months (+/- one month)

Additional visits are required to assess symptoms and safety (serum potassium/magnesium, renal function, blood pressure). Patients may be evaluated in the community or clinic setting as convenient but will have to attend hospital visits to obtain trial IMP (patiromer, spironolactone/eplerenone).

In addition, if doses of patiromer or MRA are changed, blood pressure and serum electrolytes and creatinine should be re-checked both after 7-12 days and after 30-45 days. If the patient becomes acutely unwell for any reason, blood pressure, serum electrolytes and creatinine should be re-checked. Serum potassium should also be checked within 48 hours of stopping patiromer.

8.2 Recruitment

8.2.1 Participant identification

Potential participants (including in-patients, clinic patients and community services)will be known to the heart failure team (for example doctors, specialist heart failure nurses, heart failure pharmacists) directly involved in their care because patients with worsening heart failure and peripheral oedema require intensification of treatment.

The clinical team directly involved with the care of potential participants, who will usually also be an investigator or close colleague, will notify the research team.

In accordance with Health Research Authority guidance, a de-identified screening log of all potential participants will be kept *(Section 7.1 of CTIMP Protocol Development Tool: "... give details … including information to be collected regarding participants who are screened … but not randomised … for reporting the generalisability of the results… including the reason not eligible for trial participation, or if they are eligible but declined").*

The eligibility criteria for the registry and trial should be available in the existing medical record provided the patient is being managed according to existing guidelines.

8.2.2 Screening

Patients will be brought to the attention of the investigators by clinical heart failure services.

8.2.3 Payment

If patients are required to make visits in addition to normal clinical care, reasonable travel expenses will be reimbursed. No payment is made to patients for participation in this trial.

8.3 Consent

In accordance with Health Research Authority guidance, a de-identified register of all potential participants will be kept (Section 7.1 of CTIMP Protocol Development Tool: ".give details including information to be collected regarding participants who are screened but not randomised or reporting the generalisability of the results including the reason not eligible for trial participation, or if they are eligible but declined").

Informed consent for the registry and trial will be obtained by medical staff or delegated support staff with appropriate training. A medical practitioner, either the principal investigator or delegated medical co-investigator, will verify that all inclusion/exclusion criteria have been met.

Potential registry participants with worsening heart failure, who fulfil the inclusion criteria, will be invited to read an ethics committee-approved participant information sheet and provide written consent (Consent Form 1) for inclusion in the registry. We will ask patients who participate in the registry whether they are happy to be contacted about future (hypothetical) research, either observational or randomised trials. This may include sending questionnaires directly to participants. However, enrolment in further trials would only be done in collaboration with local investigators and care-teams. Consent will specifically be sought for the collection and use of routine clinical data for research purposes and for long-term follow-up through the participant's electronic medical record (e.g. Hospital Episode Statistics).

Potential trial participants will be identified from amongst those consenting to the registry. Registry participants who fulfil the trial's inclusion/exclusion criteria will be invited to read an ethics committee-

approved participant information sheet and provide written consent (Consent Form 2) for the trial before any research-related procedures are done.

Following written consent, each signature will be dated by the signatory, the original retained in the site file, one copy provided to the patient/relative, one copy inserted into the patient's medical notes and a scanned electronic copy uploaded via the trial web portal and stored at the University of Glasgow (Glasgow Clinical Trials Unit).

Patients will be given enough time to consider whether or not they wish to participate and to discuss participation with relatives and friends. Most patients are likely to be in hospital or under frequent outpatient review. Patients may be consented and included in the registry within 24 hours but should have at least 24 hours to consider whether they should participate in the randomised trial.

Sites will be required to scan and upload signed consent forms including participants' names into a secure trial database for each consented participant via a secure trial web portal. Participants will be asked to consent to this and for their personal information, including data of birth, address and NHS identification number, to be held securely by the Glasgow Clinical Trials Unit. The central storage of consent forms will facilitate remote monitoring of participants' consent by the Sponsor's monitors who will be given secure access to view the consent forms including the patient's name.

All personal data will be encrypted in a separate linked database that is not accessible to individuals working on the research database containing clinical data for the registry and trial. All personal details will be managed according to ISO 27001:2013 compliant standard operating procedures. These data are required for linkage to electronic health records.

To comply with the Welsh Language Act 1993, the Participant Information Sheets and Consent forms will be translated into Welsh or provided bilingually where this is requested by a participant at a research site.

Where a participant consents but subsequently becomes incapacitated and is unable to take oral medication or where the incapacity puts medication compliance in doubt, patiromer will be stopped and the dose of MRA adjusted in accordance with standard care. Participants will be classified as withdrawn from trial treatment but continue to be followed through their routine medical records (including electronic records) but will not have to undergo any further protocol-specified assessment.

Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

All patients enrolled in the registry will be asked to provide a blood sample that will be stored in a central repository and shared with academic or commercial partners for this and future research into heart failure (which may include markers of heart, vascular, renal, endocrine, skeletal muscle, pulmonary, hepatic or nervous system dysfunction). The consent will make it clear that this potentially includes genetic testing.

For the registry, the blood sample for central storage is optional. Samples will be stored locally in a freezer at -20^{o}C or cooler and transferred periodically (at least annually) to a central laboratory.

Patients in either the registry or trial may decline to have genetic material stored. Results of genetic tests will not be linked to personally identifiable data. Participants will be informed that they will not receive the results of such genetic tests. Should genetic testing identify a possible benefit for clinical practice, the findings will be published to inform debate within the NHS.

Stored samples will be barcoded. Investigators may convey information to the CTU indicating that a patient wishes their samples to be disposed of, in which case the samples (including any shared with

partners) will be identified and safely disposed of. The patient may also request that the results of any research biomarkers or genetic tests be deleted from the database. This does not apply to blood tests required to assess safety or efficacy prior to the date of withdrawal of consent. The Biobank, laboratories and research partners will not be able to trace results back to patient-identifiable data. Patients will be informed of this during the consenting procedure.

8.4 The randomisation scheme

Eligible and consenting patients will be randomised on a 1:1 basis to the two groups using a mixed randomisation/minimisation algorithm that includes trial site, eGFR group (above or below 45ml/minute/1.73m^2) and systolic BP (above or below 110mmHg).

8.4.1 Method of implementing the randomisation/allocation sequence

All patients included in the registry or trial will receive a participant registration number that will be used to identify the participant throughout the registry and trial.

Randomisation using a web-based randomisation system will be provided by Glasgow CTU. The investigator will provide the participant identifier and minimisation information and, if eligible, the randomisation group will be allocated.

New participant randomisation e-mail confirmations will be sent to the research nurse(s), investigator and pharmacy staff as required.

Trial participants will be provided with a patient alert card providing details of trial participation which they will be asked to carry at all times.

8.5 Blinding

Both patiromer and MRA (spironolactone or eplerenone) will be administered open-label.
Endpoints will be evaluated blinded to treatment allocation by a clinical endpoints committee.

8.6 Emergency Unblinding

Not applicable. Electrolyte abnormalities, hypotension and renal dysfunction should be managed according to guidelines and best clinical practice.

8.7 Data Collection

MR = from **M**edical **R**ecords. If not in the existing record, variables will be recorded as "not available"
X = a test, measurement or question that research staff will do/ask if not in the existing medical record;
MR/X = either approach to obtaining data is possible; shaded cells = data not collected in this period
To be read in conjunction with schedule of assessments and narrative subsequent to this table.

			Randomised Trial		
	Screening Log #	**Registry**	**Baseline**	**60 Day**	**Long-Term**
Fulfil Entry Criteria	**MR**	**MR**	**MR/X**		
Willingness to Participate in Research	**X**	**X**			
Year of Birth	**MR**				
Date of Birth		**MR**			
Sex	**MR**				
Ethnicity		**MR/X**			
Smoking History		**MR/X**			
Alcohol Intake		**MR/X**			
Contact Details		**MR/X**			
Hospitalisation Status	**MR**	**MR/X**	**MR/X**		
Aetiology	**MR**	**MR/X**			
Co-morbidity		**MR/X**			
Duration of Heart Failure	**MR/X**				
Causes of Worsening		**MR/X**			
Frailty Score	**X**	**(X)**			
Symptom Severity		**X**	**X**	**X**	**X**
NYHA Class		**X**	**X**	**X**	**X**
PGA			**X**	**X**	**X**
CV Therapy	**MR (limited)**	**MR/X**	**MR/X**	**MR/X**	**MR/X**
Non-CV Therapy		**MR/X**	**MR/X**	**MR/X**	**MR/X**
Height	**MR**	**X**	**X**	**X**	
Weight	**MR**	**X**	**X**	**X**	**X**
Vital Signs	**MR (limited)**	**X**	**X**	**X**	**X**
Physical Exam		**X**	**X**	**X**	**X**
Orthopnoea Test #		**X**	**X**	**X**	**X**
ECG		**MR/X**	**X**	**X**	**X**
Echocardiogram or other imaging test	**MR (anytime)**		**MR/X (in prior 3 yrs)**		
Haematology		**MR**	**MR/X**	**MR/X**	**MR/X**
Biochemistry	**MR** • Sodium • Potassium • Creatinine • Urea	**MR** • Full Panel	**MR/X**	**MR/X**	**MR/X**
Spot Urine		**MR**	**X**	**X**	**X**
Biomarkers (Core Lab)		**X (optional)**	**X**	**X**	**X**
KCCQ		**X (optional)**	**X**	**X**	**X**
EQ5D		**X (optional)**	**X**	**X**	**X**
10 metre Walk Test		**X (optional)**	**X**	**X**	**X**
Events & SAE			**X**	**X**	**X**

[#] See HRA guidance in section 7.1.1.

8.7.1 Screening Log

If the patient provides consent for the registry skip this step as the information will also be collected in the consented registry

Only complete the screening log for **patients who fulfil the inclusion criteria for the registry** and have either not been approached or have declined to participate in the consented registry. Recording a limited amount of information on unconsented patients is recommended by the Health Research Authority (see section 7.1.1) in order to gauge how representative registry and trial participants are of the population encountered in clinical practice. Only existing data from the medical record should be used for the screening log.

Eligibility for Screening Log (no linkage to electronic medical records and no follow-up)

1. ≥ 18 years
2. Clinical diagnosis of heart failure (new onset or decompensated chronic heart failure)
3. Planned to receive ≥80mg/day of furosemide or equivalent* (IV, SC, or oral) in the next 24 hours.
4. Worsening symptoms & signs of congestion in the prior 10 days requiring at least **one** of the following:
   a) hospitalisation
   b) administration of intravenous diuretics
   c) an increase in the dose of loop diuretic by at least 40mg/day of furosemide (or equivalent**) to a total of at least 80mg/day of furosemide (or equivalent*)
   d) addition of a thiazide diuretic to treatment with a loop diuretic

** a dose of 80mg/day of furosemide is considered equivalent to 2mg/day of bumetanide or 20mg/day of torasemide.*

***a dose of 40mg/day of furosemide is considered equivalent to 1mg/day of bumetanide or 10 mg/day of torasemide.*

Willing to Participate in Research

Was the patient asked to give consent to participate in the registry:

- If no, why not? (mark all that apply: Patient too frail; Cognitive Dysfunction; Insufficient research time; Care-team considered participation inappropriate; other (specify))
- If yes, but refused, what was the reason given? (mark all that apply: not interested; too unwell; too old; too frightened; concerned about personal privacy; other (specify))

Demographics

- Year of Birth and Sex

Hospital Status:

- In-Patient: Yes/No

Aetiology of Heart Failure

- Yes/No (mark all that apply): Ischaemic Heart Disease; Idiopathic Dilated Cardiomyopathy; Hypertension; Mitral Valve Disease; Aortic Valve Disease; Hypertrophic Cardiomyopathy; Amyloid Heart Disease; Uncertain Cause; Atrial Fibrillation; Other (text field)
- Primary Cause – pick from above list

Duration of Heart Failure

(Defined either as initiation of loop diuretic therapy or first hospitalisation for heart failure)

- Choose one: <1 month; 1-6 months, >6-12 months, >12-18 months, >18 months

Assessment of Frailty (only needs to be completed if not done on screening log)

- Using the Clinical Frailty Scale developed for the Canadian Study on Health & Aging by Dalhousie University, investigators will be asked to rate the severity of frailty on a scale of 1 (least severe) to 9 (most severe), giving a) the best score in the previous month and b) the current score. (See https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/frailty-full_guideline.pdf.)

Concomitant Cardiovascular Therapy (if yes - names from a drop-down list) on day of assessment

- Loop Diuretic - Name, Route and Total Daily Dose
- MRA - Name and Total Daily Dose
- ACE Inhibitor - Yes/No
- Angiotensin Receptor Blocker - Yes/No
- Angiotensin-Neprilysin Inhibitor - Yes/No
- Beta-blocker - Yes/No
- Digitalis glycoside - Yes/no
- Ivabradine - Yes/No
- Thiazide - Yes/No
- Potassium Sparing Diuretic other than MRA - Yes/No
- Potassium Binding Agent - Yes/No
- Devices - Pacemaker, ICD, CRT-D, CRT-P, MCS
- NSAIDs other than aspirin - Yes/No
- Insulin - Yes/No
- Other Hypoglycaemic Therapy - Yes/No

Most recent result from patient records (dates not required)

- Height and weight from case notes or state “not available” (to calculate eGFR)
- Systolic Blood Pressure
- Serum Sodium, Potassium, Creatinine, Urea

Echocardiogram (most recent)

- Test Available Yes/No
- Left Ventricular Function
  - Left ventricular ejection fraction

  and/or
  - Systolic Dysfunction – None, Mild, Moderate, Severe, Don’t Know

  and/or
  - HFrEF, HFmrEF, HFpEF or Don’t Know
- Left Atrial Enlargement
  - None, Mild, Moderate, Severe, Don’t Know
- Valve Disease
  - Mitral Regurgitation (none / mild / mod. / severe / or state “not available”)
  - Aortic Stenosis (none / mild / mod. / severe / or state “not available”)
  - Tricuspid Regurgitation (none / mild / mod. / severe / or state “not available”)

8.7.2 Consented Registry

Willing to Participate in Future Research?

Further observational research: yes/no. If not, why not? Lack of interest; Too many requests; Concerns about personal privacy; other (specify)

Randomised trials: yes/no. If not, why not? Not interested; Too unwell; Too old; Too Frightened; Concerned about personal privacy: Other (specify)

Demographics& Contact Details

- Date of birth
- Sex
- Ethnic group: using Office of National Statistics Classification
  - https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11
- Smoking status: current/ex/never
- Alcohol intake: none, occasional, frequent, heavy
- Unique identifier for medical record linkage (e.g. NHS number in England & Wales, Community Health Index (CHI) in Scotland, Health & Social care number in N. Ireland)
- Name, Home Address & Postcode

Hospital Status:

- In-Patient: Yes/No
- If yes,
  - Date of admission
  - Is heart failure the cause of or major contributor to this admission? Yes/No
- If no,
  - Date of last discharge for any reason
  - Date of last discharge for an admission where heart failure was the cause or major contributor

Aetiology of Heart Failure

- Yes/No (mark all that apply): Ischaemic Heart Disease; Idiopathic Dilated Cardiomyopathy; Hypertension; Mitral Valve Disease; Aortic Valve Disease; Hypertrophic Cardiomyopathy; Amyloid Heart Disease; Uncertain Cause; Atrial Fibrillation; Other (text field)
- Primary Cause – pick from above list

Prior Medical History and Co-morbidity

- Yes/No (mark all that apply): Coronary Artery Disease (and, if yes, further specify if prior Myocardial Infarction, Percutaneous Coronary Intervention, Coronary Bypass Surgery or Other evidence), Diabetes, Atrial Fibrillation, Stroke, Severe Cognitive Dysfunction, Chronic Lung Disease, Cancer (and, if yes, further specify if a) in remission or cured b) locally invasive c) metastatic d) has required chemotherapy at any time e) has required radiotherapy to thorax at any time), Other (text field)
  - Other co-morbidities will be ascertained from other fields, including anaemia, iron deficiency, renal dysfunction and valve disease

Duration of Heart Failure

(Defined either as initiation of loop diuretic therapy or first hospitalisation for heart failure)

- Choose one: <1 month; 1-6 months, >6-12 months, >12-18 months, >18 months

Causes of Worsening Heart Failure

- Yes/No (mark all that apply): Worsening cardiac function, worsening renal function, poor dietary compliance, poor medicines compliance, anaemia, infection, recent myocardial ischaemia or infarction, new-onset atrial fibrillation, other arrhythmia, hypertension, iatrogenic (e.g. NSAIDs), other (specify)
- Primary Cause – pick from above list

Symptoms

- NYHA Class
- Symptom severity (see appendix for questionnaire)

Assessment of Frailty (only needs to be completed if not done on screening log)
Using the Clinical Frailty Scale developed for the Canadian Study on Health & Aging by Dalhousie University, investigators will be asked to rate the severity of frailty on a scale of 1 (least severe) to 9 (most severe), giving a) the best score in the previous month and b) the current score. (See https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/frailty-full_guideline.pdf.)

Concomitant Cardiovascular Therapy (if yes - names from a drop-down list) on day of assessment

- Loop Diuretic - Name, Route and Total Daily Dose
- MRA - Name and Total Daily Dose
- ACE Inhibitor - Name and Total Daily Dose
- Angiotensin Receptor Blocker - Name and Total Daily Dose
- Angiotensin-Neprilysin Inhibitor - Name and Total Daily Dose
- Beta-blocker - Name and Total Daily Dose
- Digitalis glycoside - Name and Total Daily Dose
- Ivabradine - Name
- Thiazide - Name
- Potassium Sparing Diuretic other than MRA - Name
- Potassium Binding Agent - Name
- Lipid lowering agents - Name
- Antiplatelet - Name (more than one possible)
- Anticoagulant - Name
- Devices Pacemaker, ICD, CRT-D, CRT-P, MCS

Current Concomitant Non-Cardiovascular Therapy (if yes - names from a drop-down list)

- NSAIDs other than aspirin - Name
- Insulin - Yes/No
- Other Hypoglycaemic Therapy Name(s)
- Antibiotics - Name
- Oral Steroids - Name
- Inhaled Medicines - Name
- Iron (oral or IV) - Name
- Treatments for indigestion - Name
- Other Medicines - Name

Taken in the prior month for those not currently receiving

- MRA Yes/No
- ACE Inhibitor - Yes/No
- Angiotensin Receptor Blocker - Yes/No
- Angiotensin-Neprilysin Inhibitor - Yes/No
- Beta-blocker - Yes/No
- Digitalis glycoside - Yes/No
- Ivabradine - Yes/No
- Thiazide - Yes/No

Taken in the prior 12 months

- **Oral iron** Yes/No
- **IV iron** Yes/No; if yes, number of times

Vaccine and COVID History

- History of COVID vaccination
- COVID vaccination details
- Other vaccination details (including but not limited to influenza, pneumococcal, and shingles vaccination)

Height & Weight
- Height to the nearest centimetre
    - For patients who cannot stand, patient-reported height should be reported
    - Height will be reported as measured or patient-reported
- Weight to nearest 100g in light clothing, empty pockets and without shoes
    - For patients who cannot be weighed, patient-reported weight should be recorded
    - Weight will be reported as measured or patient-reported

Vital Signs (this should be done as part of the orthopnoea test at this visit)
Heart rate and blood pressure should be measured with the patient sitting comfortably with the back supported. Blood pressure and heart rate should be measured using an automated sphygmomanometer. Sphygmomanometers should be calibrated regularly according to local standard operating procedures.

Oedema Grade
- Swelling of legs / ankles (mild = ankle, moderate = between ankle and knee, severe = above knee)
- Left and right ankle circumferences (cm)

Orthopnoea Test
Start with patient sitting up supported by pillows. . Patients may be sat in a chair. Measure heart and respiratory (for at least 30 seconds) rate and blood pressure. Then lie the patient flat with one pillow for comfort for up to 10 minutes. Repeat measurements of heart and respiratory rate and blood pressure. If the patient must sit up sooner than 10 minutes, then help them and measure vital signs as soon as possible afterwards. If a patient feels unable to lie flat, please record this and omit the test. If the test is not done for another reason, record heart and respiratory rate and blood pressure and record that the test was not done although you considered the patient might have been able to do it.

Record:
- Time (up to 600secs)
- Heart Rate (bpm) before and after
- Resp. Rate (rpm) before and after
- Systolic Blood Pressure before and after
- Diastolic Blood Pressure before and after

Electrocardiogram
Record the following from the most recent electrocardiogram
- Ventricular Rate
- Rhythm
    - Sinus Rhythm
    - Atrial Fib.
    - Paced
    - Other
- PR Interval (if available)
- QRS Duration
    - If QRS duration is >140msec does this reflect Left or Right Bundle Branch Block or Neither
- QT Duration (uncorrected)

Haematology (most recent test, preferably from electronic records rather than case notes; date not required)

- Haemoglobin, Mean Corpuscular Haemoglobin Concentration (MCHC), White Blood Cell, Neutrophil and Lymphocyte Counts

Biochemistry(**most recent test**, preferably from electronic records rather than case notes, dates not required, all results do not need to come from a single blood sample or date; state not available if no record found)

- Serum Sodium, Potassium, Bicarbonate, Calcium, Phosphate, Urea, Creatinine, Bilirubin, alanine and aspartate aminotransferase, Alkaline Phosphate, Albumin, Magnesium.
- The following if done in the previous two years only (low availability anticipated)
  - Plasma Brain Natriuretic Peptide (BNP) or NT-proBNP
  - Serum iron, transferrin saturation, ferritin
  - Urine for albumin/creatinine ratio

Echocardiogram (most recent test)

- **Test Available** Yes/No
  - If yes, date
- **Left Ventricular Function**
  - Left ventricular ejection fraction (provide value; may be done by an alternative imaging method for instance nuclear scan, magnetic resonance imaging or computed tomography)

  and/or
  - Systolic Dysfunction – None, Mild, Moderate, Severe, Don't Know

  and/or
  - HFrEF, HFmrEF, HFpEF or Don't Know
- **Left Atrial Enlargement**
  - None, Mild, Moderate, Severe, Don't Know
- **Valve Disease**(may also be assessed by magnetic resonance imaging)
  - Mitral Regurgitation (none / mild / mod. / severe / or state "not available")
  - Aortic Stenosis (none / mild / mod. / severe / or state "not available")
  - Tricuspid Regurgitation (none / mild / mod. / severe / or state "not available")
  - Other valve disease (none / mild / mod. / severe / or state "not available")
- **Dimensions**
  - LV end-diastolic
  - Left atrial dimension
- **Please provide video** (optional)

****The Following Questionnaires and Sets of Tests are Optional for The Registry****

Physical Examination

An appropriately trained health professional should measure these. If an appropriately qualified person is not available, then this unavailability should be recorded.

- Jugular Venous Pressure (optional for registry)
  - Not visible, Normal (<4cm above sternal angle), Raised 4-10cm above sternal angle, Raised >10cm above sternal angle
- 3rd Heart Sound (optional for registry)
  - Present / Absent
- Lung crepitations (optional for registry)
  - Absent, Unilateral, Bilateral Basal, Bilateral to Mid-Zone, All Lung-Fields
- Hepatomegaly
  - Present / Absent

Biomarkers
- 10mL of blood taken into EDTA tubes (see laboratory manual for preparation and transport to core laboratory).
- Sample taken (Yes/No)
- If Yes, barcode

Quality of Life Assessment
- EQ5D
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

Electrocardiogram (ECG)
- Transmit 12-lead electrocardiogram electronically.

10 metre Walk Test (in triplicate) https://www.physio-pedia.com/10_Metre_Walk_Test
- *Attempted (Yes/No/ If no, provide reason (many will be unable to attempt this at baseline)*
- Not attempted (reasons)–
  - patient feels unable due to a) breathlessness, b) fatigue, c) joint or muscle pains d) dizziness / instability e) not ambulatory (more than one may apply)
  - Patient feels able but unwilling
  - Insufficient investigator a) time, b) space, c) both
  - *Duration*
    - 1st Attempt (seconds)
    - 2nd Attempt (seconds)
    - 3rd Attempt (seconds)
  - *After final test (this may be after one, two or three tests)*
    - *Breathlessness rating, Fatigue rating, Respiratory rate, Heart rate*

8.7.3 Clinical Trial

Baseline
Data gathered for the registry may be used as the baseline data for the randomised trial providing the dates are the same. If the dates differ, tests as shown in the schedule of assessments should be repeated. In addition, the following tests and measurements are mandatory prior to randomisation:
1. Blood collection for biomarkers
2. EQ5D and KCCQ questionnaires
3. Walk Tests
4. Electronic transmission of the ECG: record and transmit 12-lead ECG to the Glasgow electrocardiology core laboratory. ECGs will be identified only by participant registration number.

Follow-up
Assessments will be repeated as at baseline on Days 7 and 60 and at 6, 12 and 24 months.

For safety visits (in addition to those above), vital signs consist only of measurements of heart rate, blood pressure and oedema grade and for biochemistry only includes sodium, potassium, urea and creatinine.

A Patient Global Assessment (PGA) which assesses the change compared to baseline will also be done at each follow-up visit as an assessment of symptoms.

Trial assessments
There will be two types of clinical assessments in this trial
a) Assessments for Efficacy at 7 and 60 days and at 6, 12 and 24 months

b) Assessments for Safety at 1, 3, 5, 14, 30days and at 3, 9, 15, 18, 21, 27 months and every 3 months thereafter until the end of the trial.

Visits for assessment of efficacy require all baseline assessments to be repeated with the exception of demography and prior medical history. Echocardiography is optional.

Visits for assessment of safety require evaluation only of symptoms, weight, concomitant cardiovascular therapy, severity of oedema, blood pressure and a blood test for measurement of serum sodium, potassium, urea and creatinine.

Longer-term efficacy and safety during the randomised trial will be assessed by reports of adverse reactions, serious adverse events and the primary composite endpoint and its components.

Participants should be encouraged at each visit to bring any remaining trial medicines (patiromer/ spironolactone or eplerenone). An assessment of compliance will be made at each trial visit by research staff and documented in the eCRF. Unused IMP should be returned to the site pharmacy where it will be logged and disposed of safely.

Participant retention in the randomised trial will be enhanced by regular contact with the research team and a “frequently asked questions & answers” section on a publicly accessible trial website.

Investigators will be asked to interrogate their own hospital’s electronic record to identify hospitalisations and deaths for randomised patient on a quarterly basis to ensure that events that the participant fails to mention are recorded.

Most patients will initially be hospitalised. NICE guidance recommend that patients with heart failure should be evaluated by an expert at least once every 6 months but patients with advanced heart failure require more intensive surveillance and management. Accordingly, many (more than half) of these evaluations would be required for routine care.

Vaccine Follow-Up
The following details will be captured at 6, 12 and 24 months:

- COVID vaccination details
- Other vaccination details (including but not limited to influenza, pneumococcal, and shingles vaccination)

8.8 Long term follow-up after trial completion

At the end of the trial, participants will be returned to usual care as defined by local and national guidelines at that time. The results of the trial may of course have an impact on these guidelines and the future care of patients with heart failure.

Patients will be followed through their electronic medical records via record linkage for up to 10 years after the end of the trial. This will not interfere with their routine care.

Patients will be deemed lost to follow-up on the date that contact with the investigator team ceases or the date on which the last event is recorded in their electronic medical record, whichever is later.

8.9 Withdrawal criteria

Participants may choose to withdraw at any time, either from the intervention (patiromer or MRA), the follow-up procedures or from follow-up through their electronic medical record. Reasons for withdrawal will be recorded, providing the participant agrees. Participants who withdraw from the intervention or

follow-up procedures should cease to take IMP and revert to standard-care. The costs of patiromer or MRA would no longer be reimbursed from the trial budget.

Participants who choose to stop patiromer-IMP only should have the dose of MRA adjusted to prevent hyperkalaemia. Participants who choose to stop MRA-IMP only should have the dose of patiromer adjusted to prevent hypokalaemia. Further guidance is provided in Appendix 3. Changes in serum potassium and clinical status should be evaluated carefully after any dose adjustments.

Participants may be withdrawn from IMP by their investigators if deemed appropriate (e.g. the investigator is concerned about a participant's safety because of uncertainty about adherence to IMP). Safety will be assessed by research nurses and/or investigators at each visit and after the occurrence of each SAE/SAR. Participants who have had an SAR (*e.g.* a hospital admission for the management of hyper- or hypo-kalaemia) should be reassessed for their ability to understand and comply with IMP dosing instructions.

- If the participant is, in the investigator's opinion, no longer able or willing to comply with treatment instructions, then they should stop one or both IMP and revert to standard-care, even if they have not experienced an SAE or SAR.
- Participants who are assigned to patiromer and who have or develop hyperkalaemia (serum potassium >5.0mmol/L), even if they have been withdrawn from spironolactone or eplerenone IMP, may continue on or restart patiromer.
- For participants with recurrent (two or more within a 6 month period) or life-threatening hyperkalaemia, investigators should reduce the dose of spironolactone or eplerenone to a maximum of 25mg/day or less (this includes a zero-dose), unless in the opinion of the investigator the benefit/risk ratio of receiving higher doses of spironolactone / eplerenone IMPs is still believed to be positive (*e.g.* the participant's heart failure has responded well to higher doses of spironolactone or eplerenone). Participants assigned to patiromer should have the doses adjusted to achieve a serum potassium between 4.1 to 4.9mmol/L (inclusive).

IMP may be re-initiated at any time if the investigator believes it is safe to do so and the participant is willing. However, participants should continue to have their protocol-specified assessments as far as possible whether or not on therapy. Reasons for withdrawal will be recorded.

Participants who withdraw from IMP will not be replaced. This view may be revised by the IDMC.

The IDMC may recommend that the trial should be stopped for efficacy, safety or futility and will inform the TSC of this decision.

8.10 Storage and analysis of clinical samples

10mls of venous blood will be withdrawn and collected in pre-chilled sterilins tubes containing EDTA and aprotonin. Blood will be centrifuged at 1500g for 20mins at 4^{o}C. Plasma will be siphoned, aliquoted and stored at -20^{o}C or cooler until transport to the central laboratory on dry ice. At the time of analysis plasma samples will be defrosted at room temperature and analysed in a single batch after 400 patients have completed 60-day follow-up and at the end of the trial. Further details are provided in a laboratory manual.

8.11 End of trial

The overall trial will be deemed complete once 750 patients have experienced a first-event. At that time, an end of trial date will be declared and investigators will be asked to contact all patients on or after that date for a final trial evaluation.

The 60-day outcome will be assessed after 400 patients have had their 60-day evaluation. It is anticipated that database lock will occur within three months and that these data will be analysed and presented during the course of the main trial.

9. TRIAL TREATMENTS

9.1 Name and description of investigational medicinal product(s)

Patiromer(as patiromer sorbitex calcium) is a non-absorbed cation exchange polymer that binds free potassium excreted into the gastrointestinal lumen thus increasing faecal potassium excretion and decreasing serum potassium concentrations.

Spironolactone and eplerenone

Spironolactone and eplerenone are mineralocorticoid (aldosterone) receptor antagonists (MRA) that block the actions of aldosterone, causing increased sodium excretion and potassium retention. They are both indicated for the treatment of heart failure. Spironolactone is on the World Health Organization's List of Essential Medicines

9.2 Regulatory status of trial medicines

Patiromer: Patiromer (Veltassa®) is currently licensed in the EU and UK for treatment of hyperkalaemia in adults.

Spironolactone and eplerenone: There are no restrictions on the brand(s) of spironolactone or eplerenone that may be used within the trial provided a Marketing Authorisation is held for the product in the UK.

9.3 Product Characteristics

The sponsor will use the Summary of Product Characteristics (SmPC) for Veltassa and will select a reference SmPC for spironolactone and eplerenone for the Reference Safety Information from the following website https://www.medicines.org.uk/emc/. See Section 10 for further information.

9.4 Patiromer supplies and storage

Trial sites will be supplied with Veltassa®8.4g powder for oral suspension free of charge for participants assigned to the intervention arm. Patiromer will be supplied directly to participating pharmacies by the funder (Vifor) free of charge and will not be modified in relation to its Marketing Authorisation.

Supplies will only be released to trial sites by the sponsor once all the appropriate regulatory and governance approvals are in place. All patiromer packs must be stored in a locked, secure area with access limited to the Investigator and authorised site staff. Supplies must be used as directed in the trial protocol and should not be supplied to any persons other than trial participants.

Investigators may prescribe patiromer for participants assigned to the standard care control group if they believe this is in their best interests. Participants should continue to have follow-up assessments as described in the protocol. However, participants assigned to standard care must not receive trial specific supplies of patiromer-IMP. Any costs associated with patiromer treatment in the standard care group will not be reimbursed from the trial budget and must be met by local payers.

Patiromer must be stored at the site pharmacy between 2°C and 8°C. Once dispensed for participant use, packs can be stored at room temperature below 25°C for up to six months. Visits are planned to

occur at no more than 3-month intervals. Supplies must not be used beyond the expiry date. Where possible, supplies of patiromer will be utilised in such a way as to minimise unnecessary wastage.

Further information on ordering, receipt, distribution and destruction of trial medicines is provided in the RELIEHF IMP Management and Accountability Manual.

9.5 Spironolactone and eplerenone supplies and storage

Spironolactone and eplerenone for use in the trial will be sourced from routine NHS hospital supplies and supplied to participants by local investigator site pharmacies.

Depending on participant dose and trial phase, site pharmacies may be required to supply spironolactone 25mg, 50mg and 100mg tablets and eplerenone 25mg and 50mg tablets. There is no requirement to 'ring-fence' supplies for use in the RELIEHF trial and there are no restrictions on the brand(s) of spironolactone or eplerenone that may be used within the trial provided a Marketing Authorisation for the product is held in the UK. Where possible, supplies of spironolactone or eplerenone will be utilised in such a way as to minimise unnecessary wastage. Reimbursement will be available from the trial budget where MRA usage is additional to standard care. All supplies should be stored in accordance with the relevant current Summary of Product Characteristics. Further information is provided in the RELIEHF IMP Management and Accountability Manual.

9.6 Preparation and labelling of Investigational Medicinal Products

Veltassa (Patiromer): Sites will be provided with Annex 13 compliant labels by the sponsor for application at the time of dispensing.

Spironolactone & Eplerenone: Sites will be required to label original packs of spironolactone or eplerenone with Annex 13 compliant labels at the time of dispensing. Usual NHS ward supplies may be used in the run-in phase for in-patient participants where it is in line with local arrangements.

Further information is provided in the RELIEHF IMP Management and Accountability Manual.

9.7 Dosage schedules

Patients with a serum potassium >5.0mmol/L will be shown how to prepare and ingest a single 8.4g test dose of patiromer to ensure that they are willing to take patiromer on a regular basis and to assure the investigator that they understand how to prepare the suspension and requirement to take at least 3 hours before or after other medicines (with key exceptions – see Section 9.8).

Dosing of patiromer and MRA during run-in and at randomisation will be as follows:

- **Participants with a serum potassium >5.0mmol/L** will be randomised to patiromer 8.4g once daily or not and then follow the scheme shown below with evaluation of serum potassium on Days 3, 5 and 7 and periodically thereafter (see schedule of procedures).
- **Participants with a serum potassium ≤5.0mmol/L who are not currently receiving an MRA** will first be given spironolactone (or eplerenone[#]) 25mg once daily and randomised to patiromer or not, if and when their serum potassium is >5.0mmol/L. If serum potassium does not exceed 5.0mmol/L within 72 hours, the dose of spironolactone may be increased to 50mg/day and after a further 72 hours to 100mg/day. Those intolerant of or unwilling to take spironolactone should be offered eplerenone (maximum dose 50mg/day).
- **Participants with a serum potassium ≤5.0mmol/L who are currently receiving an MRA** at a dose of <50mg/day will be initiated on spironolactone 50mg once /daily (or eplerenone[#]) or if currently already receiving 50mg/day, spironolactone 100mg/day (the maximum dose of eplerenone is

50mg/day). They will be randomised to receive patiromer or not, only once their serum potassium is >5.0mmol/L.

- **Immediately after randomisation:** Those assigned to standard care should have the dose of MRA reduced unless serum potassium is ≥6.0mmol/L, in which case MRA should be temporarily suspended altogether until serum potassium is <5.0mmol/L. Patients with a serum potassium >5.0mmol/L who are not taking any dose of MRA may need the dose of other agents that increase potassium reduced. Those assigned to patiromer should continue to receive the dose of MRA administered at the time of randomisation unless serum potassium is ≥6.0mmol/L, in which case MRA should be temporarily suspended and patiromer continued until serum potassium is <6.0mmol/L. If serum potassium is ≥6.0mmol/L, also seek medical advice and treat according to guidelines. If intravenous treatment or a potassium-binding agent for the treatment of severe hyperkalaemia is required in the investigators opinion, the participant can be randomised only after these treatments have been stopped.
- **Maintenance Phase:** doses should follow the scheme shown in the tables below.
- Participants who do not develop a serum potassium >5.0mmol/L despite 100mg/day of spironolactone or 50mg/day of eplerenone within 35 days are not eligible for the randomised trial and will return to standard care. The clinician responsible for care should select the most appropriate dose of MRA for the participant. Under these circumstances, this will usually be 50mg/day of spironolactone or eplerenone. Participants will continue to be followed in the registry and may be reconsidered for the trial at any time should they become eligible.

If eGFR falls below 30mls/min/1.73m^{2}or systolic blood pressure below 90mmHg prior to randomisation, the participant is not eligible for randomisation until these exclusion criteria have resolved. Under these circumstances, clinicians responsible for care should decide whether to continue the MRA and at what dose. Those excluded will continue to be followed in the registry and may be reconsidered for the trial at any time should they become eligible.

The following maximum doses of MRA are permitted for participants in the intervention arm after randomisation:

- **Spironolactone:** 200mg once daily. All doses must be taken orally.
- **Eplerenone:** 50mg once daily. All doses must be taken orally.

only those intolerant of, or unwilling to take, spironolactone should be offered eplerenone.

Titration of Patiromer and MRA for Patients Assigned to Patiromer				
Serum Potassium #	*Patiromer ##*	MRA ###	Potassium Supplements	Other Potassium Sparing Diuretics
<3.5mmol/L	*Withhold Patiromer for 48 hrs*	Increase MRA Dose unless already on highest dose tolerated	Consider	Consider
3.5-4.0mmol/L	*Maintain Patiromer Dose (unless already on highest dose of MRA, in which case reduce dose of patiromer)*	Increase MRA Dose unless already on highest dose tolerated	Withhold	Withhold
4.1-4.9mmol/L	*Maintain Patiromer Dose*	Increase MRA Dose unless already on highest dose	Withhold	Withhold
5.0-5.9mmol/L	*Increase Patiromer Dose unless already on highest dose*	Maintain MRA Dose unless already on highest dose of patiromer, in which case reduce dose of MRA	Withhold	Withhold
≥6.0mmol/L‖	*Increase Patiromer Dose unless already on highest dose*	Withhold MRA until serum potassium is **<6.0mmol/L** then re-start at lower dose. Seek medical advice and treat according to guidelines ‖	Withhold	Withhold

Titration of MRA for Patients Assigned to Control			
Serum Potassium #	MRA ∞	Potassium Supplements	Other Potassium Sparing Diuretics
<3.5mmol/L	Increase MRA Dose unless already on 50mg/day	Consider	Consider
3.5-4.0mmol/L	Increase MRA Dose unless already on 50mg/day	Consider	Consider
4.1-4.9mmol/L	Maintain MRA Dose	Withhold	Withhold
5.0-5.9mmol/L	Reduce MRA Dose	Withhold	Withhold
≥6.0mmol/L‖	Withhold MRA until serum potassium is **<5.0mmol/L** then re-start at lower dose Seek medical advice and treat according to guidelines ‖	Withhold	Withhold

most recent serum potassium – usually measured on the same or previous day. If doses of patiromer or MRA are changed, blood pressure and serum electrolytes and creatinine should be re-checked both after 7-12 days and after 30-45 days. If the patient becomes acutely unwell for any reason, blood pressure, serum electrolytes and creatinine should be re-checked. Serum potassium should also be checked within 48 hours of stopping patiromer.

initial dose is 8.4g/day and may be increased in steps to 16.8g/day or 25.2g/day guided by serum potassium, investigator judgement and patient-acceptance of higher doses. The maximum possible dose is 25.2g/day.

the maximum dose of spironolactone is 200mg/day and of eplerenone 50mg/day and will be guided by serum potassium, symptoms of hypotension, renal dysfunction and patient-acceptance of higher doses. Only those intolerant of or unwilling to take spironolactone should be offered eplerenone.

∞the maximum dose of spironolactone is 200mg/day and of eplerenone 50mg/day and will be guided by serum potassium, symptoms of hypotension, renal dysfunction and patient-acceptance of higher doses. Only those intolerant of or unwilling to take spironolactone should be offered eplerenone.

‖Management of hyperkalaemia with a serum potassium ≥6.0mmol/L will also follow the Renal Association guidelines of 2020 (https://renal.org/sites/renal.org/files/RENAL%20ASSOCIATION%20HYPERKALAEMIA%20GUIDELINE%202020.pdf). Participants should be recalled urgently to have serum potassium rechecked, clinical review and an electrocardiogram. Referral to an accident & emergency department may be considered. Patiromer alone should not be used for the emergency treatment of hyperkalaemia.

9.8 Preparation and administration of patiromer oral suspension

The required number of patiromer sachets should be added to 40ml (3 tablespoons) of water in a glass and then stirred. A further 40ml (3 tablespoons) of additional water should be added and the suspension stirred thoroughly. The powder does not dissolve but instead forms a suspension. More water can be added to the mixture as needed for the desired consistency. The suspension should be taken as soon as prepared but it must be taken within 1 hour. If powder remains in the glass after drinking, more water should be added, the suspension stirred and the remaining solution drunk immediately. This should be repeated as needed to ensure the entire dose is administered.

If required apple juice may be used instead of water to prepare the mixture. Whilst patiromer can be mixed with cranberry juice, its use should be avoided where possible in this trial due to the potential of interactions with other medicinal products. Other liquids should be avoided as they may contain high amounts of potassium. The patiromer suspension may be taken with or without food. The powder should not be heated (e.g. microwaved), added to heated foods or liquids, or taken as a dry powder. Further information is provided in the current Summary of Product Characteristics and package insert.

Patiromer doses must not be split and should be taken as a single oral dose once daily. Patiromer should be taken preferably at the same time each day and should be taken at least 3 hours before or after other oral medicines. This recommendation is based on concerns about possible binding of patiromer to other medicines that might reduce their absorption. This has been tested in the medicines described below.

Medicines where there is reduced bioavailability/potential interaction when co-administered with patiromer
Administration of the following oral medicines with patiromer must be separated by at least 3 hours to prevent interaction

- ciprofloxacin
- levothyroxine
- metformin
- quinidine

Medicines where there is considered to be no clinically significant effect on bioavailability/ potential interaction when co-administered with patiromer
At the discretion of the Investigator, the following oral medicines may be co-administered/administered within 3 hours prior to or after taking patiromer:

- spironolactone, furosemide, digoxin,
- lisinopril, valsartan,
- aspirin, clopidogrel,
- atorvastatin
- allopurinol, phenytoin
- amoxicillin, cephalexin, trimethoprim* (* increased risk of hyperkalaemia)
- apixaban, rivaroxaban, and warfarin.

This list may be extended as further research becomes available.

Note that at the current time there is no information available on co-administration with eplerenone therefore administration should be separated from patiromer by at least 3 hours.

Missed and omitted patiromer doses

Participants should not discontinue treatment without consulting the research team.

If a dose of patiromer is missed, it should be taken as soon as possible on the same day unless it is almost time to take the next dose in which case you should not take the forgotten dose. A double dose

should not be taken on the following day to make up for a missed dose. Participants should just resume taking their next normal dose at their usual time. If doses of patiromer are missed on more than two consecutive days, participants **must** contact the research team for advice. Participants must not discontinue patiromer without consulting the trial team. Increases in serum potassium may occur within 2-4 days after the last dose of patiromer.

If the participant stops patiromer for any reason, they must also stop their MRA and contact the investigator.

9.9 Administration of spironolactone and eplerenone

Spironolactone tablets must be administered orally and tablets should be swallowed whole with water and preferably taken with a meal. Eplerenone tablets must be administered orally and should be swallowed whole with water but may be taken with or without food. Use of unlicensed oral suspensions or solutions is not permitted.

Missed and omitted spironolactone or eplerenone doses

Participants should not discontinue treatment without consulting the research team.

Participants should take a missed dose as soon as possible on the same day unless it is almost time to take the next dose in which case the forgotten dose should be omitted. A double dose should not be taken on the following day to make up for a missed dose. Participants should just resume taking their next normal dose at their usual time. If doses of spironolactone or eplerenone are missed on three or more consecutive days, participants **must** be advised to contact the research team for advice.

If the participant stops their MRA for any reason, then they should also stop their patiromer and contact the investigator.

If the participant develops persistent vomiting and/or diarrhoea lasting more than two hours or if they become acutely unwell for any other reason they should stop MRA (control group) or both MRA and patiromer (intervention group) until they have recovered or, if symptoms are severe or persistent, seek medical advice either from their general practitioner or emergency services. The investigator should be contacted as soon as possible to determine the need for assessments of serum potassium and adjustment of MRA or patiromer dose.

Dosage modifications

The dose of patiromer and MRA should be altered according to the serum potassium concentration according to the schedule shown in section 8.6.

Trial supplies of patiromer-IMP must not be used for the emergency treatment of hyperkalaemia in either group and must not be used to manage hyperkalaemia in patients assigned to standard care.

The dose of MRA may also be limited by blood pressure and renal dysfunction. The dose of MRA should be reduced or stopped if the patient has symptomatic hypotension or eGFR falls persistently to <30mL/min/1.73m^2 after other therapeutic actions to improve hypotension and renal dysfunction have been undertaken, if appropriate (see below).

For eplerenone only:
Co-administration with mild to moderate CYP3A4 inhibitors: Eplerenone dosing should not exceed 25 mg daily when mild to moderate inhibitors of CYP3A4 are co-administered with eplerenone (e.g. erythromycin, saquinavir, amiodarone, diltiazem, verapamil, or fluconazole).

9.10 Known drug reactions and interaction with other therapies

Patiromer

Patiromer binds potassium in the gastrointestinal tract. It is insoluble and is not absorbed. Patiromer does however have the potential to bind with oral co-administered medicinal products, which could decrease their gastro-intestinal absorption. Therefore, as a precautionary measure, administration of patiromer should be separated by at least 3 hours from other oral medicines unless listed as permitted at investigator-discretion in Section 9.8.

Spironolactone and eplerenone

The concomitant use of medicines known to cause hyperkalaemia with spironolactone or eplerenone may result in severe hyperkalaemia and should be withdrawn unless the investigator believes this not in the patient's best interest. Management of hyperkalaemia that cannot be managed by adjusting doses of MRA (or patiromer if assigned to this group) will follow the Renal Association guidelines of 2020 (https://renal.org/sites/renal.org/files/RENAL%20ASSOCIATION%20HYPERKALAEMIA%20GUIDELINE%202020.pdf).

Controversy persists on possible adverse consequences of taking MRA in conjunction with the combination of both an angiotensin converting-enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB). Investigators should avoid such practice.

Strong inhibitors of CYP 3A4 (e.g. itraconazole, ketoconazole, clarithromycin, telithromycin and nefazodone) may interfere with MRA metabolism and should be avoided wherever possible in patients taking MRAs. Eplerenone dosing should not exceed 25 mg daily when mild to moderate inhibitors of CYP3A4 are co-administered with eplerenone (e.g. erythromycin, saquinavir, amiodarone, diltiazem, verapamil, or fluconazole).

Caution is required with co-administration of MRA with the following medicines:

- Heparin and low molecular weight heparins
- Non-steroidal anti-inflammatories (NSAIDs)
- Trimethoprim or trimethoprim containing combination products e.g. co-trimoxazole
- Alpha-1-blockers (e.g. prazosin, alfuzosine) and other antihypertensive medicines
- Tricyclic anti-depressants, neuroleptics, amifostine, baclofen
- Glucocorticoids, tetracosactide
- Cholestyramine
- Digoxin and warfarin: caution is warranted particularly when dosed near the upper limit of therapeutic range
- Potassium supplements and potassium sparing diuretics e.g. amiloride.

The current Summary of Product Characteristics should be consulted for detailed information on interactions with other medicinal products.

9.11 Concomitant medication

Permitted concomitant medicines

All patients should be receiving loop diuretics and most will already be taking an MRA.

We expect that most patients will also be receiving one (only one) of the following agents: ACE inhibitors, ARBs, sacubitril-valsartan. Many will also receive beta-blockers and anti-thrombotic agents. Some patients will also be receiving thiazide diuretics, digoxin and ivabradine. Many patients will be receiving non-cardiovascular medications for various indications.

The patients enrolled in this trial are inherently unstable and therefore no attempt to stabilise medications prior to enrolment is considered feasible. Investigators should attempt to stabilise and optimise treatment after randomisation during follow-up according to guidelines (investigators may choose to follow NICE, SIGN or ESC guidelines).

Where the dose of MRA is limited by hypotension or renal dysfunction, the investigator should consider whether reducing the dose of loop diuretic is possible. Thiazide diuretics could also be withdrawn but that may lead to marked fluid retention and therefore care is required. If the patient is severely congested and it is not possible to reduce the dose of diuretics then:

a) The dose of ACE inhibitor may be reduced to 2.5mg/day of Ramipril or enalapril 2.5mg bd or similar, since there is little evidence from randomised trials that outcomes are better on higher compared to lower doses of ACE inhibitors for patients with moderate or severe heart failure (14). This may also be true for ARB and sacubitril-valsartan.
b) For patients in atrial fibrillation (about half of this population) there is little evidence that beta-blockers are effective and evidence that reducing ventricular rate below 75bpm may be deleterious (16). Accordingly, reducing the dose of beta-blockers is advised to allow resting heart rate to rise above 75bpm.

Prohibited concomitant medicines
The following medicines are prohibited for all participants for safety reasons:

- Combined use of both an ACE inhibitor and ARB
- Lithium
- Cyclosporin
- Tacrolimus

The following medicines are prohibited for participants treated with eplerenone (patients must be switched to spironolactone during co-administration of these agents)

- Strong inhibitors of CYP 3A4 e.g. itraconazole, ketoconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazodone.
- Strong CPY3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort)

9.12 Trial restrictions

Patients should avoid taking potassium supplements (including dietary substitutes such as Lo-Salt) or potassium sparing diuretics other than MRA unless required for the management of hypokalaemia.

Use of strong CYP 3A4 inhibitors and combined use of both an ACE inhibitors and ARB should be avoided. Most if not all patients will have renal dysfunction and therefore the use of non-steroidal anti-inflammatory drugs should be avoided where possible. Use of non-evidence based medicines and over-the-counter treatments including herbal and other dietary supplements are discouraged.

Patiromer should not be taken within three hours of other oral medications. Patiromer should be mixed with water or apple juice, as directed.

9.13 Assessment of compliance with treatment

Compliance will be estimated at each trial visit by research staff and participants, and documented in the eCRF. For those treated with both patiromer and MRA, research staff must assess compliance with both IMPs to ensure that both are taken as intended. For those receiving both patiromer and MRA, poor compliance (<80%) should be discussed with the participant, their safety evaluated and consideration given to withdrawing patiromer and reverting their management to standard care with

MRA alone. Poor compliance with MRA should also be discussed with the participant and the benefits of MRA emphasised.

Patients must be withdrawn from treatment with IMP(s) if the investigator considers it unsafe for them to continue. Safety will be assessed by research nurses and/or investigators at each visit and after the occurrence of each SAE/SAR. Participants who have had an SAR (*e.g.* a hospital admission for the management of hyper- or hypo-kalaemia) should be reassessed for their ability to understand and comply with IMP dosing instructions.

- If the participant is, in the investigator's opinion, no longer able or willing to comply with treatment instructions, then they should stop one or both IMP and revert to standard-care, even if they have not experienced an SAE or SAR.
- Participants who are assigned to patiromer and who have or develop hyperkalaemia (serum potassium >5.0mmol/L), even if they have been withdrawn from spironolactone or eplerenone IMP, may continue on or restart patiromer.
- For participants with recurrent (two or more within a 6 month period) or life-threatening hyperkalaemia, investigators should reduce the dose of spironolactone or eplerenone to a maximum of 25mg/day or less (this includes a zero-dose), unless in the opinion of the investigator the benefit/risk ratio of receiving higher doses of spironolactone / eplerenone IMPs is still believed to be positive (*e.g.* the participant's heart failure has responded well to higher doses of spironolactone or eplerenone). Participants assigned to patiromer should have the doses adjusted to achieve a serum potassium between 4.1 to 4.9mmol/L (inclusive).

IMP may be re-initiated at any time if the investigator believes it is safe to do so and the participant is willing.

Compliance will be encouraged by patient information leaflets and education. However, even if a patient is withdrawn from IMP they should be followed according to the protocol. Patients who decline to attend trial visits will be unable to obtain trial IMP and therefore will revert to standard care. If the participant agrees, they will continue to be contacted by the investigator or followed through their medical record even if they decline to attend trial follow-up visits.

10. SAFETY AND OUTCOME REPORTING

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPC's suitability will need to be undertaken.

	• in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition as supplied above.

10.2 Operational reporting for (S)AEs

Adverse events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and this protocol. All AEs occurring during the trial that are observed by the Investigator or reported by the participant will be recorded in the participant's medical records whether or not attributed to trial medication.

All adverse reactions must be recorded within the eCRF.

All Serious Adverse Events (SAEs) occurring during the trial must be recorded in the eCRF.

The following are not considered be to be SAEs for the purposes of this trial.

- Routine treatment or monitoring of heart failure not associated with deterioration in heart failure.
- Treatment which was elective or pre-planned, for a pre-existing non-cardiac condition not associated with any deterioration in heart failure, e.g. pre-planned hip replacement operation which does not lead to further complications.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.
- Admissions for social reasons not associated with a deterioration of heart failure.

All SAEs will be reported to the IDMC and analysed as part of the final trial results.

Full details of SAEs will be recorded in the electronic Case Report Form. The following information will be collected:

- full details in medical terms and a case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- if related, whether the reaction would be considered expected or unexpected.

Any change of condition or other follow-up information should be added to the eCRF as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

Assessment of Adverse Events

All adverse events must be assessed for seriousness. All SAEs must also be assessed for severity, causality and expectedness with reference to this protocol and the Reference Safety Information (RSI).

Assessment of seriousness

An adverse event will be considered serious if it:

- results in death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- requires intervention to prevent one of the above
- Is an event of special interest as defined above

Assessment of causality

i.e. Does the event have a "reasonable causal relationship" with the trial IMPs? The following categories are used:

- **Yes** - the causal and temporal relationship between the event and the absence of a more likely explanation suggest that the trial IMP is the most likely cause.
- **No** - the event is not considered related to the trial IMPs.

Causality will be assigned for each IMP the participant is randomised to receive.

Should an SAE be considered unrelated to the administration of either trial drug then the causality of the event will be collected taking into consideration other factors, for example, concomitant medications or co-morbidities, etc.

Assessment of causality is the responsibility of the Principal Investigator or medically-qualified designee(s) at each site. The CI, their delegate(s), or the Sponsor may provide an opinion regarding causality but cannot downgrade the PI's assessment.

Assessment of expectedness

Should the event be considered to be related to the trial IMP(s), an assessment should be made regarding the expectedness of the reaction i.e. whether the reaction is a recognised adverse effect of the IMP(s).

Expected - consistent with the relevant product information documented in the RSI(s).
Unexpected - not consistent with the relevant product information documented in the RSI(s).

The CI, their delegate(s) or the Sponsor have overall responsibility for assigning expectedness as per the RSI(s) and providing the final assessment of the event. The reporting investigator may provide an opinion on the expectedness of an event and this will be taken into account.

Assessment of severity

This should be assessed and described using the following categories:

- Mild - awareness of event but easily tolerated
- Moderate - discomfort enough to cause some interference with usual activity
- Severe - inability to carry out usual activity.

Recording and reporting of SAEs
All reportable SAEs (see section 9.3) arising during the clinical trial will be recorded in the eCRF as soon as reasonably practicable and in any event within 24 hours of first becoming aware of the event. Any follow-up information should also be reported.

- If recording via the eCRF is not possible, a paper SAE form should be completed. The SAE form is downloaded from www.glasgowctu.org, printed, completed and signed. A paper copy of the SAE form is filed in the Investigator Site File at each site should this website be unavailable. The completed form is faxed to the Glasgow Clinical Trials Unit Pharmacovigilance (PV) Office on +44 (0)141 357 5588. If fax is not possible, a copy of the SAE form should be scanned and emailed to pharmacovig@glasgowctu.org.
- If necessary a verbal report can be provided by contacting the PV Office on +44 (0)141 330 4744. This must be followed up as soon as possible with an electronic or written report.

10.3 Serious Adverse Events (Sponsor reportable events)

Patiromer, spironolactone and eplerenone have well-understood safety profiles. Previous clinical trials have shown the combination of drugs to be well-tolerated (12). However, when the IMPs are used in combination there remain potential concerns regarding the effects of the IMP(s) on serum potassium.

In addition, participants in this trial are expected to have high rates of hospitalisations, cardiovascular events and death due to cardiac disease and related co-morbidities that are unlikely to be attributable to treatment with the trial IMP(s). These events will, however, inform the primary and secondary endpoints of the trial and will be subject to monitoring by the Data Monitoring Committee. As such these event will be recorded within the eCRF as per section 9.2.

Where the medicines are used in combination, the principle concern is changes in serum potassium and/or magnesium. For the purposes of pharmacovigilance, safety reporting will focus on the occurrence of hypokalaemia, hyperkalaemia, hypomagnesaemia, and events associated with these conditions, in particular potentially harmful renal insufficiencies.

Monitoring of non-reportable events

Non-reportable events will be monitored during the study. If deemed necessary, an initially non-reportable event may be added to the list of events reported to Sponsor. The process for this will be documented separately.

The following will be recorded on the eCRF as Serious Adverse Events and will be subject to expedited reporting to the sponsor:

- Any SAE that is considered, in the Investigator's opinion, related to the administration of any of the IMPs used in the trial, whether individually or in combination.
- Any incidence of an acute kidney injury meeting the criteria of a serious adverse event.
- Renal failure associated with a requirement for renal dialysis/ultrafiltration; and deaths associated with renal failure as evidenced by a preceding eGFR of 10ml/min/L/1.73m^2
- SAEs associated with one of the following electrolyte disturbances
    - Severe hypokalaemia defined as serum potassium <3.0mmol/L
    - Severe hyperkalaemia defined as a serum potassium> 6.5mmol/L
    - Severe hypomagnesaemia defined by a serum magnesium <0.5mmol/L

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any SAE assessed as related to trial IMP(s) by the PI or delegate, and unexpected (not documented as an expected reaction to the IMP(s) within the RSI(s)) by the CI, their delegate, or the Sponsor will be classified as a SUSAR and subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). Should the CI disagree with the PI's assessment of causality, both opinions will be provided on the report.

The Sponsor will inform the MHRA and the REC of SUSARs within the required expedited reporting timescales:

- **Fatal or life threatening SUSARs** - not later than 7 days of Sponsor awareness that the case fulfils the criteria for a fatal or life threatening SUSAR, and any follow up information within a further 8 days.
- **All other SUSARs** - not later than 15 days of Sponsor awareness that the case fulfils the criteria for a SUSAR.

The Sponsor will report SUSARs to the MHRA via the MHRA eSUSAR reporting system and to REC by email with accompanying CTIMP Safety Report Form.

10.4 Responsibilities

Principal Investigator (PI):

- Attendance at the initiation meeting/teleconference.
- Training of new members of the trial team in the protocol and its procedures.
- Ensuring that the ISF is accurately maintained.
- Dissemination of important safety or trial-related information to all stakeholders at their site.
- Checking for AEs and ARs when participants attend for treatment / follow-up.
- Ensuring that AEs are recorded and reported in line with the requirements of the protocol.
- Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event, and providing further follow-up information as soon as available.
- Using medical judgement in assigning seriousness, causality, and severity of SAEs.
- Providing an opinion on the expectedness of an SAE with reference to the trial protocol and Reference Safety Information.
- Using definitions in this protocol, flagging events of special interest or potential endpoints.

Chief Investigator (CI)

- Providing clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Providing clinical review of section 4.8 of the representative SmPCs on an annual basis to define the Reference Safety Information for the trial.
- Using medical judgement to confirm seriousness and causality of all SAEs.
- Reviewing expectedness of related SAEs with reference to the trial protocol and Reference Safety Information.
- Preparing the clinical sections and final sign-off of the Development Safety Update Report (DSUR).
- Using definitions in this protocol, confirming events of special interest or potential endpoints.

Sponsor:

- Central data collection and verification of AEs, SAEs, SARs and SUSARs according to the trial protocol.
- Maintaining the Reference Safety Information for the trial and ensuring it is complies with regulatory guidance.
- In the absence of the CI and their delegates, reviewing expectedness of SAEs against the Reference Safety Information.
- Reporting safety information to the CI or delegate for the ongoing assessment of risk/benefit.
- Reporting safety information to the independent oversight committees identified for the trial (Independent Data Monitoring Committee (IDMC) and/or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.

- Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
- Notifying Investigators of SUSARs that occur within the trial.
- Annual checking for updates to the Reference Safety Information for the trial, and notifying PIs of any changes.
- Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee:

Periodically reviewing recruitment and the overall progress of the trial and liaising with the IDMC and sponsor regarding safety issues. Reporting the results of the trial to the investigators and wider public and writing primary and secondary papers.

Trial Management Group:

They will be responsible for day to day running of the trial.

Independent Data Monitoring Committee:

In accordance with the Charter for the IDMC, periodically reviewing unblinded safety data in individual cases and to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis, reporting concerns to the TSC and sponsor.

Clinical Endpoint Committee (CEC):

In accordance with the Charter for the CEC, review and classify all potential clinical endpoints in the trial.

10.5 Notification of deaths

All deaths occurring within the trial will be reported within the eCRF as an SAE.

10.6 Pregnancy reporting

Women at risk of pregnancy are excluded from this trial. Patiromer is not absorbed and therefore is not considered a risk to female partners of male participants. MRA are guideline-recommended therapy and are not known to pose a risk to female partners of men who take MRA.

10.7 Overdose

Patients may take an overdose of patiromer or MRA deliberately or inadvertently.

Definition: An overdose is defined as a patient who has taken substantially more of the IMP than intended, either in a single large dose (usually this will be a deliberate act of self-harm) or a smaller deviation but over a longer period of time. For this protocol, the latter will be defined as taking a dose-level higher than intended that either persists for more than one month or results in hospitalisation or death.

Overdoses resulting in an SAE will be recorded on the SAE eCRF.

Investigators will evaluate whether it is safe for the patient to continue on IMP and if not they will revert to standard care. They will continue to be followed-up as intended in all other respects.

Psychiatric advice will be sought for patients who have attempted self-harm.

10.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor will phone the MHRA's Clinical Trial Unit on 020 3080 6456, ideally within 24 hours. This will be followed up no later than 3 days from the date the measures are taken, giving written notice to the MHRA (who will advise the format required) and the relevant REC of the measures taken and the circumstances giving rise to those measures. A substantial amendment must also be submitted to the MHRA.

10.9 The type and duration of the follow-up of participants after adverse reactions.

Adverse events and reactions will be recorded, reported and followed to completion in line with this protocol until 30 days after participant's last dose of the IMP.
Any SUSAR identified will be reported to the Sponsor and to the Regulatory Authorities irrespective of how long after IMP administration the reaction has occurred.

10.10 Development safety update reports (DSURs)

DSURs will be submitted within 60 days of the anniversary of the issue of the Clinical Trials Authorisation for the trial. DSURs will be prepared and submitted by the sponsor (PV Office) in liaison with the CI.

11. STATISTICS AND DATA ANALYSIS

11.1 Sample size calculation

The anticipated primary endpoint rate in the control group is 40%. We estimate that 999 subjects per group (yielding 719 first-events) will provide >90% power to detect a hazard ratio of 0.75 (25% reduction) at the 1% significance level and >80% power to detect a hazard ratio of 0.80 at the 5% significance level, which we believe reflect clinically meaningful benefit. This is based on a time to first event analysis using the Wald statistic in a Cox proportional hazards model. To allow for some uncertainty the trial will be stopped once 750 patients have experienced a primary endpoint. As the primary endpoint is a recurrent-event analysis, the trial should have additional power.

The primary endpoint at 60 days is a novel scoring system and therefore there are no prior data upon which to base assumptions. Assuming a normal distribution of "Congestion Index" scores, 400 patients provides >90% power to demonstrate a difference between strategies of 0.325 of a standard deviation in the effect size for the change in score between baseline and follow-up.

11.2 Anticipated recruitment rate

On average, the 100 sites participating in this trial will care for about 20,000 patients with advanced heart failure per year, of which we estimate 25% would be suitable and 10% would be both suitable and willing to participate in this trial. Accordingly, we anticipate that each site should be able to enrol 20 patients per year. We anticipate it will take 12-18 months to initiate all 100 sites and that not all sites will perform to target. Therefore, we assume that enrolment will take two to three years.

11.3 Statistical analysis

The primary analysis will be done on the intention-to-treat population. The primary endpoint is the composite of time to need for IV diuretics (subsequent to initial discharge) for worsening or recalcitrant heart failure, hospitalisation for worsening heart failure or non-cancer deaths analysed as a recurrent event. This is a novel trial endpoint and methodology for analysing such outcomes is evolving. Therefore the methods used to analyse the recurrent events will be updated based on this evolving area of research and will be finalized prior to database lock.

Time to first event outcomes will be analysed using Cox proportional hazards models with randomised treatment as a covariate. Statistical significance will be assessed using the Walk statistic and estimated hazard ratios for the treatment effect and their 95% confidence intervals calculated.

Time to event curves will be constructed using cumulative incidence functions adjusting for competing risks where appropriate. Outcomes from the Quality of Life and congestion scores will be analysed at the specified time points using t-tests with no imputation for missing data. Days dead or hospitalised and quality-adjusted days alive and out of hospital will be analysed using re-randomisation tests adjusting for potential length of follow-up. Serious adverse events will be tabulated by system organ class and preferred term. A complete statistical analysis plan will be completed and signed off before database lock.

11.4 Subgroup analyses

The primary outcome will be analysed in the following sub-groups:

- Age (by tertile)
- Sex (categorical)
- Recruitment as an in-patient or out-patient (categorical)
- MRA dose prior to inclusion (<25mg, 25mg, >25mg of spironolactone or eplerenone)
- Systolic blood pressure (by tertile)
- eGFR (by tertile)
- LVEF (<40%, 40-49%, >49%)
- COPD (categorical)
- Diabetes mellitus (categorical)

Results will be presented within each subgroup along with a test for treatment by subgroup interaction.

11.5 Interim analysis and criteria for the premature termination of the trial

Unblinded trial data will be reviewed on an ongoing basis by the IDMC. The primary role of the IDMC will be to protect the interests of the patients. The IDMC may recommend to the TSC and Co-Sponsors that the trial should be stopped prematurely because of concerns about patient safety of conclusive evidence of overwhelming benefit. The IDMC will meet after 100, 200, 400, 1,000, 1,500 and 2,000 patients have completed 60-day follow-up.

The IDMC may recommend stopping the study for safety at any time. At each meeting, the IDMC will review the overall rate of serious adverse events and serious adverse events of special interest (hypokalaemia, hyperkalaemia, hypotension, renal failure, arrhythmias and heart failure) that may be influenced (favourably or unfavourably) by intervention.

The IDMC will take into account all results and the consistency and biological plausibility of the findings in making any recommendation. The final decision on continuing or stopping the trial will lie with the TSC/Co-Sponsors. The pre-specified stopping guidelines below will be detailed in the IDMC Charter and statistical analysis plan.

Interim analysis

If the analysis of 60-day outcome for the first 400 patients evaluated at 60 days suggests a potential failure of the treatment strategy [either similar doses of MRA amongst patients assigned to patiromer and standard care or a lack of improvement in congestion by Day-60] then the IDMC will be asked to consider stopping the trial unless the conditional power of the trial to show benefit on the primary endpoint exceeds 70%.

- In order for the dose of MRA to be considered dissimilar for participants assigned to patiromer compared to standard care the following criteria should be met:-
    - The mean dose of MRA of those assigned to patiromer should be >50% higher (i.e. 25mg/day versus >37.5mg/day) than for those assigned to standard care.
    - This difference should be statistically significant
- If there is no significant difference in either the overall congestion index or in plasma concentration of NT-proBNP at 60-days, then this will be considered a lack of improvement in congestion.

If patiromer fails by either or both criteria, the trial may be terminated unless a strong trend to benefit on morbidity and mortality is observed in the overall trial data. At the time of this evaluation, we anticipate that >100 patients will have been followed for at least one year, up to 800 patients may have been randomised altogether and >200 primary endpoints will have occurred.

11.6 Participant population

Analyses will be carried out on an intention to treat basis according to randomised treatment.

11.7 Procedure(s) to account for missing or spurious data

The main analyses will be based on morbidity/mortality data for which imputation is not necessary. For quality of life outcomes, laboratory results or other continuous variables results will be analysed with and without imputation. Multiple imputation procedures will be used. Full details will be provided in the statistical analysis plan.

11.8 Other statistical considerations

A Statistical Analysis Plan (SAP) for each phase of the trial will be maintained and approved as a version controlled document prior to each formal statistical analysis. The SAP will contain full details of all analyses along with assumptions and procedures for handling problematic or incomplete data (e.g. incomplete dates).

11.9 Economic evaluation

No formal economic evaluation will be included in the statistical analysis plan, however quality of life and hospitalisation data will be collected and may be utilised in a separate economic analysis at a later date if required.

12. DATA MANAGEMENT

12.1 Source Documentation

ICH GCP defines source data as: 'All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial'. In this trial, the location of the majority of the source data will be the hospital's medical records including subject case notes, laboratory records and ECGs. The source data transcribed into the eCRF from the medical records must be accurate and verifiable. For questionnaires completed by trial subjects, the completed questionnaires will be regarded as the source data location. In cases where data is transcribed directly into the eCRF and no other paper or electronic source exists, then the eCRF will be considered the source record. In these cases, these data should be prospectively documented in the medical records to ensure a full record of the trial is available at site.

12.2 Data collection

An eCRF, developed by the Robertson Centre for Biostatistics, will capture all data required to meet this protocol's requirements. Access to the eCRF will be restricted, via a trial-specific web portal, and only authorised site-specific personnel will be able to make entries to their patients' data via the web portal. The Investigator or his /her designee will be responsible for all entries into the eCRF and will confirm that the data are accurate, complete and verifiable. Data will be stored in a MS SQL Server database.

Direct access to the web portal will be granted, on request, to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.3 Data Validation

Where it is practical, data will be validated at the point of entry into the eCRF. Any additional data discrepancies will be flagged to the investigator and any data changes will be recorded to maintain a complete audit trail (reason for change, date change made and who made the change).

12.4 Data Security

The Robertson Centre for Biostatistics systems are fully validated in accordance with industry and regulatory standards, and incorporate controlled access security. High volume servers are firewall protected and preventative system maintenance policies are in place to ensure no loss of service or data. Web servers are secured by digital certificates. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. Data are backed up on-site nightly and off-site to a commercial data vault weekly. The Robertson Centre for Biostatistics has an ISO 9001:2008 quality management system and ISO 27001:2013 for Information Security, and is regularly inspected against the standards by the British Standards Institution.

12.5 Archiving

The Trial Master File will be archived by the Sponsor at the end of the trial for a minimum period of 25 years.

Archiving of Site Files will also be for a minimum of 25 years from completion of the trial, and this action will be delegated to the sites in the Clinical Trial Site Agreement that will be put in place between Sponsor and Sites. Sites will be notified by the Sponsor when Site files can be archived. Destruction of site files can only take place with the approval of the Sponsor.

13. MONITORING, AUDIT & INSPECTION

Trial monitoring visits will be conducted by NHS GG&C monitor(s). Prior to starting the trial, a trial-specific Monitoring Plan will be developed by the monitor(s). The level of monitoring, on-site and remote, will be based on the outcome of the completed monitoring risk assessment, and will be clearly documented in the monitoring plan which will be approved by the NHS GG&C Research Governance Manager / Academic Lead Clinical Trial Monitor. As standard, monitoring visit(s) will cover site file review, review of Informed Consent Forms (ICFs), Source Data Verification (SDV) and Serious Adverse Event (SAE) review as per monitoring plan objectives.

Central monitoring objectives will be documented in the monitoring plan upon agreement between the RCB and the Sponsor.

The CI and other investigators shall be accessible for monitoring visits. Direct access to patient records for source data verification will need to be granted and prepared prior to any monitoring visits.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Research Ethics Committee (REC) review and reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (it is noted that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended (this is the Chief Investigator's responsibility).

The Chief Investigator will notify the REC of the end of the trial.

If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination

Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

14.2 Peer review

The trial protocol was reviewed by the British Society for Heart Failure sub-committee and at two UK Heart Failure Investigators Research Network meetings during 2018. Members have expertise in the care of patients with heart failure and/or the conduct of clinical trials in the relevant population. The protocol has also been reviewed by representatives of the funder (Vifor) and of the sponsor.

14.3 Public and Patient Involvement

The trial was designed by physicians with expertise in managing heart failure supported by the Robertson Centre for Biostatistics research design service.

A patient panel was convened to review the trial design and protocol. The design and protocol were revised in the light of their comments.

Patients will advise on the patient information sheet and enrolment strategy.

Patient organisations will disseminate information about the ongoing trial and, in due course, its results.

Guidance on involving patients and the public in research can be found on the INVOLVE website. http://www.invo.org.uk/

14.4 Regulatory Compliance

- The trial will not commence until a Clinical Trial Authorisation (CTA) and a favourable opinion is obtained from the MHRA and REC, respectively.

- The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

14.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time. They will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol that frequently recur are not acceptable and will trigger immediate action and could potentially be classified as a serious breach.

14.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to affect to a significant degree:

1. the safety or physical or mental integrity of trial participants; or
2. the scientific value of the trial

If any of the above occurs then the CI and Sponsor will be notified. The sponsor will notify the appropriate authorities in writing of any serious breach in accordance with their standard operating procedures.

14.7 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

- Personal information will be collected via the eCRF to enable record linkage to be carried out and to provide electronic access to trial monitors to a copy of the signed informed consent document. These data items will be encrypted and only those individuals who require to see these data i.e. the person performing the record linkage and site research team staff or the trial monitor, as appropriate, will be able to view them. All electronic data will be held securely in accordance with ISO 27001:2013 at the Robertson Centre for Biostatistics, part of the Glasgow Clinical Trials Unit. All Centre staff are required to sign confidentiality agreements and to follow Standard Operating Procedures in accordance with Good Clinical Practice and ISO certification.
- Only those that have been trained and approved will be able to enter or view any data via the web portal. Each site can only see their own patients' data.

14.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

Professor John Cleland and Professor Martin Cowie have received honoraria from Vifor Pharma for advisory boards and speaking at meetings.

Vifor are funding the trial and supplying patiromer.

If new competing interests develop, either due to changes in the status of existing trial personnel or to the inclusion of new personnel, this will be documented in the trial master file.

14.9 Indemnity

The Co-Sponsors (University of Glasgow and Greater Glasgow Health Board) will ensure that provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial in accordance with Part 2 (14) of Schedule 1 to SI 2004/1031.

Clinical negligence will be covered by the Clinical Negligence and Other Risks Indemnity Scheme in Scotland, and the equivalent schemes in other UK countries.

The Insurance cover will be subject to the appropriate authorisations being received from the MHRA, Ethics, and the NHS.

14.10 Amendments

Any change in the trial protocol will require an amendment. Any proposed substantial protocol amendments which may impact on the safety of patients or integrity of the trial will be initiated by the CI following discussion with the Sponsor and TSC and any required amendment forms will be submitted to the regulatory authority, ethics committee and Sponsor. The Sponsor will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Following a substantial amendment, favourable opinion/approval must be sought from the original reviewing REC, MHRA (where appropriate) and Research and Development (R&D) office prior to implementation. The Chief Investigator will be responsible for informing the Trial Management Group of all protocol amendments.

14.11 Post trial care

Patiromer and both MRA are already licensed for use in the UK.

At the end of the trial, participants will be returned to usual care as defined by local and national guidelines at that time. The results of the trial may of course have an impact on these guidelines and the future care of patients with heart failure.'

Spironolactone and eplerenone are generic medicines that are already widely prescribed.

14.12 Access to the final trial dataset

The data will be held securely at the Robertson Centre for Biostatistics at the University of Glasgow where it may be accessed by approved data-managers, statisticians and the Chief Investigator.

A full data-set may be shared with the funder after the trial is complete.

After the primary results have been published, data-sets may also be shared with co-investigators and others working in this field. This is subject to submission of a detailed statistical analysis plan, evidence of appropriate clinical and statistical expertise to support the analysis and its interpretation. Submissions must be approved by the TSC. Where data are shared, a data sharing agreement will be required which will detail requirements to ensure secure disposal after the analysis is complete. The TSC will oversee and coordinate manuscript proposals.

15. DISSEMINATION POLICY

15.1 Dissemination policy

The University of Glasgow will own the data arising from the trial.

On completion of the trial, the data will be analysed and tabulated. The Steering Committee will publish the primary manuscript and review proposals for further analyses. Participating investigators will be invited to propose secondary manuscripts, with priority given to those who have enrolled many patients. Colleagues who have not participated should seek 'sponsorship' from a participating investigator in order to submit a proposal. Timelines for analyses, manuscript writing and review will be agreed on a case-by-case basis subject to available resources. The sponsor and funder should be acknowledged in all publications.

Participants will be informed of results by a newsletter and may request information about the trial results after publication.

The trial protocol will be made publicly available prior to publication on a clinical trials website.

15.2 Authorship eligibility guidelines and any intended use of professional writers

The primary manuscript will be authored by the Steering Committee and the Principal Investigators from sites providing high quality data on a substantial number of patients.

The Steering Committee will delegate authorship to investigators and other colleagues after considering their proposals.

We do not intend to use professional writers for the peer-reviewed manuscripts describing the results. The funder may wish to employ professional writers for the 'commercial' press and will acknowledge any services paid for.

16. APPENDICES

Appendix 1: Risk

☐ LOW ≡ Comparable to the risk of standard medical care

☒ MODERATE ≡ Somewhat higher than the risk of standard medical care

☐ HIGH ≡ Markedly higher than the risk of standard medical care

Justification:
MRA are already recommended and widely used for patients with heart failure and are an effective treatment for congestion. Patiromer reduces serum potassium, allowing higher doses of MRA to be used

.
There are risks (hyperkalaemia, hypotension and renal dysfunction) and benefits (relief of congestion, improvement in symptoms, reduction in mortality) to use of higher doses of MRA.

Patiromer might cause hypokalaemia, although this is unlikely in a population highly prone to hyperkalaemia.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Patiromer	Hypokalaemia	Monitoring serum potassium	See schedule	
MRA	Hyperkalaemia			
MRA	Symptomatic hypotension	Monitoring symptoms		
MRA	Renal dysfunction	Monitoring serum creatinine		

An IDMC will monitor patient-safety.

Treatment is not blinded and therefore investigators may identify safety issues.

Outline any processes that have been simplified based on the risk adapted approach.

All IMP will be labelled for trial use only, including the nature of the IMP, its dose and the number of sachets/pills.

The trial is not blinded. Patients and investigators will know what is prescribed.

Patients in the control group will receive MRA only. Patients in the intervention group will receive patiromer and MRA.

Appendix 2: Symptom Questionnaire

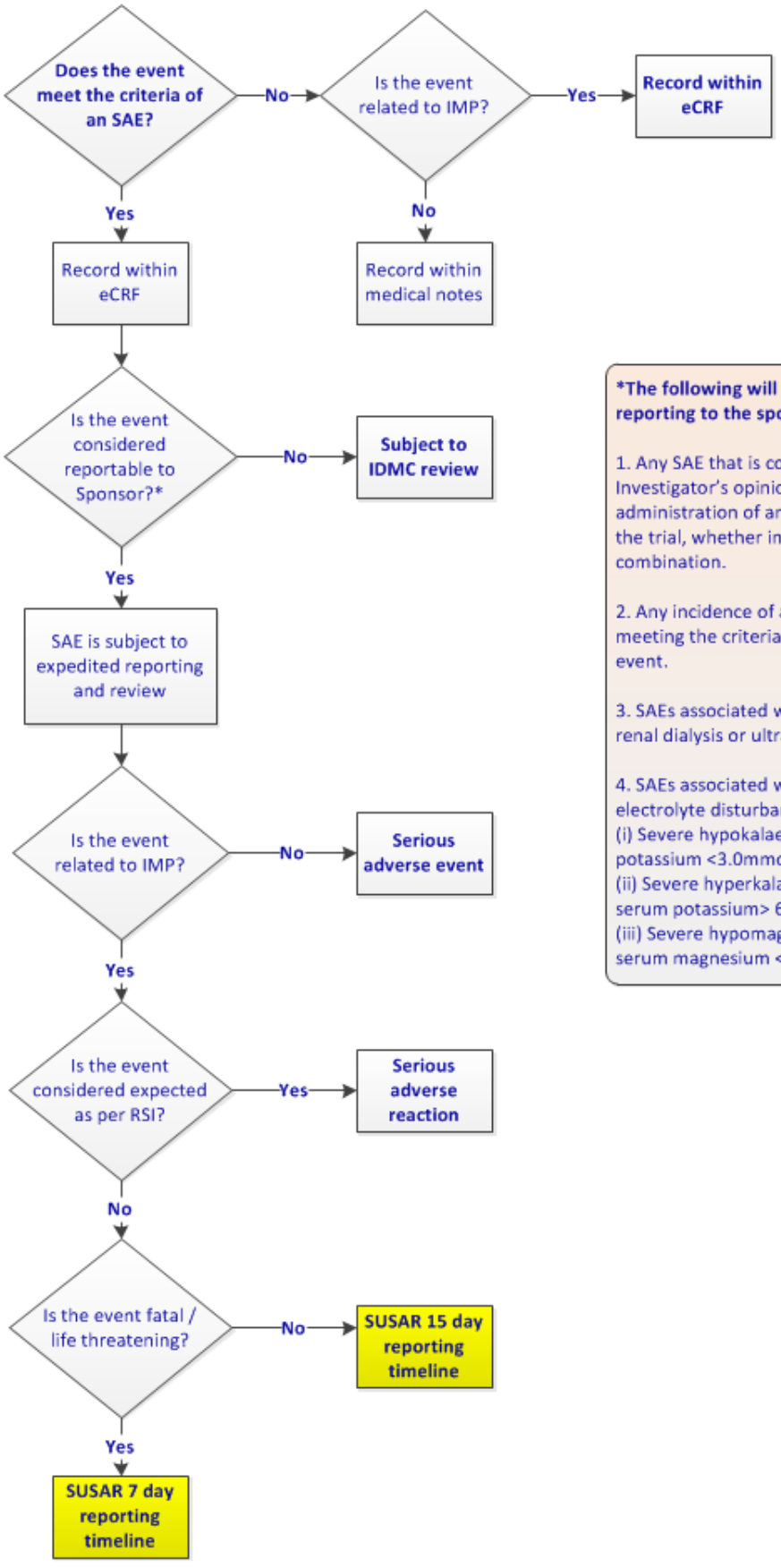
Patient ID	*Today's Date*
Symptoms With 0 meaning no problem or none, 5 meaning troublesome and 9 being severe	**Score using any number between 0 and 9**
Breathlessness	
Running (score 9 if you don't run because it makes you very breathless)	
On moderate exertion (e.g. walking quickly, climbing 2-3 flights of stairs)	
On mild exertion (e.g. walking slowly or doing light housework)	
On slight exertion (washing or dressing)	
Sitting at rest	
Do you get breathless lying flat?	
Other Symptoms	
Swelling of Ankles	
Swelling of Legs Above Ankles	
Are you troubled by tiredness during the day?	
Do you suffer much from anxiety?	
Do you feel depressed?	
Chest Pain on Exertion	
Dizziness	
Palpitations	
Muscle Aches & Pains	
Cough and/or Wheeze	
Other Symptom or Problem (Name)	
Other Symptom or Problem (Name)	
Quality of Life (with 1 = very good, 5 = average, 9 = very bad)	
How do you rate your health?	
How do you rate your overall quality of life?	
Please also answer these questions "Yes" or "No" or Give a Number	
How many pillows do you sleep with?	
Do you sometimes wake in the night fighting for breath?	
If so, how many nights in the last two months?	
Have you had any falls?	
If so, how many in the last two months?	
Have you had any blackouts?	
If so, how many in the last two months?	

Appendix 3: Managing Discontinuation of Patiromer or MRA

Patients who stop patiromer should have the dose of MRA adjusted to prevent hyperkalaemia. If serum potassium is in the normal range, the dose of MRA should be halved or reduced to 25mg/day, whichever is higher. Serum potassium should be re-checked in 7-12 days.

Patients who stop their MRA should have the dose of patiromer adjusted to prevent hypokalaemia. Many patients will be on other potassium retaining treatments and may still benefit from patiromer. If serum potassium is in the normal range, stop patiromer and re-check serum potassium in 7-12 days. If serum potassium exceeds 5.0mmol/L, patiromer should be re-started.

Appendix 4: Safety Reporting Flow Chart



***The following will be subject to expedited reporting to the sponsor:**

1. Any SAE that is considered, in the Investigator's opinion, related to the administration of any of the IMPs used in the trial, whether individually or in combination.

2. Any incidence of an acute kidney injury meeting the criteria of a serious adverse event.

3. SAEs associated with a requirement for renal dialysis or ultrafiltration

4. SAEs associated with one of the following electrolyte disturbances:
(i) Severe hypokalaemia defined as serum potassium <3.0mmol/L
(ii) Severe hyperkalaemia defined as a serum potassium> 6.5mmol/L
(iii) Severe hypomagnesaemia defined by a serum magnesium <0.05mmol/L

Appendix 5: EQ-5D

EQ-5D Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

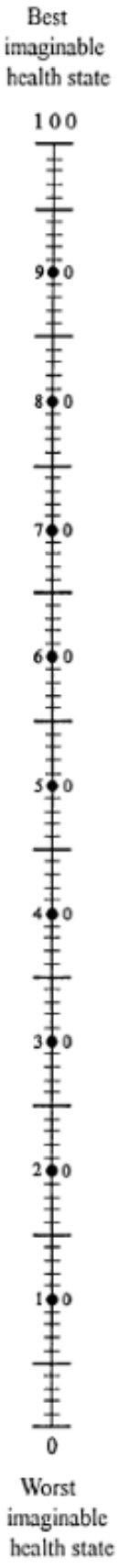
Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 6: KCCQ-12

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some may mainly feel shortness of breath while others mainly fatigue. Please indicate how limited you have been by **heart failure** (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Please put an **X** in one box on each line

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	Limited for other reasons or did not do the activity
a. Showering or having a bath	☐	☐	☐	☐	☐	☐ 04
b. Walking 100 yards on level ground	☐	☐	☐	☐	☐	☐ 05
c. Jogging or hurrying (as if to catch a bus)	☐	☐	☐	☐	☐	☐ 06

2. Over the past 2 weeks, how many times have you had **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐ 07

3. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐ 08

4. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐ 09

5. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week but not every night	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐ 10

6. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐ 04

7. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐ 05

8. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	Limited for other reasons or did not do the activity
a. Hobbies, recreational activities	☐	☐	☐	☐	☐	☐ 06
b. Working or doing household chores	☐	☐	☐	☐	☐	☐ 07
c. Visiting family or friends	☐	☐	☐	☐	☐	☐ 08

Appendix 7: Patient Global Assessment

The patient global assessment should be completed by the patient after having been asked by either the Investigator or the Study Nurse: “Compared to before starting the trial, are you better or worse?”

Patients should be provided with the following options:

- ☐ Markedly improved
- ☐ Moderately improved
- ☐ Slightly improved
- ☐ Unchanged
- ☐ Slightly worsened
- ☐ Moderately worsened
- ☐ Markedly worsened

Please note that it should ideally always be the same person who asks the question to the patient during the entire duration of the study.

Appendix 8: Frailty Scale

Figure 3: Clinical Frailty Scale[2]

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
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Appendix 9: Key Protocol Contributors

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Appendix 10: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
01	3.0	04 October 2019	Prof John Cleland	Main changes: Updated exclusion criteria; changes in line with revised SmPC; updates to Section 10 'Safety and Outcome Reporting' to clarify responsibilities; clarification relating to use of non-labelled MRA during run-in phase, and for reimbursement; inclusion of patient questionnaires (EQ5D, KCCQ, PGA, and frailty scale) in appendices.
03	4.0		Prof John Cleland	Main changes: Clarification of new information relating to drug interactions; simplification of the process for assessing IMP compliance.
06	5.0		Prof John Cleland	Main changes: Clarification of process for monitoring non-reportable events; reference to AE changed to AR for consistency; screening log inclusion criteria amendment; clarification regarding co-enrolment; removal of spirometry test; capture of COVID history and vaccination details; addition of subcutaneous loop diuretics to primary endpoint definition to adapt to changes in clinical practice; update of 2014 guidelines on management of severe hyperkalaemia to the 2020 version.

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