Clinical efficacy and mechanistic evaluation of Eplerenone for central serous chorio-retinopathy – the VICI randomised trial.

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Glossary / abbreviations

ACE	Angiotensin converting enzyme
AE	Adverse event - any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.
AF	Autofluorescence
AKI	Acute kidney injury - an acute increase in serum creatinine > 26.4 µmol/l or a percentage increase in serum creatinine of more than or equal to 50%
ARB	Angiotensin receptor blocker
AR	Adverse reaction – any undesirable experience that has happened a subject while taking a drug that is suspected to be caused by the drug or drugs
ARF	Acute renal failure
BCVA	Best Corrected Visual Acuity
CKD Stage	International classification of chronic kidney disease
CMT	Central macular thickness
CRF	Case report form
CSCR	Central serous chorio-retinopathy
CSRT	Central subfield retinal thickness
CTEU	Clinical Trials and Evaluation Unit
DM	Diabetes mellitus
DMSC	Data monitoring and safety committee
DNA	Deoxyribonucleic acid
EDI	Enhanced depth imaging
eGFR	Estimated glomerular filtration rate: derived from gender, age, ethnicity and serum creatinine
ESRF	End stage renal disease requiring dialysis, CKD stage 5
ETDRS	Early Treatment Diabetic Retinopathy Study
FBC	Full blood count
FFA	Fundus Fluorescein angiogram

FP	Fundus photography
ICGA	Indocyanine green angiography
ICH-GCP	International conference for harmonisation of good clinical practice
LFT	Liver function test
mg	Milligram
MHRA	Medicines and healthcare products regulatory agency
MR	Mineralocorticoid receptor
MRC	Medical Research Council
MV	Macular volume
NGAL	Neutrophil gelatinase associated lipocalin – a specific marker of acute kidney injury
NIHR	National Institute for Health Research
OCT	Optical coherence tomography
PDT	photodynamic laser therapy
PI	Principle Investigator
PIL	Patient information leaflet
RCT	Randomised controlled trial
REC	Research ethics committee
RPE	Retinal pigment epithelium
SAE	Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.
SAR	Serious adverse reaction
SFF	Subfoveal fluid
SOP	Standard operating procedure
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction - an untoward medical occurrence suspected to be related to a medicinal product that is not consistent with the applicable product information and is serious.
TMG	Trial management group
TSC	Trial steering committee
UH Bristol	University Hospitals Bristol NHS Foundation Trust
VFQ	Visual Function Questionnaire
WBC	White blood cell count

1. Trial summary

Central serous chorio-retinopathy (CSCR) is a poorly understood eye disease. It affects the eye tissue which senses light (the retina). In CSCR fluid spontaneously gathers under the retina. This can lead to permanent vision loss in about a third of cases. Some cases spontaneously resolve but some persist for years, recur or affect the second eye. Each year there are 10 new cases per 100,000 men and 2 cases per 100,000 women in the population. The cause is unknown although it can occur in families and some genetic changes have been found. There are no proven treatments. Recently a few patients have responded to treatment with a drug called eplerenone. This drug removes the subretinal fluid and improves vision. However, information on the long term benefit and safety of this drug is lacking.
To address this we will perform the first randomised, double-masked, placebo-controlled clinical trial of eplerenone with usual care in CSCR to find out whether it is better than placebo treatment with usual care. We hope this will establish the first scientifically proven therapy for

CSCR. We will also collect blood samples for future study. This will allow us to study proteins and chemicals in the blood stream and also DNA. With further funding we will determine a) what genetic variations are more common in CSCR patients and b) which proteins or genetic variations help predict who best responds to treatment with eplerenone. It is important to collect these samples now so we have them available for future study. To include enough patients to provide an informative result we will perform the study in about 20 different hospitals around the United Kingdom. Patients and NHS research support teams have helped design the study and will oversee the conduct of the study. The aim is to recruit 104 patients and to randomise 52 patients to each group. They will either be treated with a daily tablet called eplerenone alongside usual care, or an identical placebo tablet alongside usual care for up to twelve months. The most important comparison is how much vision improves with eplerenone compared to placebo. We will also look at changes in fluid beneath the retina after 12 months and the safety profile of eplerenone. Ethical issues include giving some patients with the disease a placebo tablet for a year. However, doctors do not know the best treatment due to a lack of robust evidence, and they will be able to use other unproven therapies if the patient's vison deteriorates during the trial. Genetic testing might identify genetic risks unrelated to CSCR. We will counsel our patients regarding these issues. The team includes retinal specialists, clinical trialists, cell biologists, statisticians, a geneticist and patients to ensure our research puts them at the centre of our study. Thus we have the necessary expertise to perform the study and answer the research questions. The trial has been carefully costed by a clinical trials unit, taking into consideration NHS Treatment costs.

2. Background

2.1 Existing Research

CSCR is a poorly understood eye disease. It affects the eye tissue which senses light (the retina) [1] . In CSCR, fluid spontaneously gathers under the retina causing a neurosensory retinal detachment. This can lead to permanent vision loss in up to 1/3 of cases [2] . Some cases spontaneously resolve but some persist for years, recur or affect the second eye [1]. Spontaneous resolution if it is going to occur typically does so within 3 months of onset [1] . So patients with persistent or recurring subretinal fluid beyond 3 months are defined as chronic CSCR and would ideally benefit from an effective treatment. Each year there are 10 new cases per 100,000 men and 2 cases per 100,000 women in the population[1] . The cause is unknown although it can occur in families and recently we identified the first genetic determinants when we identified variation in the cadherin gene in male patients with CSCR [3].

Currently there are no proven treatments. Indeed, little progress has been made in understanding CSCR since its original description in 1866 [1]. Therefore treatment is variable due to the lack of high quality evidence. One therapy is photodynamic laser therapy (PDT) but there is no definitive randomised controlled trial (RCT) to confirm its effectiveness. Further most NHS hospitals do not have access to this treatment and the drug used in PDT (verteporfin) is not licensed for this indication and is expensive (net price £850). At the preliminary stage of our application the funding board recommended not pursuing evaluating PDT due to lack of evidence of its effectiveness. Therefore most patients are not treated in the NHS due to lack of funding for PDT and/or no evidence of treatment benefit. As a result up to a third of chronic CSCR cases may have permanent visual loss [2]. However, in a rat model of CSCR, we recently showed that one of the features of the condition, choroidal vasodilation, was induced by aldosterone acting via an endothelial vasodilatory potassium channel KCA2.3. Aldosterone is a mineralocorticoid receptor (MR) activator. Blockade of this pathway prevented aldosterone-induced choroidal thickening [4].

To translate these findings, we treated 2 patients with chronic non-resolved CSCR with oral eplerenone, a specific MR antagonist, for 5 weeks, and observed impressive and rapid resolution of retinal detachment and choroidal vasodilation as well as improved visual acuity. The benefit was maintained 5 months after stopping eplerenone [4]. These results identify MR signalling as a pathway controlling choroidal vascular bed relaxation and provide a pathogenic link with CSCR, which suggests that blockade of MR could be used therapeutically to reverse CSCR. We subsequently performed a nonrandomized pilot study of 13 patients with CSCR of at least 4-months duration, treated with 25 mg/day of oral eplerenone for a week followed by 50 mg/day for 1 or 3 months [5]. We found that eplerenone treatment was associated with a significant reduction in central macular thickness, subretinal fluid level, and an improvement in visual acuity in some patients [5]. Of note, the rate of resolution differed between patients and there is no data on recurrence of disease when the drug is stopped and no definitive RCTs have been performed with this drug to evaluate its effectiveness in a large cohort of patients. However, based on these encouraging preliminary findings we believe that an RCT as proposed here is now justified.

2.2 Rational for the current study

2.2.1 Clinical Efficacy: Main Study

There is no consensus on how to treat patients with CSCR and our proposed placebo-controlled RCT will determine if eplerenone is efficacious. CSCR can cause severe vision loss. One study with long term follow up (over 3 years) identified that 30 % of patients had a mean visual acuity of 20/200 at final follow up [2]. Thus a viable treatment to prevent such visual loss is needed. An effective treatment will decrease the burden to individuals and society if permanent visual impairment in the working age group can be avoided. This trial is needed now due to the lack of reliable data to guide clinical management and emerging evidence that eplerenone could be the first effective treatment. Our review of CSCR [1] was the most highly cited paper in Eye in 2010 indicating the clinical interest in managing this condition. Clinicaltrial.gov identifies some small phase 1 studies of aflibercept, PDT and eplerenone but no definitive, adequately powered studies. This proposed study will add significantly to the evidence base as it is the only adequately powered trial that we are aware of, able to identify a clinically important visual benefit from using eplerenone. Furthermore, the aetiology of CSCR is poorly understood. We will fully utilise the well-phenotyped CSCR patients in our study to generate a biobank for future novel mechanistic studies using the latest scientific tools. Depending on funding this may include exome sequencing and generation of induced pluripotent stem cells. These investigations should significantly add to our understanding and could result in further novel therapies.

Our imaging studies will explore the retinal and choroidal changes with this condition and the effect of therapy and provide better understanding of this condition using an adequate sample size. This study will provide the evidence of whether eplerenone can be used as an effective treatment for CSCR. If so this would represent major progress as there are currently no validated treatments for the condition. Our hypotheses are:

1) Eplerenone treatment with usual care is better than placebo with usual care for CSCR
2) Aetiological insights can be achieved from imaging studies and future wet lab studies (see 2.2.2).

So that patients randomised to placebo are not placed at greater risk of disease progression, eplerenone and placebo will be administered alongside usual care. Usual care will almost always be observation without any intervention. A Cochrane review published in 2015 concluded that: “no single treatment has provided overwhelming evidence of efficacy in

published RCTs" and "it is not clear whether there is a clinically important benefit to treating acute CSCR which often resolves spontaneously as part of its natural history." [6] These conclusions were based on consideration of eight potential treatments, including thermal and photodynamic laser therapies, systemic therapies (but not eplerenone) and placebo/sham/observation. Cross-sectional audit data from one of the proposed centres (Moorfields Eye Hospital, a centre of excellence) provides illustrative data: usual care was observation at three-quarters (92/125) of visits and was photodynamic laser therapy at all other visits (personal communication).
The most common treatments explored both in research and, more importantly, used by ophthalmologists are thermal or photodynamic laser therapies. Laser therapies work by selective destruction of the retina. Therefore, ophthalmologists are reluctant to use them for a condition which may improve spontaneously, as evidenced by the conclusion of the Cochrane review.[6] Also, thermal laser treatment cannot be used (because of its destructive nature) to treat the fovea, since it would cause more harm than benefit and involvement of the fovea is the likeliest reason for deteriorating visual acuity and poor prognosis. Photodynamic laser treatment can be used to treat the fovea, as less destructive than thermal laser, but still carries risk of causing more harm than good by causing retinal scarring, retinal atrophy and/or choroidal ischaemia at the fovea. The willingness of ophthalmologists to consider using thermal or photodynamic laser therapies as visual acuity deteriorates and the benefit-risk trade off of a destructive intervention changes. For this reason we will allow use of thermal or photodynamic laser therapies in the trial if judged to be required by the treating ophthalmologist in response to a deterioration in vision.

2.2.2 Sub-study on mechanistic evaluation

As requested by the funders we will create a biobank of DNA, plasma and serum from patients who agree to donate these samples, but not perform wet lab mechanistic studies in this project.

2.3 Pilot study

We have previously reported a pilot study in 13 patients using similar methods as proposed here [5]. In brief, our nonrandomised pilot study included 13 patients with CSCR of at least 4-months duration, treated with 25 mg/day of oral eplerenone for a week followed by 50 mg/day for 1 or 3 months. Due to pilot status of the study, the primary outcome measure was the change in central macular thickness (CMT) recorded by optical coherence tomography (OCT). Secondary outcomes were the changes during the treatment period in Best Corrected Visual Acuity (BCVA) (in logarithm of minimal angle resolution, LogMAR) and sub-retinal fluid (SRF) (in micrometers, μm) at 1 and 3 months and the percentage of eyes achieving complete resolution of CSCR (defined as the absence of SRF on OCT, not only under the fovea but also in all the OCT sections length). A change of 20% in CMT (in μm) was considered significant (because none of the included patients had a spontaneous 20% change during 4 months without treatment).
Seven patients were found to have at least a 20% decrease of CMT at 1 and at 3 months (7/13, 54% and 7/10, 70% respectively), suggesting that eplerenone has a significant effect on CMT of CSCR patients. Three patients had no significant change in CMT at 3 months. A complete reabsorption of SRF was achieved in three patients (3/12, 25%) at 1 month. Note that at 3 months, of the 13 included patients, three had stopped their treatment at 1 month because of complete resolution and one was lost to follow up. Thus, at 3 months, six patients (6/9, 67%) who remained under treatment had complete resolution of the disease. Interestingly, one patient whose condition completely resolved after 1 month of eplerenone, recurred after treatment arrest. He was again treated for 3 months and again responded to the treatment.

The mean BCVA was 0.52 ± 0.24 LogMAR at baseline, 0.34 ± 0.22 LogMAR at 1 month and 0.27 ± 0.19 LogMAR at 3 months. The BCVA at 3 months was significantly improved compared with baseline BCVA (p=0.001). Central macular thickness decreased significantly from 352 ± 139 mm at baseline to 246 ± 113 mm and 189 ± 99 mm at 1 and 3 months under eplerenone treatment (p=0.05 and p= 0.01, respectively). At 3 months, the subretinal fluid significantly decreased compared with baseline subretinal fluid (p=0.01) and BCVA significantly improved compared with baseline BCVA (p=0.001).None of the patients experienced any serious adverse effect from the treatment. Two patients reported fatigue and one patient a sedative effect. Kalemia and creatinine clearance remained in the normal range for all patients at all time points. Overall, eplerenone was very well tolerated among CSCR patients.

2.4 Other studies

Others have since further investigated the role of eplerenone in CSCR. Singh et al evaluated eplerenone in chronic CSCR (defined as aniographic evidence of CSCR present for more than 4 months) in a total of 17 eyes of 13 patients [7]. In this retrospective consecutive case series a total of 17 eyes of 13 patients were treated with either 25 or 50 mg of oral eplerenone per day. Subretinal fluid (SRF) decreased over time following eplerenone therapy (p = 0.007 and p =0.002, diameter and height respectively). Maximum SRF height decreased from a mean of 131.5 um at baseline to 15.3 um at day181+. SRF diameter decreased from an average of 2174.4um at baseline to 46.9 um at day 181+. LogMAR visual acuity improved from 0.42 (Snellen equivalent: 20/53) at baseline to 0.29 (Snellen equivalent: 20/39) at day 181+ (p = 0.024). Central subfoveal retinal thickness (CSRT) decreased from 339.5 um at baseline to 270.3 um at day 181+ (p = 0.029). They concluded that eplerenone therapy resulted in significant anatomic and visual improvements in eyes with chronic CSCR.

Ghadiali et al [8] performed a retrospective observational case series. This included 23 eyes of 14 patients with CSCR treated by a single physician with either spironolactone, eplerenone, or both consecutively over a 12-month period. Choroidal thickness, central macular thickness, and best-corrected visual acuity were measured and compared with baseline values. Twelve eyes of 11 patients demonstrated subretinal fluid before or during the initiated treatment course. Subretinal fluid was measured and compared with baseline values in this subgroup. In all eyes (n = 23), best-corrected visual acuity improved at 12 months of treatment; however, central macular thickness and choroidal thickness showed no improvement. In the subgroup with subretinal fluid (n = 12), subretinal fluid was significantly decreased at 6 months and 12 months of treatment; however, central macular thickness, choroidal thickness, and best-corrected visual acuity showed no significant change. They concluded that mineralocorticoid antagonists may improve best-corrected visual acuity and decrease subretinal fluid in patients with central serous chorioretinopathy, but do not affect the choroidal or macular thickness.

Chin et al also performed a retrospective consecutive observational case series [9]. Primary outcome measures included CMT (μm), macular volume (MV, mm^3), Snellen visual acuity, and prior treatment failures. Secondary outcomes included duration of treatment, treatment dosage, and systemic side effects. A total of 120 patients with CSCR were reviewed, of which 29 patients were treated with one or more mineralocorticoid antagonists. The average age of patients was 58.4 years. Sixteen patients (69.6%) were recalcitrant to other interventions prior to treatment with oral mineralocorticoid antagonists, with an average washout period of 15.3 months. The average duration of mineralocorticoid antagonist treatment was 3.9±2.3 months. Twelve patients (52.2%) showed decreased CMT and MV, six patients (26.1%) had increase in both, and five patients (21.7%) had negligible changes. The mean decrease in CMT of all

patients was 42.4 μm (range, -136 to 255 μm): 100.7 μm among treatment-naïve patients, and 16.9 μm among recalcitrant patients. The mean decrease in MV of all patients was 0.20 mm3 (range, -2.33 to 2.90 mm3): 0.6 mm3 among treatment-naïve patients, and 0.0 mm3 among recalcitrant patients. Median visual acuity at the start of therapy was 20/30 (range, 20/20–20/250), and at final follow-up it was 20/40 (range, 20/20–20/125). Nine patients (39.1%) experienced systemic side effects, of which three patients (13.0%) were unable to continue therapy. They concluded that mineralocorticoid antagonist treatment had a positive treatment effect in half of their patients. The decrease in CMT and MV was much less in the recalcitrant group compared to the treatment-naïve group. An improvement in vision was seen only in the treatment-naïve group.

Finally Salz et al performed another retrospective review of all patients (14 eyes of 14 patients) monitored for a minimum of 3 months with chronic CSCR who were treated with oral eplerenone in a single multi-physician retina practice [10]. Visual acuity, dilated funduscopic examination, and spectral-domain OCT with enhanced depth imaging (EDI) were obtained at each visit. Measurement of subfoveal fluid (SFF) height and choroidal thickness were performed. A two-tailed paired t test was used to calculate statistical significance of pre- and post-treatment variables. At 1 month, 10 of 14 eyes had decreased SFF height on OCT and two eyes had complete resolution of SFF. Mean SFF height decreased from 13 0μm to 62 μm (P = .05). Mean choroidal thickness decreased from 315 μm to 282 μm (P = .07). Mean visual acuity improved from logMAR 0.41 to 0.40. At 3 months, 13 of 14 (93%) had decreased SFF on OCT, and nine eyes (64%) had complete resolution of SFF. Mean SFF height decreased to 21 μm (P = .004). Mean choroidal thickness decreased to 253 μm (P = .10). Mean visual acuity improved to logMAR 0.28 (P = .02). They concluded that oral eplerenone may be effective in treating patients with chronic CSCR.

3. Aims and objectives

3.1 Main Study

To compare the efficacy and safety of eplerenone with usual care versus placebo with usual care for chronic CSCR for 12 months in a phase 3 randomised placebo-controlled clinical trial.

3.1.1 Primary Objectives:

To evaluate whether BCVA following eplerenone therapy with usual care is superior to placebo with usual care in eyes with chronic CSCR.

3.1.2 Secondary objectives

Secondary objectives of this study are:

a) To evaluate whether eplerenone treatment with usual care is better than placebo with usual care for resolution of subretinal fluid
b) To describe the safety profile of eplerenone treatment with usual care (compared to placebo with usual care)
c) To evaluate whether participant-reported visual function improves with eplerenone treatment with usual care compared to placebo with usual care
d) To describe how the choroid responds to treatment in CSCR
e) To describe how retinal pigment epithelium (RPE) function changes over a year in CSCR as measured by autofluorescence
f) To evaluate how low luminance visual acuity changes with eplerenone treatment.

3.2 Sub-study on mechanistic evaluation:

3.2.1 Objectives

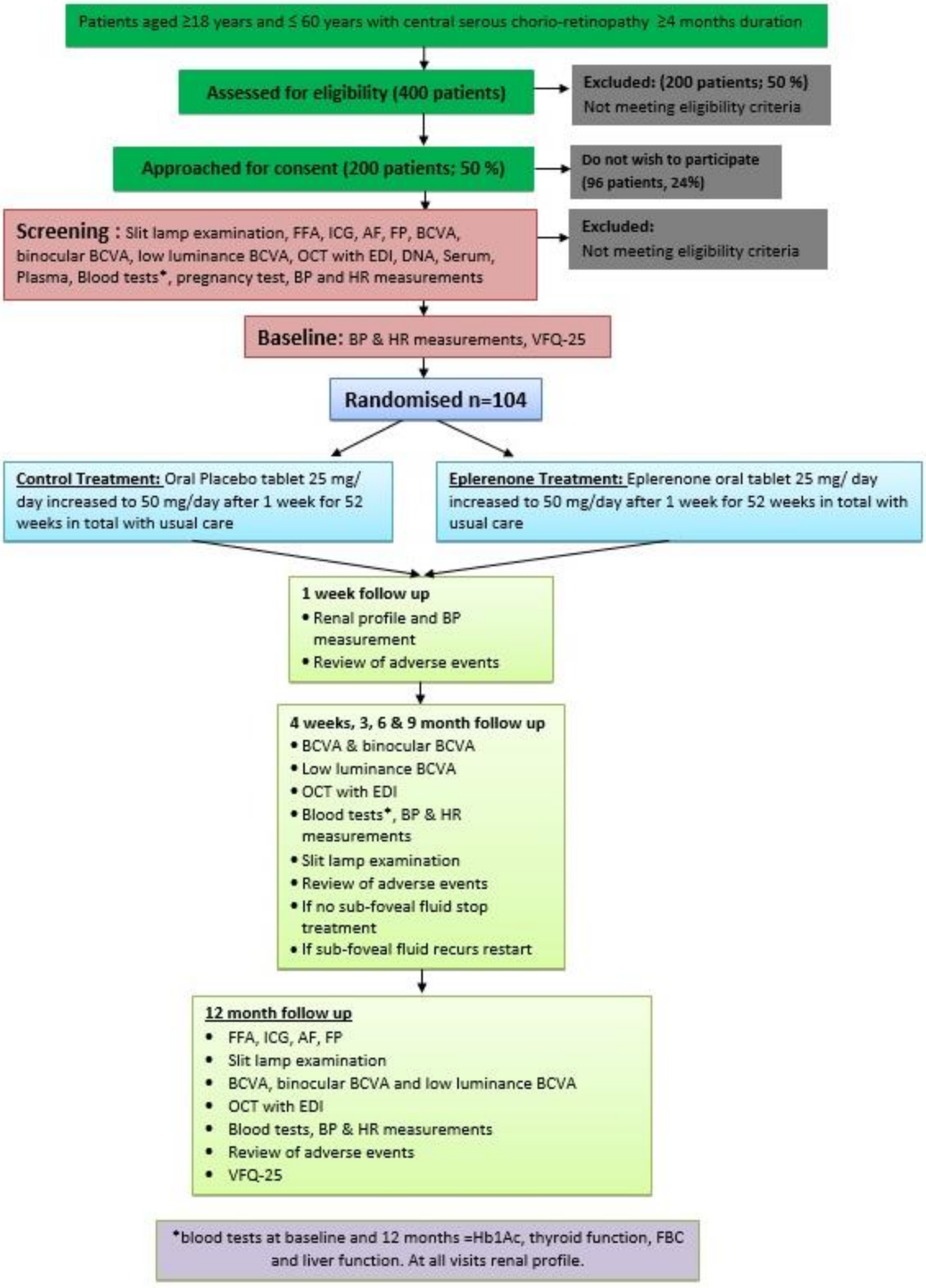
1. To generate a biobank of DNA, serum and plasma for future mechanistic studies.
2. To explore treatment response by conducting imaging studies of retina and choroid.

4. Plan of Investigation

4.1 Trial schema

Figure 1 Trial schema

NB The screening and baseline visits may be combined into one visit if tests results for blood potassium will be made available in time to establish eligibility prior to randomisation.


Patients aged ≥18 years and ≤ 60 years with central serous chorio-retinopathy ≥4 months duration
Assessed for eligibility (400 patients)
Excluded: (200 patients; 50 %)
Not meeting eligibility criteria
Approached for consent (200 patients; 50 %)
Do not wish to participate
(96 patients, 24%)
Screening : Slit lamp examination, FFA, ICG, AF, FP, BCVA, binocular BCVA, low luminance BCVA, OCT with EDI, DNA, Serum, Plasma, Blood tests*, pregnancy test, BP and HR measurements
Excluded:
Not meeting eligibility criteria
Baseline: BP & HR measurements, VFQ-25
Randomised n=104
Control Treatment: Oral Placebo tablet 25 mg/ day increased to 50 mg/day after 1 week for 52 weeks in total with usual care
Eplerenone Treatment: Eplerenone oral tablet 25 mg/ day increased to 50 mg/day after 1 week for 52 weeks in total with usual care
1 week follow up
• Renal profile and BP measurement
• Review of adverse events
4 weeks, 3, 6 & 9 month follow up
• BCVA & binocular BCVA
• Low luminance BCVA
• OCT with EDI
• Blood tests*, BP & HR measurements
• Slit lamp examination
• Review of adverse events
• If no sub-foveal fluid stop treatment
• If sub-foveal fluid recurs restart
12 month follow up
• FFA, ICG, AF, FP
• Slit lamp examination
• BCVA, binocular BCVA and low luminance BCVA
• OCT with EDI
• Blood tests, BP & HR measurements
• Review of adverse events
• VFQ-25
*blood tests at baseline and 12 months =Hb1Ac, thyroid function, FBC and liver function. At all visits renal profile.

4.2 Trial design

This is a multicentre, individually randomised, double-masked, placebo-controlled trial that will test the superiority of eplerenone therapy with usual care to placebo with usual care at 12 months. The trial design has been formulated in consultation with the UKCRC-registered Clinical Trials and Evaluation Unit (CTEU) Bristol, a trial statistician, a methodologist involved in the Research Design Service, clinical research networks, service users and a group of ophthalmologists specialising in medical retina. The basic study design and the associated clinical measurements are well established. The superiority study design has also been successfully used in numerous previous clinical trials in medical retinal conditions. 104 adult patients with chronic CSCR will be randomised 1:1 to receive eplerenone with usual care or placebo with usual care for a period of 12 months.

4.3 Key design features to minimise bias

4.3.1 Randomisation

Concealed randomisation will rule out selection bias. Randomised allocations will be generated in advance by the CTEU Bristol and supplied to the pharmacy manufacturing the overcoated eplerenone and matching placebo. 104 adult patients with chronic CSCR will be randomised 1:1 at the level of the individual taking into account prognostic and other relevant factors. Randomisation will be carried out on the day of the clinic visit by the ophthalmologist or research nurse using a secure internet-based randomisation system to ensure allocation concealment; the random allocation will not be allocated until a participant has been screened and recruited.

4.3.2 Masking

The trial will be placebo-controlled and no one except the manufacturing and local site pharmacies and coordinating centre will have code lists (for code-breaking in the event of a need to unmask allocation because of a serious adverse effect). Therefore, all outcome assessments will be masked. The visual acuity examiners (research optometrists) will receive the participants into the visual acuity lanes with a visual acuity case report form, study number and detail of study eye and non-study eye to be refracted, previous refraction log but with no previous case report forms for the participants by which the treatment group could be identified. Similarly, the other tests of secondary outcome measures of OCT scans will be done by masked technicians. The technicians will receive the subjects into the OCT room on a specific CRF that provides details of subject study number and eye to be examined. The interviewer (administrator or nurse) who will administer the questionnaire booklets at specific time points will be masked and be provided with details of subject study number only. The participants will be masked to the treatment as the eplerenone tablets and placebo tablets are identical. The retinal photographs, OCT (baseline and 12months) and autofluorescence will be graded by masked graders in the Independent Reading Centre at NetWORC UK. The graders in the Reading Centre are trained and quality assured. These masking procedures will also avoid 'performance' bias. We will describe the completeness of outcome data for each outcome, including reasons for attrition and exclusions from the analysis.

4.3.3 Other features to minimise bias

Loss to follow-up will be minimised by the regular study visits; research nurses will immediately contact a participant in the event of a missed visit to ascertain the reason and, wherever possible, to arrange an alternative appointment. Loss to follow-up in the IVAN trial which

included an elderly visually impaired trial population and monthly hospital visits and was managed by CTEU Bristol, was 4% per annum among surviving participants [11]. Selective reporting will be avoided by providing detailed definitions of all outcome measures in the protocol and by writing a statistical analysis plan before any comparative analysis is performed Any deviations from the statistical analysis plan will be reported and justified.

4.4 Trial population

4.4.1 Inclusion criteria

Participant may enter study if ALL of the following apply

1. Participants will be aged ≥18 years and ≤ 60 years
2. Visual impairment due to CSCR of ≥ 4 months duration defined as:
    a. subfoveal presence of SRF on OCT
    AND
    b. characteristic appearance of CSCR on FFA and Indocyanine-green angiography (ICGA).
    AND
    c. investigator believes that there is sufficient evidence from patient history, case note documentation or appearance of the macula that CSCR has been present for at least 4 months.
3. Women must have a negative pregnancy test and be willing to use effective contraception* for the duration of the participation in the trial and for 3 months after, be surgically sterile or post-menopausal for >12 months.
4. Able to provide written informed consent.

The following apply to the study eye:

5. A study eye should have an Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA score greater than 53 letters and less than 86 letters.
6. A study eye should have clear ocular media and adequate pupillary dilatation to permit photography.

* this includes: progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide cap, diaphragm or sponge with spermicide, combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation: (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, sexual abstinence.
NB pregnancy test only need to be repeated if there is reason to suspect the participant has become pregnant.
There are no special precautions/contraceptive requirements for male participants with female partners of child bearing potential.

It is rare but not impossible for patients to present with CSCR in both eyes or CSCR may develop in the fellow eye during the trial. We propose to measure eye-specific outcomes such as BCVA in both eyes throughout the trial, designating eyes as study eyes or not. Statistical analyses will take into account the availability of data for two eligible eyes in one patient.

If both eyes present with CSCR at baseline, the clinical trial site will decide which is the primary eye and this eye will have retinal imaging performed first. The primary eye would usually be the one with most active disease/most sub-retinal fluid. It will be identified by OCT imaging and subsequent investigations such as fluorescein and indocyanine green angiography will then be performed initially on this eye. If a patient presents with one affected eye and the fellow eye subsequently develops CSCR the eye first affected will always be the primary study eye.

4.4.2 Exclusion criteria

Participant may not enter study if ANY of the following apply

1. Hyperkalaemia (serum potassium level > 5.0 mmol/L).
2. Hepatic or renal impairment (Patients with severe renal insufficiency (Estimated glomerular filtration rate, eGFR < 30 mL per minute per 1.73 m^2) or Patients with severe hepatic insufficiency (Child-Pugh Class C).
3. Pregnancy or breast feeding.
4. Known allergy to fluorescein or indocyanine green.
5. Patients receiving potassium-sparing diuretics, potassium-supplements, or inhibitors of CYP 3A4 (e.g.amiodarone, diltiazem, fluconazole, itraconazole, ketoconazole, ritonavir, nelfinavir, saquinavir clarithromycin, telithromycin, erythromycin, verapamil, spironolactone and nefazodone)). Patients taking furosemide are eligible.
6. Patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. ibuprofen, naproxen).
7. Patients receiving the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB).
8. Patients receiving lithium, cyclosporine or tacrolimus.
9. Hypersensitivity or known allergy to eplerenone or to any of the excipients.
10. Known hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
11. Patients receiving high doses of aspirin (>75mg).

The following additional exclusions apply to a study eye only (i.e. they may be present for a non-study eye):

12. Evidence of choroidal neovascularization.
13. Previous or current treatment with eplerenone for any reason or previous or current treatment with photodynamic laser therapy / any anti-VEGF therapy in the study eye / any intra-ocular steroid use / thermal laser therapy for CSCR.
14. Presence of any other disease which could cause retinal fluid or SRF to accumulate (e.g. diabetic retinopathy*[1], polypoidal choroidal vasculopathy, domed shaped maculopathy or choroidal haemangioma) or affect visual acuity.
15. Myopia > -6 dioptres

*[1]Diabetes alone is not an exclusion criterion.

4.5 Trial interventions

Intervention: The intervention will be Eplerenone 25 mg/day increased to 50 mg/day after 1 week (as per manufacturer's recommendations for dose initiation) in addition to usual care. Treatment will be continued until there is evidence of complete resolution of SRF. The 25mg and 50mg doses will be achieved using 25mg and 50mg strength tablets respectively.

Control: placebo tablet, manufactured to match the Eplerenone tablets, with usual care.

If there is recurrence of SRF with an increase in central subfield retinal thickness (CSRT) of at least 50µm, the allocated treatment will be restarted.

Masking will be achieved by over encapsulating the tablets so that intervention and control appear identical.

Dose escalation: The patient's potassium level will be assessed at 1 week. Patients will be given the 50 mg tablets to take home but to await a phone call that to tell them whether to proceed or not (once the potassium results have been received). The potassium levels are then checked at 4 weeks. If at any time the potassium levels are out of range, study medication will be discontinued. As traumatic blood taking can raise potassium levels, in the case of a high reading the test may be repeated prior to deciding whether to discontinue treatment. If a patient restarts eplerenone during the study the same dose escalation procedure will occur i.e. patients will restart on Eplerenone 25 mg/ day increased to 50 mg/day after 1 week. Serum potassium will again be measured before initiating eplerenone therapy, within the first week and at one month after the start of treatment.

Monitoring Compliance: Patient compliance with study drug will be assessed at each visit. Compliance will be monitored by capsule counts performed by site pharmacy personnel at each visit. Compliance will be evaluated as the percentage of prescribed pills taken since the previous evaluation. If this percentage is ≤70% for the time period, then the patient will be categorised as non-compliant for the time period since previous evaluation. Non-compliance will not be a reason for withdrawal from the study but the reasons for non-compliance will be explored and documented. Site personnel will take extra efforts to ensure that non-compliant patients improve their compliance by frequent telephone reminders and counselling. Any deviations from the prescribed dosage regimen will be recorded.

Rules for treatment decisions: For individual patients, treatment will be stopped at week 4, month 3, 6, 9 or 12 if there is complete resolution of SRF under the fovea in the study eye. Treatment will be restarted at a subsequent visit if there is recurrence of sub-foveal SRF. Also treatment will be stopped for individual patients if they develop a complication of taking eplerenone. The most likely complications to result in treatment ceasation include serum potassium levels being >5 mmol/l, eosinophilia or symptomatic hypotension.Other adverse events that may result in treatment ceasation are listed in section 8.1. If any serious adverse reaction to the drug / placebo occurs, the patient will be advised to stop treatment but will continue to be followed in the study unless the patient asks to withdraw from the trial. If the BCVA drops by 15 or more letters from baseline assessment, the ophthalmologist may consider alternative therapies or may decide to stop the study intervention. The use of PDT or thermal laser is not recommended unless the visual acuity drops by at least 15 letters or more from baseline assessment; even then, such treatments are not mandated but can be used at the discretion of the treating ophthalmologist. A decrease of 15 or more letters is an established criterion for a sight threatening adverse event and has been used in many clinical trials of retinal diseases. [12, 13] Treatment will also be stopped if a participant falls pregnant.

4.6 Primary and secondary outcomes

4.6.1 *Primary outcome*
The primary outcome is the BCVA at the 12 month visit, adjusted for baseline BCVA, measured using validated ETDRS vision charts with measurements made in accordance with a standardised protocol for trials in medical retina. Refracted visual acuity will be done at baseline, 4 weeks, 3, 6 9 and 12 months.

4.6.2 Secondary outcomes
Secondary outcome measures are:

1. Low luminance BCVA. This is measured immediately after measuring BCVA by adding a 2 log neutral density filter and recording the number of letters read.
2. CSRT as measured by OCT recorded at 12 months, including CSRT measured at interim visits and adjusted for baseline CSRT.
3. Change in sub-retinal fluid thickness as measured by OCT
4. Systemic and ocular adverse events at any time during the 12 month follow-up period
5. Proportion of patients with macular atrophy of the RPE defined as hypoautofluorescence at 12 months
6. Area change in macular RPE hypoautofluorescence at 12 months.
7. Choroidal thickness as measured by enhanced depth imaging OCT at 12 months, adjusted for baseline choroidal thickness. Measurements to be made sub-foveally.
8. Proportion of patients with reduced choroidal permeability on ICG at 12 months
9. Time to resolution of SRF.
10. Classification of all study eyes as complete, partial or no resolution of SRF at each time point of the study. Partial resolution of SRF is defined as a decrease of >25 % of CMT from baseline due to resolution of SRF. A non-responder is defined as having an increase in SRF or decrease in SRF ≤25% from baseline. Recurrence will be defined as the appearance of new SRF in a study eye after complete resolution of SRF at any point.
11. Patient-reported visual function using Visual Function Questionnaire VFQ 25 will be assessed at baseline and 12 months.
12. Classification of all study eyes by each FFA phenotype, such as smoke stack, ink-blot and chronic epitheliopathy
13. Classification of all study eyes as early, late, or non responder. An early responder is defined as complete or partial resolution of sub-foveal SRF by 3 months. A late responder is defined as complete or partial resolution of sub-foveal SRF after 6 months.
14. Incidence of CSCR in the fellow eye as measured by OCT, FFA, ICGA or AF.

A validated ophthalmic reading centre will assess images obtained from OCT, ICGA and FFA at baseline and 12 months.

4.7 Sample size calculation
A sample size of 45 patients in each of the 2 groups would be sufficient to detect a difference of 5 letters in BCVA between the eplerenone and placebo groups with 90% power and 5% significance (2-tailed), assuming that the standard deviation is 9 letters [14], the correlation between baseline and any follow up assessment is 0.5 [15], and that, on average, there will be a minimum of 2 follow up assessments per patient [16] with a correlation between BCVA on follow-up visits of 0.8. The total sample size has been increased to 104 to allow for up to 15% dropout over the 12 month period, which should be a conservative estimate in this patient

group. This sample size justification does not take into account the extra power that will be obtained from including data for two eyes, coded as CSCR or not.

5. Trial methods

5.1 Description of randomisation and code breaking

The randomisation scheme will be generated by statisticians at CTEU Bristol, and supplied to the manufacturing pharmacy so that study drug and placebo can be labelled with appropriate randomisation label. The randomisation system will be part of the study database so that patient eligibility has to be confirmed before their randomisation number is revealed. The randomisation system will not reveal the actual allocation, therefore any team member who is authorised to use the study database may randomise.

Participants will be randomised in a ratio of 1:1 to study drug with usual care and placebo with usual care, and the randomisation scheme will take into account prognostic and other important factors. Randomisation will take place within in one month of the screening visit. Where this does not happen all screening tests (with exception of bloods samples taken for the biobank) must be repeated to ensure inclusion criteria are still met.

Unmasking will either be performed by CTEU Bristol or the local pharmacy at the request of the treating investigator.

5.2 Masking

This is a double masked trial, as the intervention and placebo will appear identical. The treating investigator will be able to request unmasking of treatment in case of medical emergency. The chief investigator/co-lead will have the final decision and unilateral right to unmask allocation.

5.3 Research procedures

We will collect 30mls of blood from patients to create a biobank of DNA, serum and plasma. Patients will have the opportunity to decline participating in this part of the study if they so wish. However our previous experience in the IVAN and other clinical trials is that most participants are happy to contribute to a biobank for future mechanistic studies.

Demographic data will be collected on participants but this will include demographic history, smoking history, medical history of significance, history of any steroid use and duration used and approximate duration since last usage.

Patients will undergo all study procedures on both eyes at each visit as dictated by the study protocol (see table 1 below). FFA, ICGA, AF and OCT imaging should be done using standard techniques, and it is mandatory that the AF and OCT must be performed using Heidelberg equipment. To obtain standardised autofluorescence measurements the eye should be bleached with laser light for 15 seconds before taking the AF image. The FFA and ICGA will be performed on the study eye first. Where OCT angiography equipment is available, OCT angiography should be carried out at baseline, or an interim follow-up visit if equipment becomes available a later date, and at the 12 month follow up.

5.4 Duration of treatment period

See section 4.5

5.5 Definition of end of trial

The end of the trial for a participant is at the completion of follow-up at 12 months (or earlier if a participant withdraws). The end of the trial as a whole is when all follow-up is completed, data collected and cleaned and the database is locked. DNA, serum and plasma will be banked after the end of the study under appropriate arrangements.

Ongoing treatment if the study is successful: All participants will be made aware of the results of the study. If the study successfully establishes efficacy, the patients will be informed of its efficacy. They will be able to continue the treatment if their primary physicians and ophthalmologists are happy to continue monitoring. Otherwise, they will be treated in accordance with normal standard of care if the disease recurs.

5.6 Data collection

Data collection will include the following elements:

(a) A log of patients presenting with CSCR and those who are approached for the trial (including the date when they are given the Patient Information Leaflet (PIL)).

(b) Patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility.

(c) Consent and baseline information collected prior to randomisation. See Table 1 for data collected as baseline.

(d) Treatment compliance – capsule count by pharmacy

(e) Data to answer primary and secondary outcomes (see below)

Table 1 Data collection

	Time-point and visit number						
	Screening/ baseline	**week 1**	**week 4**	**3 months**	**6 months**	**9 months**	**12 months**
Data to be collected	0	1	2	3	4	5	6
Medical history	x						
Ophthalmic history	x						
Concomitant medications*[6]	x	x	x	x	x	x	x
Pregnancy test (women only)	x						
FFA	x						x
ICGA	x						x
AF	x						x
FP	x						x
BCVA (to include binocular BCVA)	x		x	x	x	x	x
Low luminance BCVA	x		x	x	x	x	x
OCT with EDI*[1]	x		x	x	x	x	x
OCT angiography*[5] *[7]	x	x	x	x	x	x	x
DNA, serum and plasma*[2]	x						
Hba1c*[3]	x						x
Thyroid function tests*[3]	x						x
Full blood count (FBC) *[3]	x						x
Liver function tests*[3]	x						x
Urea and electrolytes profile*[3] *[4]	x	x	x	x	x	x	x
Blood pressure measurement	x	x	x	x	x	x	x
Heart rate measurement	x	x	x	x	x	x	x
Slit lamp examination	x		x	x	x	x	x
Adverse event form	x	x	x	x	x	x	x
VFQ-25	x						x

*[1] Images at baseline & 12 months to be graded by Independent Reading Centre at NetWORC UK. Images from other at time points to be graded by specialists within the study team.
*[2] Samples sent to Southampton hospital laboratory.
*[3] Tests conducted at local hospitals.
*[4] To include creatinine
*[5] Where equipment available
*[6] At each visit we will check whether patients are taking any drugs that have been shown to treat CSCR (e.g. rifampicin, finasteride, melatonin).
To minimise bias, outcome measures are defined as far as possible on the basis of objective criteria. All personnel carrying out outcome assessment will be masked; this will minimise detection bias. Biochemical markers will be measured by an independent laboratory technician, without knowledge of treatment allocation.

*[7] A maximum of two OCT angiography image sets will be collected per participant. OCT angiography will be collected at baseline, or at an interim time-point if imaging equipment is not available at baseline, and at 12 months.

Visit windows
Week 1 (+/-1 day)
Week 4 (+/- 5 days)
All other follow up visits (+/- 10 days)

5.7 Source data

The source data will be made up of the patient's medical records, questionnaires, CRFs, visual acuity score sheets, images from FFA, ICGA, AF and OCT, FP, image grading data files and outputs from blood tests including but not limited to hospital pathology reporting systems.

5.8 Planned recruitment rate

Recruitment is expected to take 12 months. Participating sites have confirmed that they can recruit 5 patients in one year.

5.9 Participant recruitment

Patients presenting with CSCR will be invited to participate. Patients will be identified and approached according to local procedures. At some hospitals patients may be identified through hospital databases and initially contacted by the study team by phone/email. All potential participants will be sent or given an invitation letter and PIL (approved by a Research Ethics Committee (REC)) describing the study. The patient will have time to read the PIL and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wish. Most patients will have at least 24 hours to consider whether to participate.

Potential participants will be seen by a member of the local research team (study clinician/ research nurse/trial co-ordinator) in clinic who will answer any questions, confirm the patient's eligibility and take written informed consent if the patient decides to participate. The PI or a delegated doctor must confirm the eligibility prior to randomisation. Details of all patients approached for the trial and reason(s) for non-participation (e.g. reason for being ineligible or patient refusal) will be documented.

Patients will be identified from searching hospital administration systems for existing patients as well as from patients attending clinics.

5.10 Discontinuation/withdrawal of participants

It is important to distinguish cessation of treatment (drug or placebo) from withdrawal from the trial. Participants have the right to request cessation of treatment (and may simply not take trial tablets) or to withdraw from the study at any time, without giving a reason. An excessive rate of withdrawals can render the study uninterpretable. Therefore, it is desirable to avoid participants stopping treatment or asking to withdraw from the trial. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Moreover, participants who wish to withdraw from the study because they want to stop treatment will be asked to confirm whether they are still willing to attend study visits for outcome assessments, in particular the end-of study visit at month 12.

If a participant wishes to withdraw, we will continue to analyse any data already collected, unless the participant expresses a wish for their samples and any associated data to not be used.

If individual participants meet any of the following criteria they will be told to stop taking the trial treatment (drug or placebo): any adverse events that in the opinion of the investigator may jeopardise the safety of the trial participant; pregnancy. If there is disease progression or worsening (15 or more letter decrease in BCVA) the treating ophthalmologist may use other therapies and/or stop study drug (see Treatment decisions in section 4.5).

5.11 Frequency and duration of follow up

The participants will be followed up at: 1 and 4 weeks, and 3, 6, 9, and 12 months.

5.12 Likely rate of loss to follow-up

Clinical trials on retinal conditions that require regular follow-up visits have shown that approximately 5% withdraw consent and 5% are lost to follow-up. Our previous clinical trial experience on retinal conditions demonstrates that the patients' attendances in relation to the trial schedule are good because of their fear of visual loss. The usual cause of non-adherence with study visits is due to co-morbidities and we have estimated this to be <15%. Statistical analyses will include data for all participants up to the time of completion of follow-up or withdrawal from the trial and will accommodate missing data for some visits (assumed to be missing at random) with only minor loss of power.

5.13 Expenses

Patients will be reimbursed for travel expenses for all study visits.

6. Statistical analyses

6.1 Plan of analysis

The statistical analysis plan will be written prior to any comparative analyses.

Outcomes measured at multiple time points (e.g. BCVA) will be compared between the two treatment groups using mixed models for repeated measures, adjusting for baseline. Mixed models allow all patients with data to be included in the analysis, i.e. partial missing data (assumed missing at random) is permitted. Appropriate transformations of continuous outcomes may be applied if necessary. Interactions between treatment and time will be examined and, if significant at the 5% level, a treatment by time interaction will be included in the model and the treatment effect at 12 months will be reported with 95% confidence intervals.

Non-adherence to random allocations will be documented. With the exception of adverse events the trial will be analysed on an intention-to-treat basis, i.e. outcomes will be analysed according to the treatment allocation, irrespective of future management and events, and every effort will be made to include all randomised participants. However we do not expect any crossovers due to the placebo-controlled design.

Non-adherence to drug/placebo will also be monitored and this information will be included in reports prepared for the Trial Steering Committee. Depending on the level of adherence

observed, the statistical analysis plan for the trial may include additional analyses to investigate the interaction between adherence to medication and treatment.

Additional analyses of the overall trial cohort will investigate:

1. The association between final visual acuity and age of patient;
2. The association between presence of granular / confluent hypoautofluorescence in the macula at randomisation and final visual acuity.

6.2 Subgroup analyses

No subgroup analyses are currently planned. However, depending on the level of adherence observed during the trial, and the ability of participating centres to carry out OCT angiography, two subgroup analyses may be carried out, testing the following interactions:

1. Interaction of good/poor adherence (to be defined) and treatment;
2. Interaction of the presence/absence of new vessels (determined by OCT angiography) and treatment.

If accruing data indicate that these subgroup analyses could be informative, further details will be included in the statistical analysis plan.

6.3 Frequency of analyses

No formal interim analysis is planned. Safety data will be reported to the Data Monitoring and Safety Committee (DMSC) on a regular basis, together with any additional analyses the committee request. In these reports the data will be presented by group but the allocation will remain masked.

6.4 Criteria for the termination of the trial

The study may be prematurely discontinued on the basis of new safety information or the results of another study supersede the necessity for completion of this study, or for other reasons given by the Data Monitoring Safety Committee (DMSC) and/or Trial Steering Committee, Sponsor, regulatory authority or Research Ethics Committee concerned.

6.5 Economic issues

There are no Health Economic analyses planned.

7. Trial management

The trial will be managed by the CTEU Bristol. CTEU Bristol is an UK Clinical Research Collaboration registered Clinical Trials Unit. CTEU Bristol will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators.

7.1 Day-to-day management

An appropriately qualified person by training will be responsible for identifying potential trial participants, seeking informed participant consent, randomising participants, liaising with pharmacy, collecting trial data and ensuring the trial protocol is adhered to.

The overall management structure of this study will consist of:

1. A Trial Management Group (TMG)
2. A Trial Steering Committee (TSC) see 7.3.1

3. A Data Monitoring and Safety Committee (DMSC) see7.3.2

7.1.1 Trial Management Group (TMG)

The TMG will be responsible for the day-to-day running and management of the trial. Chaired by the Chief Investigator, the membership will include: at least one Principal Investigator (PI); the Trial Manager; Trial Statistician; Data Manager; and a Patient and Public Involvement representative. The TMG will oversee the development and operation of the study, monitor and maintain recruitment rates, and devise any necessary workarounds that may arise in patient management or the conduct of the trial, ensure that all required financial, insurance and indemnity arrangements are instigated, organise site agreements between each of the clinical centres and the Study Office and, draw up the study publication policy and strategy. The TMG will meet quarterly.

7.2 Monitoring of sites

7.2.1 Initiation visit

Before the study commences training session(s) will be organised by CTEU Bristol. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study.

7.2.2 Site monitoring

Site monitoring will be delegated by the Sponsor to CTEU Bristol. A monitoring plan will be agreed between CTEU Bristol and the Sponsor, and will be based on the risk assessment. Central monitoring will be employed, and on site visits will only be performed when required.

7.3 Trial Steering Committee and Data Monitoring and Safety Committee

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7.3.1 Trial Steering Committee (TSC)

The key purpose of the TSC will be to ensure the overall integrity of the study by monitoring its progress and taking account of regular reports from the DMSC and Trial Management group. Ultimate responsibility for any decision required on the continuation of the trial will lie with the TSC. The TSC will consist of an independent Chair and other independent members (a retinal specialist, a physician, a Patient and Public Involvement representative and an ophthalmology research network representative); other TSC members with observer status will represent the trial team, the Sponsor and the funder. The TSC is expected to meet five times across the study (or more often, if determined by the Chair).

7.3.2 Data Monitoring and Safety Committee (DMSC)

The DMSC will review accruing data about emerging external evidence, recruitment in the trial, alignment of the data with the sample size assumptions, safety and other aspects of the trial agreed in advance and specified in the DMSC charter. CTEU Bristol will be responsible for providing a confidential report to the DMSC in advance of DMSC meetings containing data to the DMSC's specification. Review of adverse events will be a key task. The DMSC will consist of an independent Chair and two other independent members. The Chair will be a senior clinician with expertise in ophthalmic retinal trials or a senior statistician and other members with expertise to review adverse events will be nominated. The Chief Investigator, the Trial Statistician and Trial Manager will attend DMSC meetings to provide information but will have no decision making role; the independent members will be expected to have the opportunity for confidential discussion at all meetings. The DMSC will meet five times, in advance of the TSC.

The DMSC can recommend to the TSC that the trial should be stopped at any time should a significant safety issue become apparent.

8. Safety reporting

Serious and other adverse events will be recorded and reported in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the Sponsor's Policy (see Figure 2).

All serious adverse events will be coded using the Medical Dictionary for Regulatory Activities, masked to allocation. Expected serious adverse reactions will be listed in the protocol and will comprise those reported as related to eplerenone in the Summary Product Characteristics. All serious adverse events and reactions will be reported in tabular form.

All adverse events and reactions will be recorded on CRFs and subsequently transferred to the database throughout the study regardless of their severity or relation to study participation. Participating centres will be required to report all SAEs within 24 hours to CTEU Bristol. CTEU Bristol will report SAEs to the Trial Sponsor.

The assignment of the causality should be made by the investigator responsible for the care of the participant. If any doubt about the causality exists, the investigator should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others,

all parties will discuss the case. In the event that no agreement is made, the MHRA, main REC and other bodies will be informed of both points of view.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning AE recording/reporting should be directed to the Trial Manager in the first instance

All SAEs, SARs and SUSARs will be recorded on the CRF and reported to CTEU Bristol within 24 hours of learning of its occurrence. The initial report will be made by completing the serious adverse event form, and faxing to CTEU Bristol or submitted via the database. If faxed a record of this notification (including date of notification) must be clearly documented to provide an audit trail. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available.
Relationship of the SAE to the treatment must be assessed by the investigator/delegate (must be a clinician) at site, as should the expected or unexpected nature of any SARs.

SUSARs will be reported to the MHRA and REC by the Sponsor. Reporting timelines are as described in Figure 2.

All investigators will be informed of all SUSARs occurring throughout the study on a case-by-case basis. This will be regardless of treatment allocation in order to avoid the risk of inadvertently unmasking investigators, unless this information is needed for medical management of patients.
The Chief Investigator will provide a Development Safety Update Report of all SARs (expected and unexpected) and SAEs, prepared by the CTEU, which will be distributed to the Sponsor, the MHRA and the Research ethics committee (REC). SAEs will be reported to the respective REC as mandated by them. The DMSC will be provided listings of all SAEs on an ongoing basis

8.1 Expected adverse events

The following adverse events are ‘expected’:

In two studies (Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study [EPHESUS] and Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure [EMPHASIS-HF]), the overall incidence of adverse events reported with eplerenone was similar to placebo. The most frequent adverse event reported in the EMPHASIS-HF study was hyperkalaemia with an incidence rate of 8.7% and 4% for eplerenone and placebo respectively. Adverse events reported below are those with suspected relationship to treatment and in excess of placebo or are serious and significantly in excess of placebo, or have been observed during post marketing surveillance. Adverse events are listed by body system and absolute frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable effects
Infections and infestations	Uncommon	Pyelonephritis,infection, pharyngitis
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Endocrine disorders	Uncommon	Hypothyroidism
Metabolism and nutrition disorders	Common	Hyperkalaemia, hypercholesterolaemia
	Uncommon	Hyponatraemia, dehydration, hypertriglyceridaemia
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Common	Dizziness, syncope, headache
	Uncommon	Hypoaesthesia
Cardiac disorders	Common	Left ventricular failure, atrial fibrillation,
	Uncommon	Tachycardia
Vascular disorders	Common	Hypotension
	Uncommon	Arterial thrombosis limb, orthostatic Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Common	Diarrhoea, nausea, constipation, vomiting
	Uncommon	Flatulence
Skin and subcutaneous tissue disorders	Common	Rash, Pruritus
	Uncommon	Hyperhidrosis, angioedema
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, back pain
	Uncommon	Musculoskeletal pain,
Renal and urinary disorders	Common	Renal impairment
Hepatobiliary disorders	Uncommon	Cholecystitis
Reproductive system and breast disorders	Uncommon	Gynaecomastia
General disorders and administration site conditions	Common	Asthenia
	Uncommon	Malaise
Investigations	Common	Blood urea increased, blood creatinine increased
	Uncommon	Epidermal growth factor receptor decreased, blood glucose increased

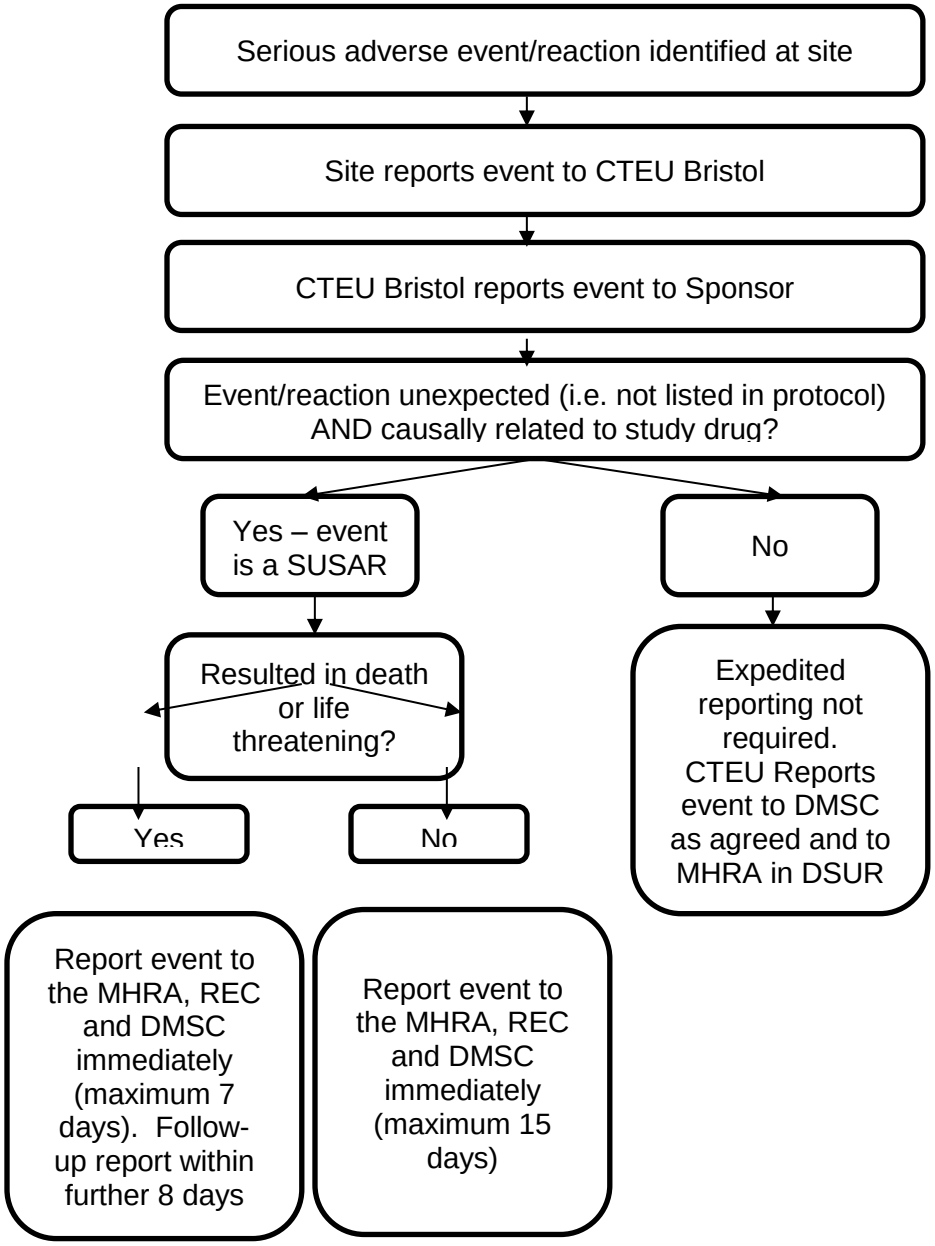
In EPHESUS, there were numerically more cases of stroke in the very elderly group (> 75 years old). There was however no statistical significant difference between the occurrence of stroke in the eplerenone (30) vs placebo (22) groups. In EMPHASIS-HF, the number of cases of stroke in the very elderly (≥ 75 years old) was 9 in the eplerenone group and 8 in the placebo group.

Incident choroidal neovascularisation and a decrease in visual acuity of 15 letters or more are also expected adverse events in this population.

Data on these adverse events collected during the trial will be reported regularly to the trial DMSC for review.

Note: the time point for adverse events is not specified so any of these events occurring at any time during follow-up are considered expected.

Figure 2 Serious adverse event reporting flow chart



8.2 Period for recording serious adverse events

Data on adverse events will be collected from consent for the duration of the follow-up period.

9. Ethical considerations

9.1 Review by an NHS Research Ethics Committee

Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL and consent form) will be carried out by a UK Research Ethics Committee (REC).

Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC for approval prior to implementation.

9.2 Risks and anticipated benefits

Potential benefits to participants / Potential harms to participants / Possible adverse effects of each intervention:

Potential Risks and benefits to participants - Risks include the risks of side-effects from the intervention such as hyperkalaemia but we will monitor for this. However our short-term efficacy and safety data suggests eplerenone will be efficacious and safe. The benefit is that this treatment is a simple oral medication and if proven efficacious and safe will be easily deliverable to our patients.

Our preliminary study shows this treatment is well tolerated by patients with CSCR. There are 3 extra visits that the participants need to undergo in excess of normal standard of care (baseline, week 1 and 4). In addition, extra blood tests (thyroid function, liver profile and renal profile and full blood picture) will be needed. The potential risks and benefits of participating in the clinical study will be described carefully in the patient information sheet (PIS); this document will be drafted with service user involvement.

The patients who consent to biobanking will have to undergo an additional 10 minutes for blood collection at baseline. Patients may find out they have a genetic predisposition for disease. This will be covered in the PIL. We have experience of conducting similar genetic studies in other retinal diseases and dealing successfully with these ethical issues

Benefits to society
If successful, this study will provide high quality evidence about whether eplerenone can benefit patients with CSCR, and potentially improve the treatment of this condition for future patients.

9.3 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL.

9.4 Obtaining informed consent from participants

All participants will be required to give written informed consent. This process, including the information about the trial given to patients in advance of recruitment, is described above in section 5.9.

The research nurse/trial coordinator/PI/clinical research fellow will be responsible for the consent process, which will be described in detail in the Trial Manual.

We will design patient information leaflets containing this information and consent forms with service user involvement. We will supply individuals with as much information as they require to make an informed decision about participation in the study. They will be given as long as they wish to make a decision about their involvement and will be informed that any decision will not affect any ongoing or future treatment within each Trust. The investigator will review the consent and answer questions. The participant will be informed that participation is voluntary and that he/she may withdraw from the study at any time, for any reason. They will be assured that confidentiality will be maintained at all times. Each participant will be assigned a sequential identification number. This unique number will be used to collect, store and report participant

information. All participants will be required to read, sign, and date a consent form before participating in the study.

9.5 Co-enrolment

Participants may take part in other observational research whilst participating in VICI, providing the requirements for follow-up are not too onerous when combined with follow-up for VICI. Patients should not take part in another CTIMP whilst participating in VICI; participating in a non-CTIMP should be considered on a case-by-case basis.

10. Research governance

This study will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- Research Governance Framework for Health and Social Care
- European Union Directive 2001/20/EC on clinical trials (if a drug study)

10.1 Sponsor approval

Any amendments to the trial documents must be approved by the sponsor prior to submission to the REC.

10.2 NHS approval

Approval from the local NHS Trust is required prior to the start of the trial.

Any amendments to the trial documents approved the REC will be submitted to the Trust for information or approval as required.

10.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or CTEU Bristol or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved the REC that they receive and ensure that the changes are complied with.

10.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the Sponsor or CTEU Bristol (see 7.2.2), the relevant REC and for inspection by the MHRA or other licensing bodies.

10.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

10.6 Clinical Trial Authorisation

Eplerenone is classed as an investigational medicinal product and a Clinical Trial Authorisation from the MHRA must be in place before starting the trial.

11. Data protection and participant confidentiality

11.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 1998.

11.2 Data handling, storage and sharing

11.2.1 Data handling

Data will be entered onto a purpose designed database and data validation and cleaning will be carried out throughout the trial. Working instructions for database use, data validation and data cleaning will be available and regularly maintained.

Data will be submitted to the CTEU Bristol directly into the database which will be accessed by via the NHS portal. Imaging files (e.g. OCTs) will be uploaded by secure methods to the central Angiographic Resource facility; images will be pseudonymised with the VICI patient ID.

11.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial. In compliance with the MRC Policy on Data Sharing, relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). A secure electronic 'key' with a unique participant identifier, and key personal identifiers (e.g. name, date of birth and NHS number) will also be held indefinitely, but in a separate file and in a physically different location (NHS hospital server). These will be retained because of the potential for the raw data to be used subsequently for secondary research.

OCTs will be stored by the reading centres, these will be pseudonymised with the VICI patient ID.

11.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is

compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be retained for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body. Patient identifiers would not be passed on to any third party.

12. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available.

13. References

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14. Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
NA	1.0	01/02/2016	2.0	23/03/2016	Usual care added to treatment groups; exclusion criteria added to exclude other concomitant medications; rescue criteria added.	REC approval – 30/04/2016 MHRA approval – 31/03/2016
1	2.0	23/03/2016	3.0	15/06/2016	The trial schema and data collection table have been updated due to inconsistencies in the previous version of the protocol. Time frames for study visits have been added. Coordinating centre will also have code lists for unmasking. OCT images will only be graded by an independent reading centre at baseline and 12 months. Updated exclusion criteria, only patients receiving a combination of an ACE inhibitor and an ARB are excluded. The following exclusion criteria has been added due to guidance in the SmPC	REC approval – 04/07/2016 MHRA approval – 16/08/2016

					‘Patients receiving high doses of Aspirin (>75mg).’ Randomisation must take place within one month of taking screening blood tests. Otherwise screening tests must be repeated.	
2	3.0	15/06/ 2016	4.0	05/10/ 2016	Detail added to say that optometrists are allowed logs of previous refractions when carrying out visual function assessments. The following inclusion criterion has been added: ‘Investigator believes that there is sufficient evidence from patient history, case note documentation or appearance of the macula that CSCR has been present for at least 4 months.’ Patients with BCVA scores of up to 85 are now eligible for inclusion. Conconmittant medication list has been updated. Lists of primary and secondary outcomes have been edited. OCT A is to performed where equipment is available at screening and 12 months. Unmasking requires approval from CI/Co-Lead. Analyses section has been updated based on feedback from DMSC meeting.	REC approval – 15/11/2016 MHRA approval – 23/11/2016 HRA approval – 14/12/2016
3	4.0	05/10/ 2016	5.0	26/01/ 2017	Correction to say that VICI is a phase 3 trial not a phase 2 trial Fundus photography has been added to the trial schema and data collection table. This procedure will be carried out twice (screening &	REC approval – 06/02/2017 MHRA approval – 16/02/2017 HRA approval – 14/02/2017

					12 month follow up visit) and takes around 5 minutes. This had been omitted in error from previous versions of the protocol. We are not measuring fasting blood glucose. This had been removed from the trial schema before the protocol was submitted for approval but in error not removed from section 9.2 of the study protocol.	
6	5.0	26/01/ 2017	6.0	20/03/ 2018	Section 4.7. Updated minor text error in sample size justification. Sections 5.3, 6.2 and Table 1. Updated to include OCT-A at baseline or an interim time-point and at 12 months. Section 8.1. Updated reference safety information.	