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CORAL
COENZYME Q10 IN HEART FAILURE

# The effectiveness and cost effectiveness of COenzyme Q10 in heaRt fAiLure with reduced ejection fraction (CORAL): a pragmatic, patient-centred, data-enabled trial in primary care

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|---|---|
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**This protocol has regard for the HRA guidance**

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| Signed (Sponsor): | | Date: | |

Contents

**GLOSSARY OF ABBREVIATIONS**

| | |
|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| BTC | Bristol Trials Collaboration |
| CI | Chief Investigator |
| CEHR | Centre for Ethnic Health Research |
| CRF | Case Report Form |
| CTA | Clinical Trial Authorisation |
| CTU | Clinical Trials Unit |
| DMC | Data Monitoring Committee |
| DSA | Data Sharing Agreement |
| DSUR | Development Safety Update Report |
| EC | European Commission |
| EF | Ejection Fraction |
| EU | European Union |
| GCP | Good Clinical Practice |
| HFrEF | Heart Failure with reduced Ejection Fraction |
| HRA | Health Research Authority |
| HRQoL | Health Related Quality of Life |
| HTA | Health Technology Assessment |
| IMP | Investigational Medicinal Product |
| ISRCTN | International Standard Randomised Controlled Trials Number |
| ITT | Intention to Treat |
| KCCQ | Kansas City Cardiomyopathy Questionnaire |
| LVSD | Left Ventricular Systolic Dysfunction |
| MACE | Major Adverse Cardiovascular Events |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MLTC | Multiple Long-term Conditions |
| NIHR CRN | National Institute of Health Research Clinical Research Networks |
| NICE | National Institute for Health and Care Excellence |
| NYHA | New York Heart Association |
| PI | Principal Investigator |
| PIL | Participant Information Leaflet |
| PPI | Patient and Public Involvement |

| | |
|---|---|
| PPIE | Patient and Public Involvement and Engagement |
| QALY | Quality Adjusted Life Years |
| RCT | Randomised Control Trial |
| RDSF | Research Data Facility Storage |
| REC | Research Ethics Committee |
| RSI | Reference Safety Information |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| 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 |
| UHBW | University Hospitals Bristol and Weston NHS Foundation Trust |

**TRIAL SUMMARY**

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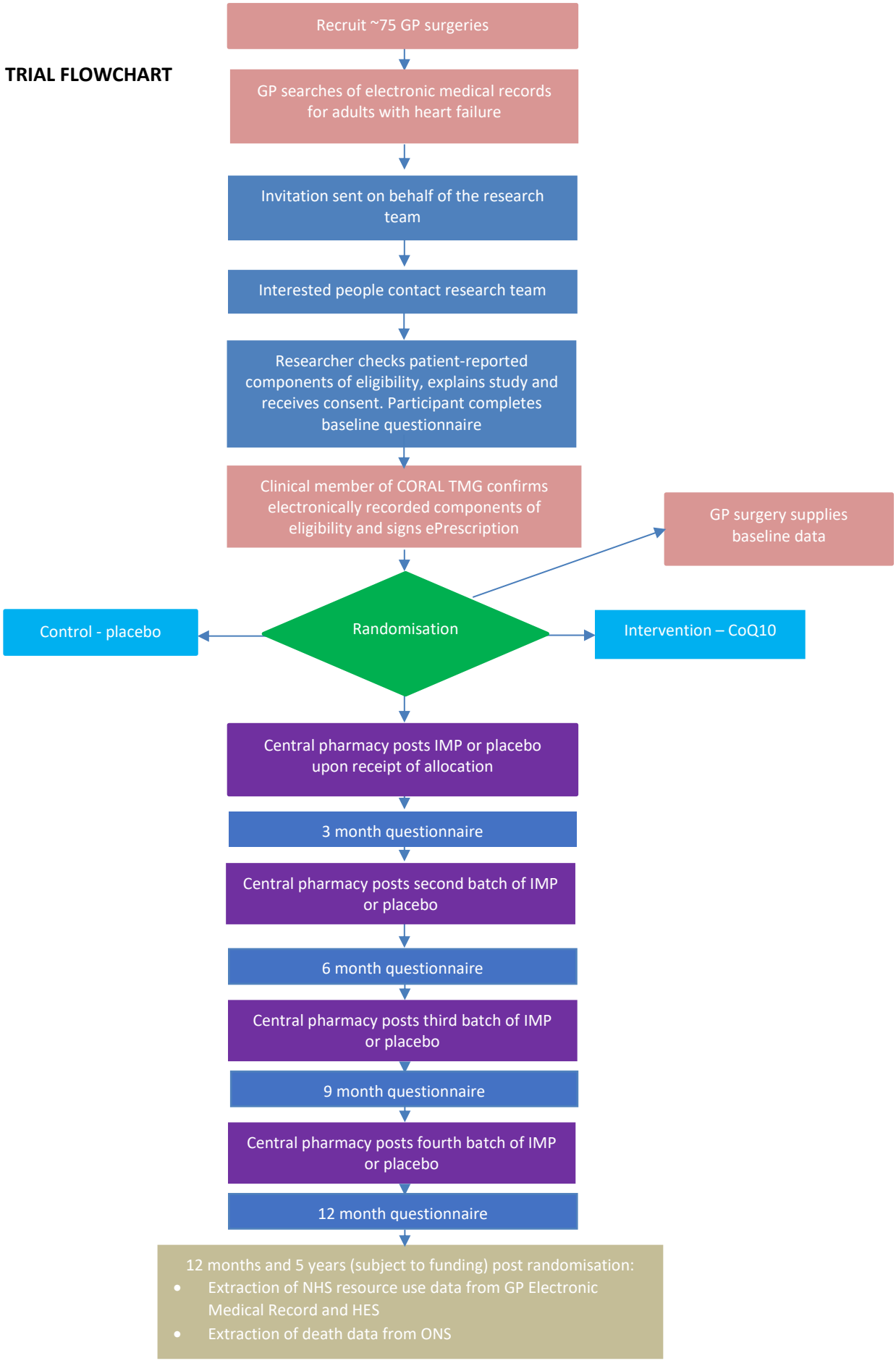
|---|---|
| Trial Title | The effectiveness and cost effectiveness of **CO**enzyme Q10 in hea**R**t f**A**i**L**ure with reduced ejection fraction (CORAL): a pragmatic, patient-centred, data-enabled trial in primary care |
| Short title | CORAL |
| Chief Investigator | Dr Rachel Johnson (Clinical Lead) |
| Joint Lead | Dr Maria Pufulete (Non-Clinical Lead and Lead Applicant) |
| Sponsor | University of Bristol |
| Funder | NIHR Health Technology Assessment |
| Trial Design | Pragmatic, patient-centred, data enabled, placebo-controlled randomised controlled trial (RCT), with internal pilot and economic evaluation. |
| Trial Participants | Adults ≥18 years, with a diagnosis of heart failure with evidence of left ventricular systolic dysfunction (LVSD) (ejection fraction (EF) <50%) |
| Sample size | 950 |
| Number of study sites | Around 75 GP surgeries |
| Intervention | CoQ10 (ubiquinone) 100mg dose or matched placebo capsule three times daily in addition to usual care. |
| Treatment duration | 12 months |
| Inclusion criteria | Aged >=18, evidence in the GP record of LVSD, and New York Heart Association (NYHA) class >=II |
| Exclusion criteria | Diastolic dysfunction with EF>50% or preserved left ventricular function, supplementary CoQ10 intake within the last 6 weeks, current warfarin use, allergy to soy, allergy to peanuts, currently involved in another interventional clinical trial, unable to provide informed consent, unwilling to take part due to diet choices (capsules contain halal bovine gelatine). Women only: pregnant, breast feeding. |
| Primary objectives | 1. Estimate the difference between groups (intervention (CoQ10) and control (placebo)) in the primary endpoint of HF specific Health Related Quality of Life (HRQoL).<br>2. Determine the cost effectiveness of CoQ10 compared with control. |
| Primary outcome | Participant reported HF-specific HRQoL using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months (52 weeks) |

| | |
|---|---|
| Secondary objectives | Estimate the difference between groups (intervention and control) with respect to:<br>1.A composite hierarchical endpoint including all cause death, all cause hospitalisation and HF-specific HRQoL, analysed using the win ratio.<br>2.Death (all cause and from cardiovascular causes).<br>3.Hospitalisation (all cause, cardiovascular and HF related).<br>4.Major adverse cardiovascular events (MACE); a composite endpoint comprising cardiovascular death, cardiovascular hospitalisation, mechanical assist implantation, or urgent cardiac transplantation.<br>5.NYHA functional classification.<br>6.Resource and health service use.<br>7.Quality of life assessed by EQ-5D-5L.<br>8.Formal and informal care.<br>9.Adverse events related to the interventions.<br>10.Adherence to study interventions. |
| Internal pilot | Aim: To have randomised 310 participants from ~30 GP surgeries by month six of participant recruitment. |
| Study duration | Funding start date: 1 August 2023<br>Anticipated duration: 42 months<br>Anticipated end date: 31 January 2027 |

**TRIAL FLOWCHART**



## 1. BACKGROUND AND RATIONALE

Heart failure (HF) is long-term clinical syndrome that causes breathlessness, fatigue and leg swelling, which can markedly impair quality of life. HF affects between 10 and 15% of people over the age of 75, is responsible for a high proportion of hospital admissions (2% of bed days and 5% of emergency admissions) and costs the NHS around £2bn per year (1).

HF is often suspected because of symptoms and diagnosed using ultrasound examination of the heart (echocardiography). Echocardiography can be used to classify HF into subtypes, based on assessment of the systolic (contracting) and diastolic (relaxing) function of the left ventricle (LV) in the heart. LV systolic function is measured using the left ventricular ejection fraction (EF). Approximately half of people with HF have LV systolic dysfunction (LVSD). HF with LVSD can be classified as HF with mildly reduced ejection fraction (EF 41-59%) and HF with reduced ejection fraction (EF <40%). If LV systolic function is preserved, HF is classified as HF with preserved ejection fraction (EF >50%). Functional limitations because of heart failure can be assessed using the New York Heart Association (NYHA) classification, a classification with four categories from I (no limitation of physical activity) to IV (symptoms of heart failure at rest).

Most people with HF have multiple long-term conditions (MLTC) (two or more long-term conditions) and are typically taking multiple medications, both for HF and for other long-term conditions (2). They are largely managed in primary care or community HF clinics (3), with input from specialist services for some patients. HF may be managed with a combination of treatments including combination drug therapy, physical therapy, implantable medical devices, and, when appropriate, palliative care.

CoQ10 is a vitamin-like compound sold as the over-the-counter supplement ubiquinone (oxidised form) or ubiquinol (reduced form). CoQ10 acts as an antioxidant and is an essential component in the production of cellular energy in mitochondria (4, 5). Therefore, CoQ10 may improve exercise capacity and functional status in people with HF, which in turn may improve quality of life (QoL). CoQ10 protects organs other than the heart, such as the liver, lungs and kidneys, therefore its benefits may extend beyond the heart in people with HF, who have a high burden of MLTC (6).

### 1.1. Evidence explaining why this research is needed now

The relevant literature has been recently reviewed (7). The meta-analysis highlighted a possible benefit of CoQ10 on all-cause mortality (relative risk 0.68, 95% confidence interval (CI) 0.45 to 1.03), cardiovascular mortality (relative risk 0.57, 95% CI 0.33 to 0.98) and hospital admission for HF (relative risk 0.61, 95% CI 0.49 to 0.77). In contrast, the results for outcomes such as ejection fraction (EF) and NYHA class, and quality of life (QoL) were uncertain. There is no evidence that CoQ10 increased adverse events up to doses of 1200/mg/kg/day (8). The authors conducted a model-based economic evaluation and found that CoQ10 is potentially highly cost-effective (7). However, due to uncertainty and potential impact on the NHS budget they indicated that more evidence on costs and QoL is required to inform NHS decision makers.

## 2. AIMS AND OBJECTIVES

### 2.1. Research question

In patients with heart failure with reduced ejection fraction (HFrEF), is the addition of CoQ10 to usual care clinically- and cost-effective?

### 2.2. Aim

To determine the clinical and cost effectiveness of CoQ10 added to usual care in people with HFrEF.

### 2.3. Primary objectives

1. Estimate the difference between groups (intervention (CoQ10) and control (placebo)) in the primary endpoint of HF specific Health Related Quality of Life (HRQoL).
2. Determine the cost effectiveness of CoQ10 compared with the control.

### 2.4. Secondary objectives

Estimate the difference between groups (intervention and control) with respect to:

1. A composite hierarchical endpoint including all cause death, all cause hospitalisation and HF-specific HRQoL, analysed using the win ratio.
2. Death (all cause and from cardiovascular causes).
3. Hospitalisation (all cause, cardiovascular and HF related).
4. Major adverse cardiovascular events (MACE); a composite endpoint comprising cardiovascular death, cardiovascular hospitalisation, mechanical assist implantation, or urgent cardiac transplantation.
5. NYHA functional classification (severity of physical symptoms caused by HF).
6. Resource and health service use.
7. Quality of life assessed by EQ-5D-5L (EQ-5D descriptive system and EQ visual analogue scale).
8. Formal and informal care.
9. Adverse events related to the interventions.
10. Adherence to study interventions.

### 2.5. Primary outcome

Participant-reported HF specific measure of HRQoL assessed using the 23-item self-administered Kansas City Cardiomyopathy Questionnaire (KCCQ) (9) at 12 months after randomisation. These data will also be collected at four other timepoints (baseline, 3-, 6- and 9-months after randomisation).

### 2.6. Secondary outcomes

At 12-months and 5 years (subject to funding) post randomisation:

a. All cause death, all cause hospitalisation and HF-specific HRQoL analysed using the win ratio (major secondary outcome).
b. All cause death.
c. Cardiovascular death.
d. All cause hospitalisations.
e. Cardiovascular hospitalisation.
f. HF specific hospitalisation.
g. Major adverse cardiovascular events (MACE) including death, cardiovascular hospitalisation, mechanical assist implantations or urgent cardiac transplantations.
h. Resource and health service use.

At baseline and 3-, 6-, 9- and 12-months post randomisation:

i. Self-assessed NYHA functional classification.
j. Quality of life assessed using the EQ-5D-5L questionnaire.
k. Formal and informal care.

l. Time off paid employment.

At 3-, 6-, 9- and 12-months post randomisation:

m. Adverse events related to the study interventions.
n. Self-reported adherence to study interventions.

**Table 1: Trial Outcomes**

| Objective | Outcome | Collection timepoints (post randomisation) | Data Source |
|---|---|---|---|
| **Primary Objectives** | | | |
| 1 | Participant-reported HF specific measure of HRQoL assessed using Kansas City Cardiomyopathy Questionnaire (KCCQ) | Baseline, 3-, 6-, 9- and 12-months | **Participant-reported**: KCCQ score |
| 2 [and secondary objective 8] | Quality of life | Baseline, 3-,6-, 9- and 12-months | **Participant reported :** EQ-5D-5L questionnaire |
| | Resource use | Baseline, 3-, 6-, 9- and 12-months | **Participant reported:** Formal and informal care Time off paid employment |
| | | 12-months and 5 years* | **HES:** Admitted patient care Outpatient appointments Accident and emergency attendance **GP medical records**: GP consultations Referrals Prescribed medications |
| **Secondary Objectives** | | | |
| 3-6 | All cause death Cardiovascular death | 12-months and 5 years * | **ONS** |
| | All cause hospitalisation Cardiovascular hospitalisation HF-specific hospitalisation | 12-months and 5 years* | **HES** |
| | MACE (death, hospitalisation, mechanical assist implantation or urgent cardiac transplantation) | 12- months and 5 years* | **HES/ONS** |
| 7 | Self-assessed New York Heart Association (NYHA) Functional Classification of HF | Baseline, 3-, 6-, 9- and 12-months | **Participant-reported**: NYHA score |
| 9 | Adverse events related to the interventions | 3-,6-,9- and 12-months | **Participant reported:** adverse events |
| | | 12-months | **GP medical records** |
| 10 | Self-reported adherence to trial interventions | 3-, 6-, 9- and 12-months | **Participant reported**: Adherence to trial intervention<br><br>Formal pill counting for first 20% of all participants at 3 months to monitor adherence |

* 5-years post randomisation follow up subject to funding; Hospital Episode Statistics (HES); Office for National Statistics (ONS); Major Adverse Cardiovascular Events (MACE).

## 3. TRIAL DESIGN AND SETTING

CORAL is a multi-centre, individually randomised, pragmatic, patient-centred, data enabled, placebo-controlled superiority trial in primary care with internal pilot and economic evaluation.

### 3.1. Clinical Trial of an Investigational Medicinal Product

Trial design and delivery will be pragmatic. We seek to include a population that is relevant for the intervention and collect outcomes that are meaningful to end users. The trial has been designed with the patient's needs at the centre and as such, participants do not have to attend extra healthcare visits and medication will be delivered directly to the participants' homes. Inclusivity features (see section 3.3) have also been embedded in the trial to enable participation of under-served groups. By 'data enabled' trial, we mean data routinely collected in electronic health records to identify potential participants and to assess the benefits and harms of CoQ10 without the need for primary data collection for variables that are already recorded in electronic health records (GP records, HES or ONS).

### 3.2. Trial setting

Participants will be recruited from primary care (~75 GP surgeries in England) via NIHR Clinical Research Networks (CRN) including (but not limited to) West of England, South West Peninsula, East Midlands and North East/North Cumbria.

### 3.3. Inclusivity and diversity

To ensure that the CORAL study addresses the needs of diverse socio-economic and ethnic populations we will recruit some GP surgeries in areas that have high socio-economic deprivation (20% most deprived, as quantified using the English Indices of Multiple Deprivation), and in areas of ethnic diversity. Across the study we aim to recruit at least 10% of participants from ethnic minority groups. We will also collect anonymous data from sites on the demographics (age, gender, ethnicity and measure of deprivation) of patients with heart failure who do and do not have LVSD coded. This will be used to describe the demographics and deprivation profile of the heart failure population with and without LVSD coded and to identify whether the proportion of people with coded LVSD differs by demographic group or deprivation profile. It will also allow us to determine the effect of trial processes in improving the proportion of people with coded LVSD at GP practices.

In Leicester, the Centre for Ethnic Health Research (CEHR) will facilitate recruitment of a Community Engagement Officer to support the project. They will be responsible for recruiting additional public contributors from diverse backgrounds to join the Patient and Public Inclusion and Engagement (PPIE) group and facilitate sessions to optimise recruitment strategies and dissemination. The Community Engagement Officer will also support the recruitment of participants within Leicester.

We have worked with our PPIE group and Community Engagement Officer from the CEHR to co-develop participant facing materials (invitation letter, participant information leaflets (PIL), and consent form). This will include a short video describing the study translated into a several different languages, chosen to suit the communities in which we are recruiting, study information materials in 'Easy Read' versions which includes infographic formats to cater to those with low literacy or people with learning difficulties. All potential participant-facing materials will be translated into the languages that are most spoken across our target CRNs. Where needed and relevant, we will use professional interpretation services to assist with data collection (i.e. interpreting of questionnaires where we are unable to obtain validated versions in a specific language) and support participants with completing the questionnaires either face-to-face, by telephone or video call. The EQ-5D-5L interviewer administration version of the questionnaire will also be available for use if the participant is unable to read or write or cannot be physically present when the questionnaire is being completed. For example, when the follow up interview must be completed over the phone with the participant as they are unable to complete the postal or online version of the questionnaire.

We will employ a variety of methods to increase the diversity of the participants in the study including, but not limited to, the employment of local Community Champions and embedding cultural competency training into the Site Initiation Training.

### 3.4. Trial promotion

Participating GP surgeries will be offered the chance to display posters in waiting rooms and put information about the study on practice websites and social media.

The study website will contain the PIL for the study and link to a short, animated video describing the study. Other wording will be based on approved documentation.

### 3.5. Internal pilot

The first six months of participant recruitment will constitute an internal pilot, with the criteria and thresholds for progression shown in Table 2. By the end of month six of participant recruitment, we aim to have randomised 310 from ~30 GP surgeries.

If all the criteria are green, the trial will continue as planned. If any of the criteria are in the amber or red zones, the Trial Management Group (TMG) will consider remediable issues and, if supported by the Trial Steering Committee (TSC), the trial will proceed with regular monitoring. The study team will also engage in consultation with the Funder to determine whether study continuation is feasible.

**Table 2. The traffic light system for progression from internal pilot to main trial**

| Progression criteria | Red | Amber | Green | Notes |
|---|---|---|---|---|
| % threshold | 16% | 48% | 100% | |
| Total number of participants randomised | 50 | 150 | 310 | Staggered opening of sites and lower recruitment in first month of opening |
| Trial recruitment | 5% | 17% | 32% | Total trial recruitment: 950 participants |
| Number of sites open | 7 | 15 | 30 | Two trial managers to achieve efficient site set up |
| Recruitment rate/site/month | Aiming to recruit a total of 15 participants per site, but recruitment will be at the discretion of each site (it may all happen within a month or may be staggered over several months) | | | |

### 3.6. Adherence

Adherence with the IMP will be assessed through participant-completed questionnaires and a pill counting exercise.

The first 190 randomised participants (20% of total) will be contacted at the 3-month time point and asked to return their unused IMP to the Bristol Trials Centre (BTC) for counting and disposal. After counting all unused IMP will be destroyed following approval from the Sponsor. Adherence rates will be reported to the TMG and TSC and, if a risk of nonadherence is identified, medication-taking reminders such as, but not limited to, telephone calls and text message reminders will be implemented into the trial.

## 4. ELIGIBILITY CRITERIA

### 4.1. Subject population

Adults ≥18 years with a diagnosis of HF and any evidence of left ventricular systolic dysfunction (LVSD) in their electronic GP records.

### 4.2. Inclusion criteria

a. Age ≥18 years
b. Evidence in GP record of LVSD
c. NYHA class ≥II

### 4.3. Exclusion criteria

a. Diastolic dysfunction with EF≥50% or preserved left ventricular function
b. Supplementary CoQ10 intake within the last 6 weeks
c. Current warfarin use (CoQ10 may reduce the anticoagulant effect of warfarin)
d. Known allergy to soy
e. Known allergy to peanuts
f. Currently enrolled in another interventional clinical trial
g. Unable to provide informed consent
h. Unwilling to take part due to diet choices (placebo and CoQ10 capsules contain halal bovine gelatine)

Women only:

i. Pregnant
j. Breast feeding

### 4.4. Prior and concomitant therapies

Concurrent use of warfarin and prior (in the 6 weeks before informed consent) or concurrent use of CoQ10 or supplements containing CoQ10 is not permitted.

### 4.5. Emergency contact procedure for participants

Details of what a participant should do if they experience any problems or side effects whilst taking part in the trial is detailed in the PIL. Side effects or troublesome symptoms are not anticipated as CoQ10 poses a low risk, is generally well tolerated and available over the counter in the same dose as used in this trial.

However, if a participant experiences symptoms that are troublesome or serious, they are advised to seek medical help in the normal way e.g. via 111, their GP, or in an emergency phoning 999 or via an Emergency Department. The trial team will only advise a participant on action to take with respect to the IMP and will not provide any other medical advice. The participant's GP will retain medical responsibility for them throughout their participation in the trial.

Participants will be given a card to carry with them to show to any medical professionals they encounter to explain that they are taking part in the trial, potentially taking CoQ10 and the contact details of the study team. In the event of a medical emergency the participant's treating clinician can contact the University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) central pharmacy who will hold the treatment allocation and will be available 24 hours a day, 7 days a week. During office hours (8.30-17.00 Mon to Fri) call 0117 342 4175. Out of hours contact the UHBW switchboard on 0117 923 0000 and ask for the Emergency Duty Pharmacist.

## 5. TRIAL PROCEDURES

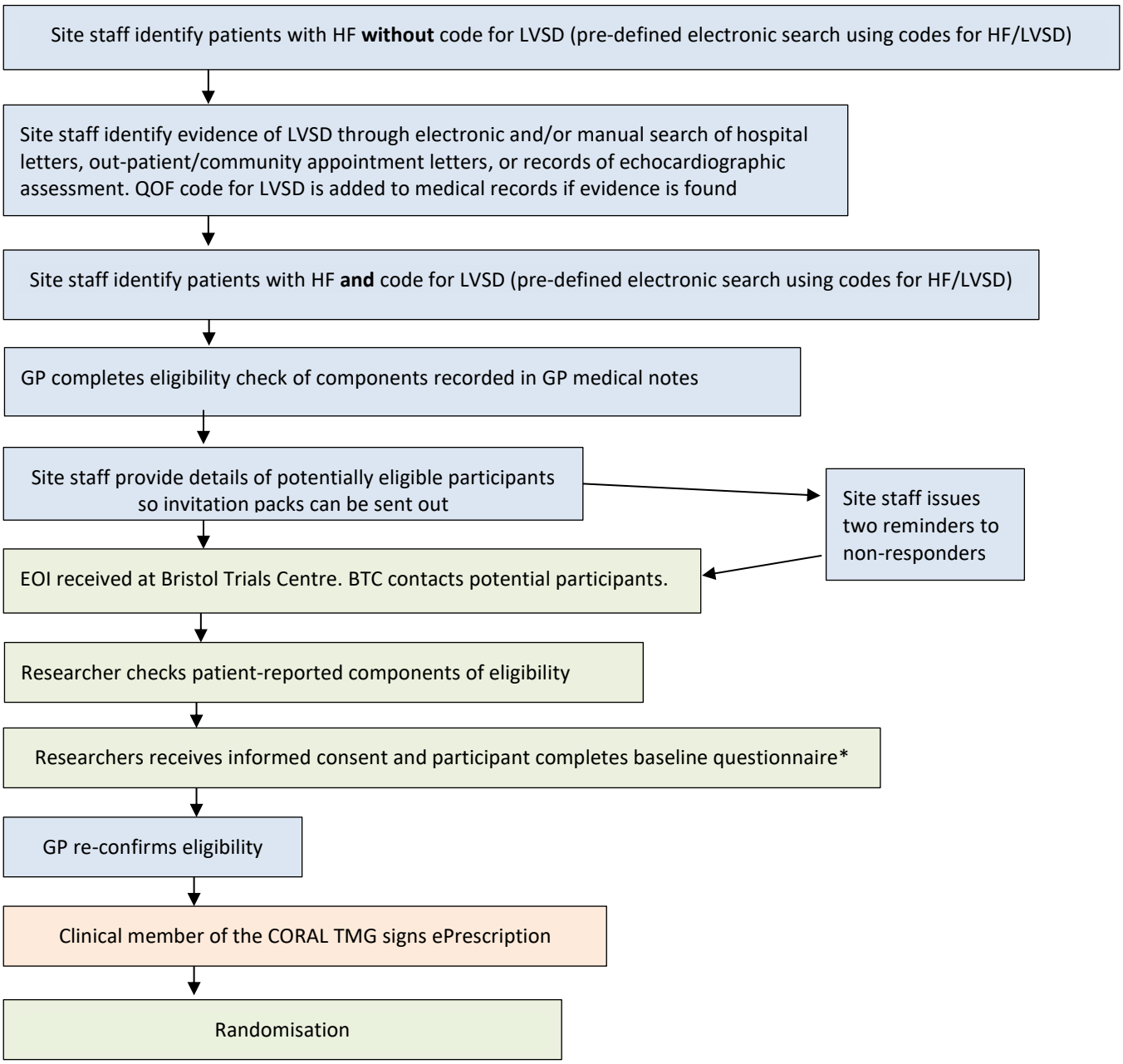
### 5.1. Screening and identification of potential participants

Adults with HFrEF will be identified from electronic GP records using standardised codes for HF and/or LVSD and from electronic/manual record searches for evidence of LVSD. Participating GP surgeries will be given full training and written instructions of how to run the participant search.

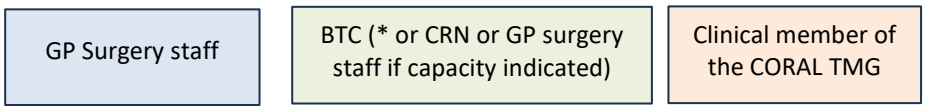
People with evidence of LVSD will be eligible for the study (See Figure 1 for the screening schema). Support and expertise will be provided for GP surgeries to review the remaining people with coded HF but no code for LVSD to determine if they have LVSD and code them appropriately. The reporting of EF on echocardiograms is variable and may be reported textually rather than with a precise figure. By including people with text description of reduced EF we are both following real-world practice and ensuring that we do not exclude people who do not have access to highly specialised services. This is in line with recent recommendations to design and run trials that reflect real world practice (10).

Following completion of the initial ineligibility checks of the components recorded in the GP medical records, potential participants identified will be allocated a unique CORAL participant identifier code and sent one invitation pack. The invitation pack will contain an invitation letter (which will have a link to the online PIL and online expression of interest (EOI) form), a study summary, paper EOI and freepost envelope. At least two weeks after the invitation packs have been sent, the participant identifiers on the returned and completed EOIs will be compared at the GP surgeries to the original mailing list. Any participants who have not returned an EOI within two to four weeks of being sent an invitation pack will be contacted by their GP surgery by text message, if they have agreement on medical records to receive text messages from their GP. After at least another two weeks, the GP surgeries will compare the list of responders to the original mailing list and remaining non-responders will be contacted by phone by staff at the GP surgery to see if they are interested in taking part. After these two reminders, no further attempts to contact the non-responders will be made and GPs will be instructed to document this participant as not interested. Anyone contacting us subsequently would be considered for participation and re-screened.

**Figure 1: Screening Schema**




**TASK KEY**



### 5.2. Consent

Once an EOI has been received at the central research office (BTC) potential participants will either be sent a screening questionnaire by email (if an email address has been supplied) or complete the screening questionnaire over the phone with a member of the research team. The screening questionnaire will collect contact preferences for the study, including an option to receive text message reminders which can be opted out of at any time. Following completion of the screening questionnaire, eligible participants will be sent a Participant Information Leaflet (by email, the study website or post, as suits an individual participant) and given time to read it. A trained member of the research team will then speak with the patient, confirm understanding about the study and answer any questions, before receiving informed consent to take part in the study. Consent will also be sought for access to the participant's medical records (HES, ONS and GP records) 12 months post randomisation and HES and ONS records again at 5-years post randomisation (subject to funding). It will be made clear that participants are free to stop their participation in the study at any time, without giving reasons and without prejudicing their future treatment.

We will use a mixed researcher model, whereby the trained researcher can be based at the GP surgery, be part of the BTC team or working for the CRN. Practice-based researchers may be able to receive consent face-to-face. Otherwise, interested and eligible patients will be contacted by telephone (or video call, according to participant preference). Any video calls will be conducted using a platform approved for this purpose by the University of Bristol, Information Governance Team.

We anticipate that most participants will be willing and able to give consent online (e-consent). Where possible, consent will be taken online, using REDCap. The acceptability of e-consent has been confirmed by our Sponsor and PPI and is in-line with HRA guidance (11). If paper consent is required, two copies of the consent form will be sent to the participant with a freepost envelope. The participant will complete both forms and return them to the central research team to countersign. The participant will then be sent one of the fully signed forms for their records.

For those participants who are unable to read, write, or require the study information to be translated, an impartial witness (as defined by GCP) will be involved in the consent process. If the participant is unable to read the PIL, for any reason, the witness' role is to confirm that they have read the PIL and that all information within it was explained to and understood by the participant. If the participant is unable to confirm their willingness to participate in writing, for any reason, the witness' role is to attest that the participant provided verbal consent. An impartial witness cannot be a member of the research team, regardless of who employs them, but could be an allied health professional/nurse/doctor (if they are not on the study delegation log) or a friend/relative of the participant. The reasons for requiring an impartial witness will be recorded on the consent form. If a translator is required to facilitate the consent discussion, the translator's code will be recorded on the consent form.

To allow inclusion of participants with a low level of literacy, both the 'Easy Read' version of the PIL, which contains the study information in an infographic format, and the 'full' version of the PIL will be supplied. If it is deemed necessary by the research team receiving consent, then an impartial witness will also be involved to confirm the participant has fully understood the PIL.

### 5.3. Eligibility and prescription of IMP

The eligibility criteria of consented participants will be re-checked by an appropriate clinician at the GP practice. If the criteria have been met a Clinical member of the CORAL TMG, will prescribe study medication using a study-specific ePrescription to initiate the study medication dispensing process.

Alternatively, if the Clinical member of the CORAL TMG believes that the eligibility criteria have not been met and that prescriptions cannot commence, the researcher will notify the individual that it is not suitable for them to take part in the trial and update the records, as required.

### 5.4. Randomisation

Trial participants will be allocated in a 1:1 ratio, stratified by GP practice (to account for difference in case mix) with cohort minimisation for statin use (which may deplete CoQ10 levels, see section 6.3 for more details), and NYHA score (group 1: NYHA score = II, group 2: NYHA score of III or IV) to balance groups

according to their symptom burden) to receive one tablet three times a day for 12 months of 100mg CoQ10 (intervention) or placebo (control).

The randomisation sequence will be generated by Sealed Envelope™ using their online randomisation system, which will allocate the participant to a treatment pack number. The person undertaking the randomisation and the participant will remain blinded as to which treatment group this code refers.

The trial pharmacy (Pharmacy2U) will be directly informed of the randomisation code and dispatch the allocated IMP. The unblinded randomisation code will be held by the University Hospital Bristol and Weston NHS Foundation Trust Pharmacy for emergency unblinding, and a BTC safety statistician not involved in any other aspect of the study.

The participant's GP will be informed that they are taking part in the CORAL study, and a request will be made that their participation is noted on their electronic medical record and that they may be taking CoQ10 during the intervention period.

### 5.5. Dispensing timepoints

At the time of randomisation participants will be sent their first batch of IMP or placebo (control). A further three shipments of IMP or placebo will be sent to ensure adequate supply for 12 months.

### 5.6. Schedule of assessments

Table 3 specifies the timepoints for outcome data collection. All timepoints are counted from randomisation.

Participants will be asked to complete questionnaires (online or paper, according to preference) at baseline, 3-, 6-, 9- and 12-months post randomisation, with reminders for non-responders. Completion of core data over the telephone or by videocall will be offered if necessary. Instructions are provided on each of the questionnaires and in the IMP secondary boxes to contact the study team if participants have any questions.

With permission, we will request data on demography, long term conditions, medical history and current medication data from the participant's GP records at baseline. At least 12 months post randomisation, healthcare resource and clinical outcome data will be extracted from the participant's electronic GP medical records and from the HES and ONS databases. A further check on clinical outcomes recorded in HES and ONS databases will occur 5 years post randomisation (subject to funding).

**Table 3: Schedule of assessments**

| Outcome | Baseline | 3 months | 6 months | 9 months | 12 months | Long term follow up[++] |
|---|---|---|---|---|---|---|
| **Baseline data from electronic GP records / HES**<br>Demography; long term health conditions; medical history[*]; current medications | ✓ | | | | | |
| **Baseline data (participant reported[**])**<br>• KCCQ<br>• Ethnicity<br>• Coenzyme Q10 use<br>• SILS<br>• NYHA class<br>• Formal and informal care<br>• Time off paid employment<br>• EQ-5D-5L (or EQ-5D-5L Interview***) | ✓ | | | | | |
| **Follow up data (participant-reported[**])**<br>• KCCQ<br>• Adherence<br>• NYHA class<br>• Formal and informal care<br>• Time off paid employment<br>• EQ-5D-5L (or EQ-5D-5L Interview***)<br>• Adverse Events<br>• Serious Adverse Events | | ✓ | ✓ | ✓ | ✓ | |
| **Follow up data (clinical outcomes) HES / ONS[++]**<br>• All cause deaths<br>• All cause hospitalisations<br>• All MACE including deaths, cardiovascular-specific and HF-specific hospitalisations, mechanical assist implantation or urgent cardiac transplantation<br>• Serious Adverse Events | | | | | ✓ | ✓ |
| **Follow up data (resource use) GP records / HES**<br>• Admitted Patient Care<br>• Outpatient appointments<br>• Accident and emergency<br>• GP consultations<br>• Referrals<br>• Prescribed medications<br>• Pregnancy and delivery outcome<br>• Serious Adverse Events | | | | | ✓ | |

New York Heart Association (NYHA); Kansas City Cardiomyopathy Questionnaire (KCCQ); Single Item Literacy Screener question (SILS); General practitioner (GP); Hospital Episode Statistics (HES); Office for National Statistics (ONS); Major Adverse Cardiovascular Events (MACE). [*]e.g. duration of HF, N-terminal-pro-B type natriuretic peptide, EF, device therapy, previous hospital admissions. [**] Anticipated time for completion 20-30 min. [++]All participants will be followed through routine data 5 years after randomisation (subject to funding). ***EQ-5D-5L Interviewer Administered version to be completed when a participant is unable to read or write or is unable to complete questionnaires online or send completed paper questionnaires to the study team.

### 5.7. Blinding and unblinding

The co-investigators, investigator site staff, lead trial statistician, methodology lead, health economists, study statistician, BTC study team and participants will be blinded to the allocation of treatment group. Only the dispensing pharmacists, UHBW pharmacy for emergency unblinding and a BTC safety statistician not directly involved with CORAL will be unblinded to the allocation.

Treatment codes will only be released to the investigative team once written confirmation has been received that the trial database has been locked. The dispensing pharmacy will then send a list of all participants and their treatment allocation. Participants and their GPs will be informed of their allocation at the time of publication of the study's findings.

### 5.8. Emergency unblinding

Considering the perceived low risk nature of the IMP, emergency unblinding should not be expected unless clear clinical need or another emergency dictates this. If emergency unblinding is required, the participant's treating clinician will contact the central pharmacy (UHBW) who will provide a 24-hour unblinding service. Contact details for emergency unblinding will be on the PIL and trial participation card. Sites will follow the trial specific instructions for unblinding.

### 5.9. Discontinuation of study treatment

Participants can choose to discontinue study medication at any time. If a participant wishes to discontinue taking study medication (receiving the allocated trial treatment), efforts will be made to continue to obtain follow up data. Following discontinuation of IMP participants will return to usual care from their GP for any subsequent medical care.

### 5.10. Withdrawal from the trial

Participants can choose to withdraw for any reason at any time during their involvement in the trial. The CI or PI can also decide to withdraw participants based on clinical opinion at any time during the trial. Although it is the participant's right to withdraw without giving a reason, it is a GCP requirement that a reason be sought and recorded if given.

In the event of any form of withdrawal and unless participants indicate otherwise, data obtained up to this point will be retained for analysis, as advised in the PIL. At the point of withdrawal, we will also request the option to collect data from their electronic records, in the future.

### 5.11. Participant payments and communication

In recompense for their time and as a thank you, participants will be offered a £10 voucher at baseline; and further £10 voucher for completed questionnaires at each timepoint (3-, 6-, 9- and 12-months).

Participants will be sent a newsletter twice yearly (accompanying a follow-up questionnaire) with updates about the study progress and, at the end, a summary of the trial findings.

### 5.12. End of Trial

Participants end their involvement with the trial when their last follow up questionnaire is completed (or efforts to obtain the final questionnaire have been unsuccessful), or they have withdrawn from the study.

The end of trial will be when the last participant has completed their final follow-up questionnaire, data extracted from the medical records (GP records, HES and ONS), all data queries have been resolved and the database has been locked, with subsequent data analysis completed.

### 5.13. Trial stopping rules

The trial may be prematurely discontinued by the Sponsor, CI, Regulatory Authority or Funder based on new safety information or for other reasons given by the Data Monitoring Committee (DMC), regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC, who will advise on whether to continue or discontinue the trial and make a recommendation to the Funder.

If the trial is prematurely discontinued, no new participants will be recruited, and a decision on data collection on active participants will be made in discussion with the TSC/DMC and Sponsor.

## 6. INTERVENTION/IMP

### 6.1. General information

Within the trial, the following are classed as IMPs:

- Coenzyme Q10 (CoQ10, ubiquinone): one capsule contains 100mg ubidecarenone
- Placebo: formulated and manufactured according to a standard placebo composition to match the appearance (shape, dimension, colour and taste) of the active capsule

### 6.2. Coenzyme Q10

Coenzyme Q10 (CoQ10) is a natural, vitamin-like compound that all cells need for production of ATP (adenosine triphosphate) molecules, the basic source of energy in the body. It also functions as an antioxidant in cell membranes and lipoproteins. CoQ10 concentration is particularly high in organs with a high metabolic rate, such as the heart, kidneys and liver as it is needed to sustain efficient energy transfer. (4) CoQ10 is a commonly used non-prescription nutritional supplement and supplementary oral administration has been found to increase CoQ10 levels in plasma, platelets and white blood cells. (12)

### 6.3. Assessment and management of risk

CoQ10 is not licensed as a medicine in the UK. However, it is readily available as the over-the-counter dietary supplement ubiquinone (oxidised form) or ubiquinol (reduced form).

CoQ10 is well tolerated. In trials of CoQ10, including people with HF, the rates of adverse events were no different between CoQ10 and placebo groups (7, 8). Undesirable effects as listed on the Summary of Product Characteristics (Myoqinon, PharmaNord tradename dated 22 December 2022) are rare (≥ 1/10,000 – < 1/1000) or very rare (<10,000) and include gastrointestinal symptoms, headache, dizziness and cutaneous reactions. The symptoms are usually mild and often subside with continued treatment. A temporary or permanent dose reduction may be considered if the undesirable effects do not resolve. Occasional irritability and dizziness have been reported, but their association with CoQ10 use has not been confirmed.

CoQ10 can potentially reduce blood pressure (BP) in patients with hypertension. Participants taking anti-hypertensive medication concurrently to the study pills will be routinely monitored by their local health care team, as part of standard care.

Participants will not be eligible for the study if they have taken CoQ10 in the 6 weeks prior to giving their informed consent. To minimise the risk of concurrent doses of CoQ10, participants will be asked in the follow-up questionnaires to provide details of any new supplements they have begun taking since the previous follow-up time point. Any participants who stipulate that they have been taking supplements that contain CoQ10 and wish to continue to take them, will be instructed to stop taking the study medication immediately but efforts will be made to continue to obtain follow up data.

Pregnant and breastfeeding individuals will be excluded from participation. Interested female participants who are under 55 will be asked if they are post-menopausal (12 consecutive months without menstruation). If they are not (i.e., are pre-menopausal), a pregnancy test will be provided, and they will be requested to report the result before participating in the study.

Statins are a group of medications that are commonly taken for primary or secondary prevention of cardiovascular disease. There is evidence that statin therapy may reduce CoQ10 levels (13). Some case reports suggest that in some people, CoQ10 my reduce the effect of coumarin-type (vitamin K antagonist) drugs (such as warfarin). Therefore, people currently taking warfarin are excluded from the study.

To manage this risk, the PIL will outline that the participant should notify the study team in the event that they are prescribed warfarin during the study. Participants will also be provided with a trial participant card with each IMP delivery which will inform them to stop taking the study pills if they begin taking warfarin and again provide contact details to notify the study team. Study questionnaires will inquire about new warfarin prescriptions at each follow-up point. Additionally, participants who are enrolled in the trial will

have a flag recorded on medical notes to advise that the patient is part of a clinical trial and warfarin is contraindicated and if there is a clinical need for the participant to begin taking warfarin, GPs will be instructed to notify the study team and inform the participant that they should stop taking the study pills.

### 6.4. Manufacture of IMP

CoQ10 (trade name Myoqinon) 100mg soft capsules will be manufactured by PharmaNord (Denmark). This formulation has been shown to have the highest bioavailability of seven different formulations tested (14). PharmaNord will also provide the matching capsule placebo, whose composition will be approved by the MHRA. This will be formulated and manufactured according to standard placebo composition to match the appearance of the active CoQ10 capsule.

### 6.5. Packaging, labelling, storage and shipping of IMP

PharmaNord will package, label the primary packaging (blister packs) and one side of the secondary packaging, complete QP release of IMP, and arrange transport of the IMP (active and matching placebo) to Eramol, in the UK.

Eramol are a UK Manufacturing and Import Authorisation (UK MIA(IMP)) holder and will check the IMP have been certified by an approved delegated Qualified Person (QP) in Denmark. Eramol will also attach an additional label with tear-off section to the secondary packaging this will include a unique kit code. Eramol will complete a QP check following additional labelling before releasing the IMP to trial pharmacy. The packages of active and placebo will be treated identically and each contains two blister packs of 21 capsules for oral administration.

Eramol will arrange transport of the IMP to Pharmacy2U who will store and dispense the IMP to the participant's preferred address using a tracked delivery service (e.g. Royal Mail tracked) at four timepoints.

The label texts for all packaging will comply with the requirements of Annex 13 of the Rules Governing Medicinal Products in the European Union.

Storage requirements will be detailed in trial specific working instruction.

### 6.6. Kit allocation

Each packet will be allocated a unique kit code during production. Management of kit codes will be conducted by a study statistician who will not be involved in any other aspects of the study. Any information that could unblind members of the investigative site teams will be stored electronically in folders accessible only to authorised unblinded individuals, or physically in a locked cupboard.

### 6.7. Dispensing of IMP to participants

Following randomisation, the dispensing pharmacy will be notified. The dispensing pharmacist will access the CORAL study database to view the signed study-specific ePrescription, the participant's name, trial identification number and randomised allocation. The dispensing pharmacist will pick the next packets from the relevant allocation and record the unique kit codes against the participant's ID in the records. They will dispense the trial specific supply of IMP and post it to participants. Unless the participants indicate that they wish to stop taking the study IMP, the IMP will be dispensed in four batches over 12 months.

The trial IMP packs will be sent directly to the participant by tracked delivery to their home address.

### 6.8. Return and destruction of IMP

Twelve months after randomisation the participants will be asked to safely dispose of unused trial medication by returning them to a local pharmacy for destruction. Any unused IMP held by Pharmacy2U at the end of the study will be destroyed (when authorised by the Sponsor) in line with the trial specific instructions on the disposal of IMP.

If the study medication packets are lost or damaged between randomisation and the end of the participant's treatment period, the study team will order replacement study medication from the

dispensing pharmacy. New packets will be dispensed from the relevant allocation and the kit codes recorded.

### 6.9. Post-trial

Continuation of the treatment following the end of the intervention phase is the responsibility of the participant's normal clinician but it will be advised to GPs that this recommendation for continuation can only occur after collection of the primary outcome at 12 months post randomisation.

### 6.10. Drug accountability

As the study is a pragmatic trial/class A CTIMP, a full reconciliation (capsule count) is unnecessary and would be difficult to undertake. Drug accountability records will be maintained throughout the course of the study by the Pharmacy2U central pharmacy. Designated pharmacy staff will document the date and quantity of IMP as it is received and dispensed to study participants.

**Table 4: Drug accountability activity and who is responsible**

| Activity | Responsibility |
|---|---|
| Supply of IMP (active and matched placebo) | PharmaNord |
| Provision and QP release of IMP | PharmaNord |
| Package and initial labelling of IMP | PharmaNord |
| UK Manufacturer's Authorisation check | Eramol |
| Additional labelling of IMP and QP check | Eramol |
| Release of IMP to trial pharmacy | Eramol |
| Dispense IMP in line with prescription to participant | Pharmacy2U |
| Maintain dispensing log | Pharmacy2U |
| Report stock levels at site | Pharmacy2U |
| Return location for unused trial medicines (where applicable) | Pharmacy2U |
| Destruction of unused trial medicines | Pharmacy2U |
| Unblinding | UHBW |

## 7. PHARMACOVIGILANCE

### 7.1. Operational definitions

Tables 5, 6, 7 and 8 list the definitions and classifications that will apply to all safety reporting in this trial.

**Table 5: Definitions of adverse events and reactions**

| 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.<br><br>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.<br><br>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 Summary of medical Product Characteristics (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:<br>• results in death<br>• is life-threatening<br>• requires inpatient hospitalisation or prolongation of existing hospitalisation<br>• results in persistent or significant disability/incapacity<br>• consists of a congenital anomaly or birth defect<br><br>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.<br><br>[a] *"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.*<br><br>[B] *"Hospitalisation" is defined as an unplanned overnight stay. Note, however, that the patient must be formally admitted – waiting in outpatients or an Emergency Department would not count as hospitalisation (even though this can sometimes be overnight). Prolongation of an existing hospitalisation qualifies as a SAE. Planned hospital stays would not be counted as SAEs, nor would stays in hospital for "social reasons" (e.g. respite care, the fact that there is no-one at home to care for the patient). Also, if patients had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as an SAE. Hospitalisations for the purpose of the intervention are an exception to SAE reporting unless complications occur.* |
| **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:<br>• 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 SmPCs suitability will need to be undertaken.<br>• in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question |
| **Suspected serious adverse reaction (SSAR)** | A suspected serious adverse reaction (SSAR), is any serious adverse reaction that is suspected (possibly or probably) to be related to the investigational medicinal product/medical device/intervention. |

**Table 6: Classification of Severity**

| | |
|---|---|
| **Mild event**: | An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. |
| **Moderate event** | An event that is sufficiently discomforting to interfere with normal everyday activities. |
| **Severe event**: | An event that prevents normal everyday activities. |

**Table 7: Classification of Relatedness**

| | |
|---|---|
| **Not related** | Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event. |
| **Unlikely to be related** | Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause which can by itself explain the occurrence of the event. |
| **Possibly related** | Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause. |
| **Probably related** | Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause. |
| **Definitely related** | Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive. |

**Table 8: Classification of Expectedness**

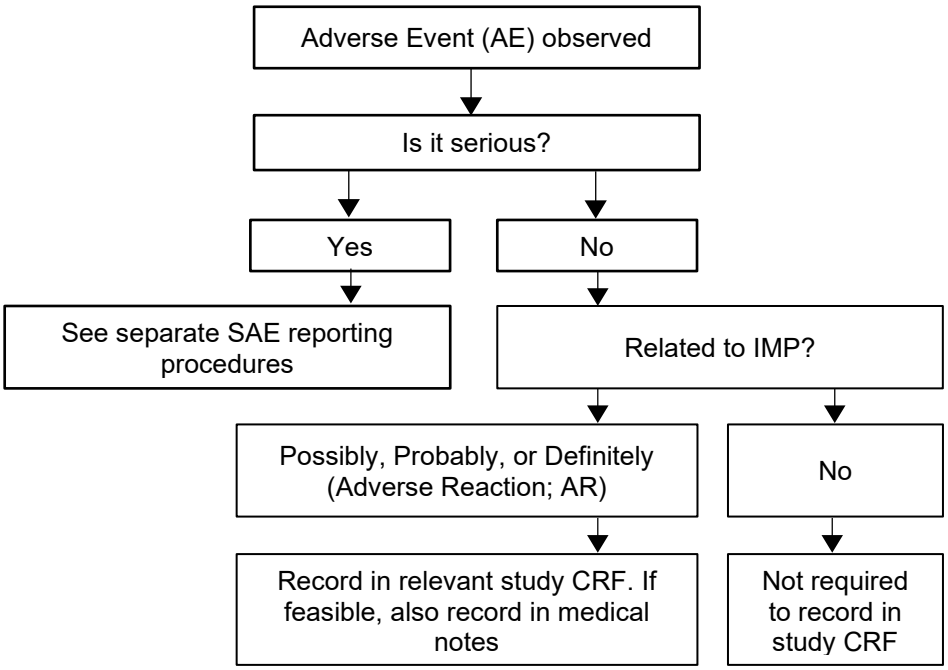
| | |
|---|---|
| **Expected** | Reaction previously identified and described in the Reference Safety Information (RSI), in the Summary of medicinal Product Characteristics (SmPC). |
| **Unexpected** | Reaction not previously described in the RSI, in the SmPC. |

### 7.2. Identification of Adverse Events (AEs)

Only non-serious adverse events that are assessed as being possibly, probably or definitely related to the IMP (adverse reaction AR), will be recorded in the relevant study documentation from the first study treatment until completion of the last trial-related procedure. Non-serious adverse events that are unrelated to the IMP will not be recorded (figure 2).

It is anticipated that the majority of AEs will be detected via the follow-up questionnaires. The lead centre will assess whether events meet the Serious criteria and will communicate with the local PI, Clinical CI or other study team clinicians for them to determine causality. Non-serious AEs that are assessed as being possibly, probably or definitely related will be reviewed by the DMC at their next booked meeting.

**Figure 2. Recording framework for non-serious Adverse Events (AEs)**

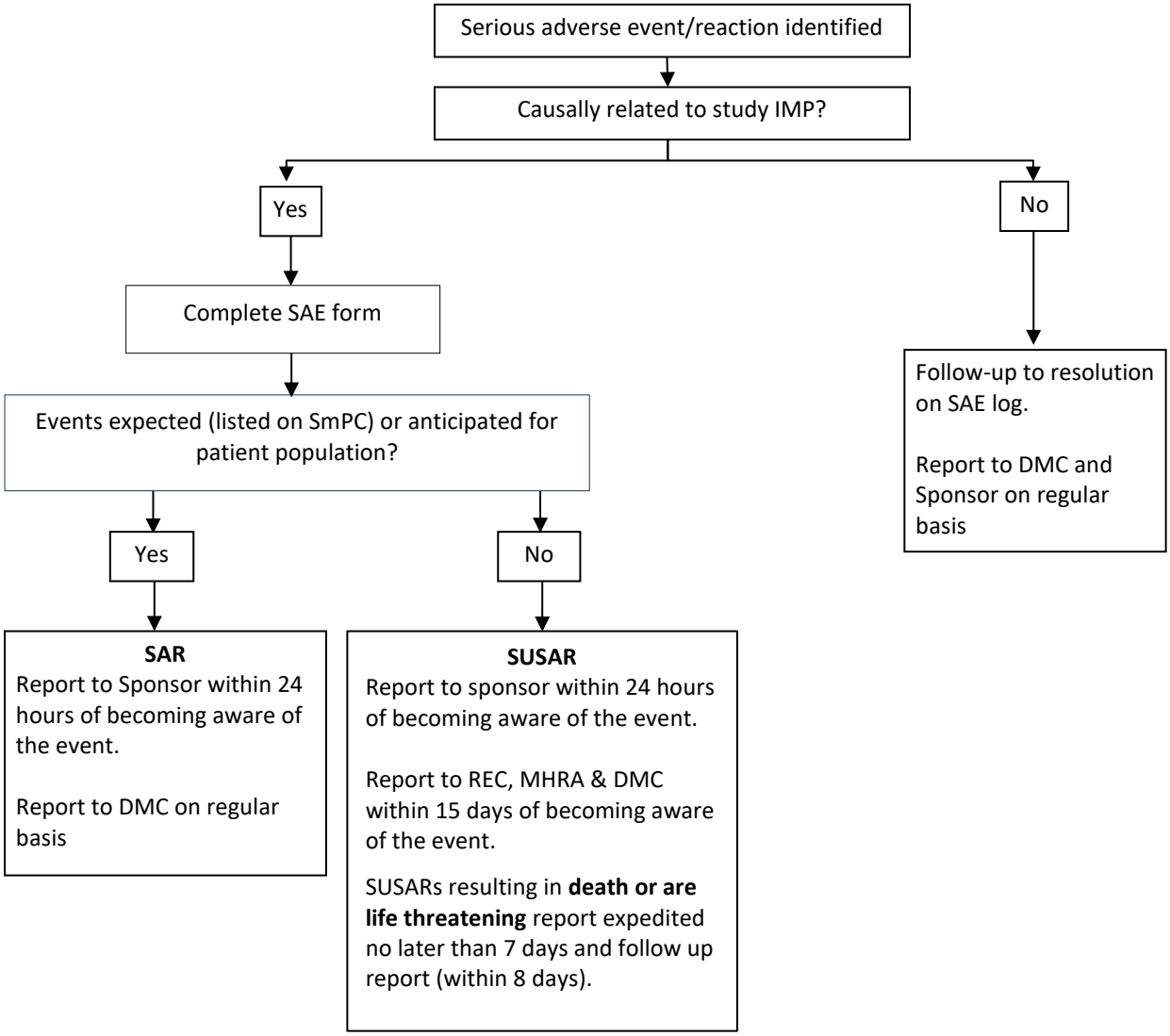



### 7.3. Serious Adverse Events

The reporting framework for SAEs is presented in figure 3. SAEs will primarily be detected via the follow-up questionnaires and HES/ONS and GP Medical records. If an SAE is detected that is deemed to be possibly, probably or definitely related to the IMP, an SAE form will be completed by the central research team (BTC), with input from a clinician (e.g., the local PI, Clinical CI or other study team clinician) to determine relatedness and expectedness.

We will be requesting historic HES data to characterise the cohort and to be able to check whether an event is a new event or an old recurring event. Outcomes from HES data will be matched against this list and a summary table of SAEs will be generated and reported to the DMC, TSC, Sponsor and MHRA.

**Figure 3. Recording framework for Serious Adverse Events (SAEs)**




### 7.4. Expectedness of Events

The expectedness of a serious adverse reaction shall be determined according to the current approved reference safety information (see Summary of Product Characteristics – Myoqinon, PharmaNord trade name dated 22 December 2022).

### 7.5. Anticipated Events

The following events are anticipated for this patient population. Events of this nature will be recorded in the SAE log but not immediately reported to the Sponsor, unless deemed to be related to the study drug:

- All-cause death
- Cardiovascular death
- Cardiovascular-specific hospitalisation
- HF-specific hospitalisation
- All cause hospitalisation
- Acute / decompensated heart failure
- Mechanical assist implantation
- Implantable cardiac defibrillator implantation

- Urgent cardiac transplantation
- Myocardial infarction
- Arrhythmias
- Other cardiac events

### 7.6. Serious Adverse Reactions (SARs)

If an SAE is detected that is deemed by a clinical investigator (doctor) to be possibly, probably or definitely related to the IMP (a Serious Adverse Reaction), an SAE form will be completed by the local PI and site team and reported to the Sponsor (via University Hospitals Bristol and Weston, in accordance with their agreement with UoB and their Safety Reporting SOP) within 24 hours of the trial team becoming aware of it.

### 7.7. Suspected Unexpected Serious Adverse Reactions (SUSARs)

All confirmed SUSARs, as assessed by a clinical investigator, will be reported to the Sponsor (via University Hospitals Bristol and Weston, in accordance with their agreement with UoB and their Safety Reporting SOP) within 24 hours of the trial team becoming aware of it. The Sponsor will report these to the MHRA and the REC within 15 days (or 7 days if fatal). They will also be shared with the Chair of the DMC and study investigators.

Safety information relating to adverse events not subject to expedited reporting that are captured as trial endpoints will be closely monitored by the DMC throughout the trial. The DMC will be provided with a report at least annually (unless specified by the DMC) where study outcomes will be matched against SAEs/SARs.

### 7.8. Urgent safety measures

In line with UHBW's Research Safety Reporting procedures, the Sponsor and investigator may take appropriate urgent safety measures to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the competent authorities (i.e. the MHRA) and ethics committee.

The first action is to protect participant safety/health. Following that, the CI/Sponsor should discuss the urgent safety measure by telephone as soon as it has been put in place with an MHRA safety scientist in the first instance. This should be followed-up with written notification within 3-days to the MHRA. Notification should be in the form of a substantial amendment and describe the event, the measures taken and justification for the measures taken.

### 7.9. Notification of deaths

Deaths will be detected via the HES/ONS or GP medical records collected 12 months post randomisation. We will also ask GPs to inform the central research team if they become aware of a participant's death. Instructions for reporting deaths will also be included in the documentation sent with the intervention.

### 7.10. Pregnancy Reporting

Participants will be reminded on the PIL and via a trial participant card (supplied with every IMP delivery to the participant) to report any new pregnancy to the CORAL study team who will ensure prompt notification to Sponsor. Participants who become pregnant will be asked to stop taking the IMP immediately but we will continue to follow them up as normal until the end of the study. Pregnancies will be followed up to delivery and the outcome will be reported to the Sponsor.

### 7.11. Development Safety Update Reports (DSURs)

The Sponsor will submit DSURs once a year throughout the clinical trial, or as necessary to the MHRA and where relevant the Research Ethics Committee. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

## 8. STATISTICS AND HEALTH ECONOMICS ANALYSIS

### 8.1. Sample size calculation

950 participants will be required to detect a clinical relevant proportionate reduction of at least 3 point difference in KCCQ Overall Summary Score (KCCQ OSS) at 12 months with 90% power and a 2-sided alpha of 0.05 assuming a correlation between baseline and follow-up of 0.46 (15), correlation between repeat follow up scores 0.68 and a 5% loss to follow up (participants who will provide no follow up QoL data).

### 8.2. Statistical analysis

Analysis and reporting will be in line with CONSORT (16) and CONSORT PRO (17) guidelines with the primary analyses being conducted on an intention to treat (ITT) basis using complete cases. This differs slightly from a true ITT analysis which would use imputation or other methods of addressing missing data to ensure that all randomised patients are included in the final analysis. Analysis and presentation of the trial data will be in accordance with CONSORT guidelines. A full analysis plan will be completed and reviewed by the TSC and DMC prior to the end of recruitment.

For all outcomes, we will present summary statistics (overall and by sex, IMD status, etc) and will quantify differences between groups (e.g., hazard ratio, mean difference, relative risk, absolute risk difference) as appropriate with 95% confidence intervals. Analyses will be adjusted for design variables included in the randomisation (i.e. GP practice, statin use and NYHA score) and baseline scores where measured as fixed effects and GP practice fitted as a random effect; except for the analyses using the win ratio where stratification variables will be used in selecting pairs for participants for comparison (see section 8.4). Model assumptions will be checked (e.g., normally distributed errors, proportional hazards etc.) and if violated alternative models will be sought.

Adherence will be analysed using instrumental variable analysis, using randomisation as the instrument, as a sensitivity analysis assessing the impact of non-adherence on the effectiveness of the treatment (18). Adherence will be defined as levels of adherence (e.g. good, average, poor).

The following subgroup analyses will be conducted for the primary outcome: men vs women; statin use vs no statin use; loop diuretic use vs no loop diuretic use (in previous 3 months); MLTC (>= 3 QOF conditions vs <3 QOF conditions); participant's prescribed guideline-directed quadruple therapy vs ace inhibitor (ACEi) / beta blocker (BB); and baseline KCCQ clinical summary score (0-24 vs 25-49 vs 75-100). Sub-group effects will be determined by including a treatment by subgroup interaction term in the model.

### 8.3. Analysis of primary endpoint

Patient reported outcomes scores (KCCQ) will be compared using a mixed regression model, adjusted for baseline measures where appropriate. Changes in treatment effect with time will be assessed by adding a treatment x time interaction to the model and comparing models using a likelihood ratio test. Mortality in this population is relatively high, so we will analyse the KCCQ jointly with survival to account for the missing KCCQ data due to death (19). Model fit will be assessed and alternative models and / or transformations (e.g. to induce normality) will be explored where appropriate.

Reasons for non-completion of any assessment will be recorded and coded. Missing items or errors on baseline questionnaire measures will be dealt with according to the scoring manuals or via imputation methods. Compliance rates will be reported in results, including the numbers of patients who have withdrawn from the study, have been lost to follow up or died. Causes of death for trial participants will be recorded. Additional exploratory analysis considering the proportion of patients experiencing clinically important changes will also be undertaken.

### 8.4. Analysis of major secondary endpoints

The analysis of the composite of all-cause death, all-cause hospitalisation and KCCQ-OSS will be undertaken using the win ratio approach (16). The hierarchy for the win ratio analysis will be: 1) all-cause death; 2) all cause hospitalisation; 3) KCCQ-OSS. An unmatched pairs approach with each individual in the intervention group compared to each individual in the placebo group from the same strata will be used, using the stepwise sequence below, to adjudicate a winner/loser or declare a tie. For each comparison the follow-up

period considered will be the duration of follow-up common to both participants. For example, if one participant has been followed for 6 months (e.g. discontinued participation) and the second participant for 1 year then for the comparison of these two individual events up to 6 months are considered. Similarly, if one participant has a KCCQ-OSS missing at 12 months, then for the comparison the 9-month period will be considered. The analysis will be as follows:

Step 1. Compare all-cause mortality. If one participant died, the survivor is the winner; if both participants died, the participant who survives longer is the winner; if neither participant died (or both die at the same time from randomisation) proceed to step 2.

Step 2: Compare the number of hospitalisations. The participant with the least number of hospitalisations occurring during the common follow-up period is the winner. If the same number of hospitalisations occurred in both participants, the participant who survives longer before the first hospitalisation is the winner. If neither participant had a hospitalisation in this period, proceed to step 3.

Step 3: Compare KCCQ overall clinical summary score (during the common follow-up period); the participant with the higher score is the winner.

From this the proportion of winners, the win ratio and associated 95% confidence intervals will be calculated.

Table 9 details the combinations of event rates and effect sizes considered, and the resulting power achieved with 950 participants using simulated data replicated over 1000 datasets. A conservative scenario for the cohort in our trial is an all-cause death and hospitalisation of 10% and 20%, respectively, at 1 year. With these event rates, a sample of 950 participants will have 82% and 90% power to detect a 20% or 25% difference in clinical events, respectively, with a 2-sided alpha of 0.05 (Table 9). Event rates may well be higher given those reported in the literature in both RCTs (20) and real-world cohorts; if so, the power will increase accordingly as shown in Table 9.

**Table 9: Power that will be achieved with the win ratio analysis for a range of event rates (death and hospitalisation from all causes) and effect sizes**

| Event rate in control group | | Power achieved with 950 participants | | |
|---|---|---|---|---|
| | | Relative effect size | | |
| All cause death | All cause hospitalisation | 15% *Treated vs control* | 20% *Treated vs control* | 25% *Treated vs control* |
| 7% | 10% | 68.8% | 76.8% | 83.3% |
| | 15% | 67.9% | 79.0% | 87.3% |
| **10%** | 15% | 67.4% | 78.6% | 87.2% |
| | **20%** | **68.6%** | **81.5%** | **90.2%** |
| 13% | 20% | 68.3% | 82.8% | 91.1% |
| | 25% | 68.7% | 83.3% | 91.8% |
| 15% | 25% | 68.2% | 84.1% | 92.9% |
| | 30% | 71.6% | 86.4% | 94.6% |
| 20% | 30% | 69.6% | 87.3% | 95.3% |
| | 35% | 70.7% | 88.3% | 96.6% |

### 8.5. Analysis of other secondary endpoints

Other secondary outcomes will be analysed using standard methods (e.g. linear or generalised linear mixed models as appropriate or Cox regression for time-to-event outcomes).

### 8.6. Economic evaluation

The aim of the economic evaluation is to evaluate whether CoQ10 is cost-effective for people with HFrEF compared to usual care. The primary analysis will be a cost-utility analysis conducted over a 12-month time horizon from an NHS and personal social services perspective. The secondary analysis will cover a broader perspective including productivity, patients and carers.

The measure of health benefit will be quality-adjusted life years (QALYs) as measured by combining participant-reported Health Related Quality of Life (HRQoL) and information on survival. EQ-5D-5L data will be collected at baseline, 3, 6, 9 and 12 month follow up. Utility values will be estimated from EQ-5D-5L scores using the NICE-recommend approach at the time of analysis. The current recommended approach is provided by Hernández-Alava and Pudney (21). QALYs will be estimated using the area under the curve approach and will be adjusted for baseline EQ-5D-5L score (22).

Intervention (CoQ10) dispensing, including quantity, will be recorded by Pharmacy 2U in the trial database. NHS and PSS resources will include primary, secondary and emergency care, prescribed medications, and government-funded home care. All primary care resource use will be captured from GP administration systems (e.g. EMIS, SystmOne). Relevant primary care resource-use data (including consultations, prescribed medications and referrals) will be extracted by each GP practice running an automated database search at their practice. Secondary and emergency care will be captured from national routine datasets e.g. Hospital Episode Statistics and the Emergency Care Data Set. Patient, carer and productivity perspectives will include: home care paid for by patients, informal 'unpaid' care provided by relatives, friends or the community, and time off paid employment. These will be collected from the participants at 3, 6, 9 and 12 months follow up in a brief questionnaire.

Primary and social care resource use will be valued using the national Unit Cost series published by the Personal Social Services Research Unit (23). Secondary and emergency care use will be valued using the latest NHS costs from the National Cost Collection (24). Prescribed medications and the cost of the intervention (CoQ10) will be assigned a unit cost from the Prescription Cost Analysis or British National Formulary. Informal care will be valued using the proxy good method, where informal care will be valued using the price of an appropriate substitute (25). Time off paid employment will be valued using the ONS Annual Survey of Hours and Earnings (26).

Our primary cost-utility analysis will combine cost and QALY data to calculate the incremental cost-effectiveness ratio and the incremental net monetary benefit statistic at a willingness to pay threshold of £20,000 per gain in QALY. Uncertainty will be addressed using bootstrapping, plotting cost-effectiveness acceptability curves and in sensitivity analyses.

## 9. DATA MANAGEMENT

### 9.1. Source Data and documents

Potential participants will be allocated a unique participant identification number at screening. Those who consent to take part in the trial will keep this number throughout the trial. Personal data entered directly onto the password protected database and maintained on a SQL Server database system within the University of Bristol will only be accessible to members of the research team. Any data stored on laptops will be encrypted. Any information that is analysed or transferred outside the European Economic Area will be anonymised. Participants will be asked to consent to their name, date of birth, and contact details being stored on the secure database with the central research team.

Data obtained by paper will also be entered onto the password protected database by the central research team. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to trial staff. Information capable of identifying participants will not be removed from University of Bristol or clinical centres or made available in any form to those outside the trial, for the exception of NHS Digital for linkage.

Consent forms and clinical letters with personal identifiable data will be stored separately in a locked filing cabinet. Participant details will be anonymised in any publications that result from the trial.

Source data for this trial will consist of certified scanned copies and/or paper copies of the consent form, participant completed questionnaires as well as the electronic CRFs designed specifically for the study.

### 9.2. Data collection

Clinical outcomes will be assessed by participant-completed questionnaires at baseline and at 3-, 6-, 9- and 12-months post randomisation during follow-up. The database will be set up to prompt the central research team when participant questionnaires are due. All other outcome data will be requested from GP medical records, HES or ONS at 12-months and 5-years post randomisation (subject to funding). We are using standardised outcome instruments. The components and timing of follow-up measures are shown in Table 3.

### 9.3. Case Report Forms (CRFs)

Questionnaires from participants will be identifiable only by participant trial number and will be returned by the participant by post or via electronic means to the central research team. Any postal questionnaires will be entered onto the password protected database by members of the central research team. Any paper copies will be stored in a secure locked cabinet in an access-controlled area. CRFs will be completed using the secure trial database (by default).

### 9.4. Data handling and record keeping

Data will be collected and retained in accordance with the Caldicott Principles, UK Data Protection Act 2018 and General Data Protection Regulation (GDPR).

For this trial, research data will be kept for at least 5 years. Personal data (e.g. name and address, or any data from which a participant might be identified) will not be kept for longer than is required for the purpose for which it has been acquired. Documents will be reviewed by the CI before being destroyed.

### 9.5. Access to data

For monitoring purposes, the CIs will allow monitors from the Sponsor (or delegate), persons responsible for the audit, representatives of the REC and other Regulatory Authorities to have direct access to source data/documents.

The Trial and Data Manager (in collaboration with the CIs) will manage the access rights to the data set. The access rights will be reviewed annually to ensure they remain appropriate and to ensure personnel updates have been accounted for. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable meta-analyses.

### 9.6. Archiving

This trial will be sponsored by the University of Bristol who are also the data custodian. All research data will be retained in a secure location during the conduct of the trial and for 5 years after the end of the trial, when all paper records will be destroyed by confidential means. An archiving plan will be developed for all trial materials in accordance with the University of Bristol archiving policy and BTC SOPs.

## 10. TRIAL MANAGEMENT

A Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) will be established in conjunction with a Trial Management Group (TMG) to provide oversight of the trial on behalf of the funder.

### 10.1. Host organisation: NHS Bristol, North Somerset and South Gloucestershire (BNSSG) ICB

NHS Bristol, North Somerset and South Gloucestershire (BNSSG) Integrated Care Board (ICB) is the host organisation. They will ensure NHS engagement and their Research Team will support the project. The Host will be responsible for delivering the contract, including financial obligations and will work with the Sponsor to monitor and manage supplier contracts.

### 10.2. Sponsor: University of Bristol

The University of Bristol has agreed to be the Trial Sponsor and will ensure the study meets its contractual, legal, insurance, financial and regulatory obligations, including reporting of Safety Events.

### 10.3. Trial Management: Bristol Trials Centre

Trial management will be coordinated by the Bristol Trials Centre. They will develop, test and maintain the study database, monitor conduct and deliver the study.

### 10.4. Trial Management Group (TMG)

The TMG will comprise of all investigators, including the PPI co-applicant. The TMG have responsibility for the day-to-day management of the trial, including trial design and delivery, budget, data analyses and publication and will report to the TSC. The TMG will meet on a regular basis with a core working group of staff having frequent progress meetings.

### 10.5. Data Monitoring Committee (DMC)

The Data Monitoring Committee will meet once prior to recruitment of the first participant and convene prior to the TSC meeting to review the adverse event data and any other ethical aspects that arise and report to the TSC. The DMC will comprise a chairperson, statistician and clinician as independent members. The CIs will attend the open session only, with the study statistician attending both open and closed sessions.

### 10.6. Trial Steering Committee (TSC)

Membership, responsibilities, and reporting mechanisms of the TSC will be formalised in a TSC charter. The TSC will make recommendations/key decisions during the trial to the TMG and minutes will be sent to the funder. The TSC will comprise of independent members including a Chairperson, Statistician, relevant experts in the clinical and academic field of this research, Health Economist, and PPI representative(s). The CIs, lead statistician and trial manager will represent the TMG as non-independent members and any other TMG members will be agreed by the TSC chair.

## 11. PATIENT AND PUBLIC INVOLVEMENT (PPI)

People with lived experience of HF or caring for someone with HF will be involved in every phase of the research trial. This will involve group meetings, specific roles on the TMG, review of the protocol, participant information, consent and data collection forms and informing dissemination of the research findings to participants.

We will observe the principles set out in the UK Standards for Public Involvement (27)

- Use plain language for well-timed and relevant communications, including meetings involving PPI, we will avoid jargon and provide a glossary of definitions for commonly used terms.
- Value all contributions, building and sustaining relationships. Terms of reference will be agreed during trial set-up and activities that support this will be reviewed in an on-going manner. We will also offer training opportunities, so members can build their skills and hence confidence to contribute.
- Involvement in research governance, management and decision making, identifying and sharing the difference this makes to our research: Our previous experience is that good PPI often heads-off problems and reassures the relevant regulatory authorities (Sponsor, ethics committee, etc.) about the design and acceptability of clinical trials. We will prospectively record how PPI influences decisions and actions and report these at the end, using the GRIPP2 checklist.(28)
- Communicate with a wider audience about public involvement and research, using a broad range of approaches that are accessible and appealing.

## 12. MONITORING, AUDIT & INSPECTION

### 12.1. Monitoring

The trial will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations 2004. All trial related documents will be made available on request for monitoring and audit by the Sponsor, the relevant REC and for inspection by MHRA and other licensing bodies.

The University of Bristol holds a Service Level Agreement with University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). Under the Agreement UHBW undertakes to monitor and carry out pharmacovigilance for certain UoB sponsored studies. These activities should be carried out in accordance with the Service Level Agreement, the identified risks, subsequent proposed monitoring and the trial's specific Monitoring Plan.

A Trial Monitoring Plan will be developed by the Sponsor based on the trial risk assessment which may include on site monitoring. This will be dependent on a documented risk assessment of the trial.

The central research team routinely conduct internal auditing which will be shared during Sponsor monitoring processes. The central research team will undertake the following activities:

- Written informed consent has been properly documented
- Data collected are consistent with adherence to the trial protocol
- CRFs are only being completed by authorised persons
- SAE recording and reporting procedures are being followed correctly
- Key data is recorded
- Data is valid
- Review of recruitment rates, withdrawals and losses to follow up

On a regular basis we will monitor the percentage of people that meet the eligibility criteria and report the percentage of participants who give consent. To assess the generalisability of the participants, the characteristics of consenting participants and non-consenting will be compared. We will also report to the DMC if requested, preliminary data on adverse event and dropout rates observed in the trial population.

### 12.2. Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol breaches will be documented and reported to the Trial Manager, CIs and Sponsor immediately. Information about protocol breaches will also be included in routine reports to the TMG, TSC and DMC. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CIs, Sponsor, TSC, DMC and the TMG.

All protocol breaches will be reported to the Sponsor as soon as possible after they occur/are identified. The Sponsor will determine whether it constitutes a serious breach, requiring onward reporting to the REC and MHRA.

## 13. ETHICAL AND REGULATORY CONSIDERATIONS

### 13.1. Governance and legislation

This trial will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- Good Clinical Practice (GCP)
- UK Policy Framework for Health and Social Care Research
- Data Protection Act 2018
- General Data Protection Regulation

Before any site can enrol participants into the trial, the CI or designee will obtain confirmation of capacity and capability (or equivalent organisation approval) for each site in-line with HRA processes along with other documentation required for the sponsor to grant sites with a greenlight letter.

For all amendments, the CI or designee will confirm with the Sponsor and relevant CRNs that permissions are ongoing prior to implementation.

This research trial will be run in accordance with GCP as outlined in The Medicine for Human Use (Clinical Trial) Regulations 2004.

GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial, the level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to GCP guidelines.

### 13.2. Combined review approvals and reports

HRA and ethics review of the protocol for the trial and other trial related participant facing documents (e.g., consent form) will be carried out by a UK NHS Research Ethics Committee (REC) and Health Research Authority (HRA). MHRA review of the protocol for the trial and other trial related documents relating to the IMP/placebo will be carried out by MHRA. The trial will comply with the necessary regulations and will gain Sponsor and HRA approval. The trial will not commence until Clinical Trial Authorisation (CTA) is obtained from the MHRA and favourable REC opinion and HRA approval have been provided, and sponsorship is issued. All correspondence with the REC, HRA or MHRA will be retained in the Trial Master File (TMF).

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

An annual progress report 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. The CI will notify the REC/HRA of the end of the trial and if the trial is ended prematurely (including the reasons for the premature termination). Within one year after the end of the trial, a CI will submit a final report with the results, including any publications/abstracts, to the REC.

In addition to the expedited reporting required for Suspected Unexpected Serious Adverse Reactions (SUSARs) and Suspected Adverse Reactions (SARs), a Development Safety Update Report (DSUR) will be submitted to the MHRA, once a year throughout the clinical trial or on request until the end of the trial is declared. The annual safety report should consider all new available safety information received during the reporting period and assess the safety of subjects included in the study.

### 13.3. Amendments

Any amendments to the protocol or other trial related participant facing documents will be approved by the Sponsor before being submitted to the REC/HRA for approval prior to implementation. After the initial CTA has been approved, any amendments which affect the safety (physical or mental integrity) of the participants, the scientific value of the study, the conduct or management of the study or the quality or safety of any IMP will constitute a substantial amendment and a request to the MHRA for approval will be submitted once the amendment has been approved by the Sponsor.

It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC, in accordance with the legislation and HRA processes. All amendments will be documented on the HRA amendment tool regardless of substantiality.

### 13.4. Peer review

The proposal for this trial has been peer-reviewed through the NIHR HTA process, which includes independent expert and lay reviewers.

### 13.5. Data quality

The quality of the trial data will be monitored throughout the trial (see 12.1) and data completeness will be reported to the DMC and TSC, and any cause for concern over data quality will be highlighted and an action plan put in place.

### 13.6. Financial and other competing interests

The research team and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

### 13.7. Indemnity

The necessary trial insurance is provided by the Sponsor. The PIL provides a statement regarding indemnity.

### 13.8. Access to the final trial dataset

Anonymous research data will be stored securely and kept for future analysis. Members of the TMG will develop a data sharing policy consistent with UoB policy. Data will be kept anonymously on research data facility storage (RDSF). Requests for access to data must be via a written confidentiality and data sharing agreements available from the RDSF website which will be confirmed by a co-CI (or appointed nominee).

The data sharing agreement should cover limitations of use, transfer to third parties, data storage and acknowledgements. The person applying for use of the data will be scrutinised for appropriate eligibility by members of the research team.

## 14. DISSEMINATION POLICY

A plan for disseminating the trial results will be developed by the TMG.

The main results of the trial will be published in a high impact peer-reviewed journal. Initial findings will be submitted to relevant national and international meetings. Innovative methods of dissemination will be explored such as videos, YouTube clips and blogs to accompany scientific papers that are accessible to everyone as well as providing a lay summary.

On completion of the trial a final report will be prepared for the Funder (NHR HTA) and once approved, made publicly available on their website.

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## 16. AMENDMENT HISTORY

Record of protocol version numbers and amendments:

| Version | | Notes |
|---|---|---|
| **Number** | **Date** | |
| 1.0 | 07 Mar 2024 | Version submitted for regulatory approval |
| 2.0 | 26 Apr 2024 | Section '6.3 Assessment and management of risk' – processes to monitor blood pressure, pregnancy and warfarin prescription during study participation added<br><br>Section '5.1 Screening and identification of potential participants' – processes clarified<br><br>Section '5.2 Consent' – process for collecting contact preferences clarified<br><br>Addition of section '7.10 Pregnancy reporting'<br><br>Table 3 'Schedule of assessment' - Sources of AE and SAE reporting added |
| 3.0 | 21 Aug 2024 | Minor typographical changes corrected<br><br>Clarification in the trial flowchart (p13) of the approval process for prescribing<br><br>Section '3.3 Inclusivity and diversity' – details on the anonymous data being collected about the heart failure population added.<br><br>Section '3.4 Trial promotion' - removal of social media accounts.<br><br>Section '4.5 Emergency contact procedure for participants' - emergency unblinding details added.<br><br>Section '5.1 Screening and identification of potential participants' – Fig. 1 screening schema updated.<br><br>Sections '5.5 Dispensing timepoints' and '5.6 Schedule of assessments'- amended to confirm where contact details of the study team can be found.<br><br>Section '6.3 Assessment and management of risk' – procedure added describing process if a participant starts taking CoQ10 or supplements containing CoQ10 during the study.<br><br>Sections '7.2 Identification of Adverse Events (AEs) and '7.3 Serious Adverse Events' – addition that causality and relatedness can by determined by the Clinical CI or other study team clinicians.<br><br>Section '7.9 Notification of deaths' - processes for reporting deaths updated. |
| 4.0 | 16 Dec 2024 | Section '3.3 Inclusivity and diversity'- details of the anonymous database searches that GPs complete amended. |

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|---|---|---|
| | | Section ‘3.5 Internal pilot’ - statement added regarding consultation with funder to determine progression from pilot to main trial.<br><br>Section ‘5.2 Consent’ – clarification on how and when independent witnesses and translators will be used in the consent process added.<br><br>Sections ‘6.3 Assessment and management of risk’ and ‘7.4 Expectedness of Events’ – version date of SmPC added. |