University of York
Centre for Reviews and Dissemination

Evaluation of Coenzyme Q10 (Co-Q10) in Chronic Heart Failure (CHF): An international collaborative systematic review and individual participant data meta-analysis (IPD-MA) with linked economic evaluation and value of information (VOI) analysis

PROSPERO registration number: CRD42018106189

INITIAL DRAFT: A full draft will be developed during the initial period of this project, which will, as is usual for IPD meta-analyses, incorporate a provisional listing of potentially eligible trials. This will then be further refined based on collaborative group feedback at which point a final protocol produced. No data will be obtained until the protocol is finalised.

Protocol v1.1

August 2018

Funded by NHS National Institute for Health Research

ORGANISATIONAL DETAILS

Collaboration

This individual participant data meta-analysis (IPD-MA) is an international collaborative project. All trial investigators who share data and contribute individual level data from their trials to the project will become part of the international collaborative group on whose behalf the project will be conducted and published.

IPD-MA and economic analysis research team

The project will be carried out by a research team based at the Centre for Reviews and Dissemination (CRD) at the University of York, UK, working under the direction of Lesley Stewart, Klaus Witte (University of Leeds), Mark Simmonds and Claire Rothery (Centre for Health Economics). Team members will include, Lindsay Claxton, Melissa Harden, Alexis Llewellyn, Sahar Sharif, Kath Wright, and NIHR Training Fellow Lucy Beresford.

The IPD-MA and the economic evaluation and VOI analyses will be undertaken as two separate but interlinked projects. The IPD meta-analysis will focus on clinical effectiveness and have universal relevance; the economic evaluation and VOI will take a UK and NHS perspective.

Centre for Reviews and Dissemination
University of York
Heslington
York
YO10 5DD
https://www.york.ac.uk/crd/research/epppic/

Funding

This research is funded by the NIHR Health Technology Assessment programme. Views expressed in this protocol are those of the research team and collaborative group and do not necessarily those of the NHS, the NIHR or the Department of Health.

Advisory Group

The project will be supported by an advisory group, which will include three independent clinical experts, one independent methodologist and two patient experts/PPI partners including Nick Hartshorne-Evans (who is part of the project team).

Advisory group members currently include Mark Dayer, consultant cardiologist, Taunton and Somerset NHS Trust, Nick Hartshorne-Evans, Chief Executive, The Pumping Marvellous Foundation and John Young, Professor of Elderly Care Medicine, University of Leeds and Bradford Teaching Hospitals Foundation Trust. A GP, a clinical trial/ evidence synthesis methodologist and an additional PPI member will be recruited to the group.

This group will provide advice and guidance over the course of the project.

Approval by ethics committee

The IPD-MA will use existing data provided by contributing trials, and addresses the same clinical question to which trial participants consented originally. Data supplied will contain no identifying names or numbers and will be held securely under controlled access

The Chair of the University of York Health Sciences Research Governance Committee has confirmed that ethics review is not required.

Patient and public involvement

Two PPI partners will be involved throughout the project through their advisory group roles and by commenting project materials. Their perspective on patient experience and the outcomes that matter most to patients will be particularly helpful in informing the design of the decision model and in contextualise project findings. Both will be invited to attend the results meeting and will work with us in developing plain language summaries of project findings tailored to patient and public audiences. They will contribute particularly to dissemination and knowledge translation activity including co-presenting project findings.

Publication policy

The results of the IPD-MA will be published in an academic journal, authored by the collaborative group, which will include all trial investigators who provide individual level data for analysis, all members of the IPD-MA research team and all members of the advisory group. Each contributing trial may nominate one member to join the group. Each contributing trial will also have the opportunity to nominate one additional person to be specifically acknowledged in the final journal publication. Individuals outside of the group who provide input to, or feedback on the project will also be acknowledged in the publication. The protocol will be published by the IPD-MA research team on behalf of the forming collaborative group.

The linked economic analysis which will have a UK perspective, will be published by the research team with acknowledgement of the role of the IPD-MA collaborative group and additional authors as appropriate and defined by contribution.

Results meeting

Results of the IPD-MA will be presented and discussed at a meeting of the group to which trial investigators who have provided data for analysis will be invited. The meeting will be held in summer 2020, with the date and venue to be confirmed.

PLAIN LANGUAGE SUMMARY

CHRONIC HEART FAILURE

Around a million people in the UK suffer from chronic heart failure (CHF). This number will increase as the population ages and more people survive strokes and heart attacks. In CHF the heart is weakened which can cause shortness of breath, ankle swelling and tiredness. People with CHF live shorter lives, are frequently admitted to hospital and have a reduced quality of life. CHF costs the NHS around £2.3 billion per year.

Co-enzyme Q10 is a vitamin-like substance that helps cells in the body produce energy. Low levels of Co-Q10 in heart muscle may lead to heart failure or worsening of heart failure. Taking Co-Q10 supplements might improve this and might be particularly relevant for patients taking statins (as statins are thought to block production of Co-Q10 as well as cholesterol). Co-Q10 is not available on prescription in the UK but can be bought 'over the counter'.

EXISTING EVIDENCE

The research that has been done on Co-Q10 in CHF has not produced conclusive answers. Clinical trials have been small and mostly looked at clinical measures such as heart pumping function. Few trials have reported impact on outcomes that are important concerns for patients, such as whether taking Co-Q10 reduces hospital admissions or allows people with CHF to live longer lives. Previous systematic reviews that have looked at all the evidence from these studies have been limited by the way trials have been reported in journal articles and have not been able to investigate possible differences between different types of patient.

METHODS

To get round these problems we aim to obtain and re-analyse the 'raw' data from each individual patient included in trials of Co-Q10 trials for secondary prevention of CHF. We will try to get all data that trials collected including any that they didn't report in publications, will check all data thoroughly, and carry out new analyses that were not done in the individual trials. IPD-MA allows us to carry out more detailed and flexible analysis looking at the risks and benefits in different types of patient. For example, we hope to find out whether the effect of Co-Q10 for people who have diabetes is the same as for people who do not have diabetes, and whether the effect is the same for people taking statins and people not taking statins.

We will search carefully for randomised trials that have compared Co-Q10 with placebo, given alongside standard treatments, such as statins or ACE-inhibitors. We will look for unpublished trials and collect data from each patient entered in each relevant trial. This will include information about them (for example their age and sex), their health, the treatments they received and what happened to them - including whether they had a cardiovascular event such as a heart attack, how often they were admitted to hospital and how long they lived. No names will be collected.

We will also develop an economic model that will use IPD results to examine the benefits and costs of giving Co-Q10 alongside statins and other usual medicines in the NHS. We will consider whether it would be useful to set up a new trial to explore gaps in the evidence or to get more information about the effects of Co-Q10 in certain types of patients. And if so, whether a new trial would be a good use of money.

Background

Chronic heart failure

CHF is a significant and growing healthcare challenge as increasing numbers of people live longer and survive ischemic heart disease. In Western societies 10-15% of individuals over the age of 75 suffer from the disorder (1, 2) and despite substantial improvement over the last two decades (3, 4) overall prognosis remains poor, with 50% of patients dying within 5 years of diagnosis.(5) Those living with CHF may experience shortness of breath, ankle swelling and tiredness, frequent stays in hospital and reduced quality of life, as well as a shorter life expectancy.

CHF accounts for a large proportion of UK hospital admissions (2% of bed days and 5% of emergency admissions) (6) and an NHS annual spend of around £2.3 billion.(7) The King's Fund has identified heart failure as an Ambulatory Care Sensitive Condition where effective primary care interventions could avoid hospitalization, have significant benefit on patients' quality of life, and reduce service costs.(8) There is therefore an unmet and increasing need for effective therapies both to improve health and wellbeing and to help keep patients out of hospital and reduce the economic burden on the NHS. To achieve comprehensive coverage of the at-risk population and to maximise both clinical and cost effectiveness, new treatments should be easy to deliver in primary care settings and be acceptable and safe in a broad spectrum of patients, including the elderly and those with multiple co-morbidities.

Heart failure and Co-Q-10

Heart failure is characterised by cardiomyocyte energy depletion (9) due to mitochondrial dysfunction (10) and adenosine triphosphate (ATP) depletion (11), leading to abnormal calcium handling and impaired contractile function.(12) Co-Q10 is an endogenous vitamin-like, fat-soluble quinone found in high concentrations in myocardium, liver and kidney mitochondria. It is an electron carrier crucial to mitochondrial ATP production (13) and has antioxidant (14, 15) and antiatherogenic properties.(16) Natural production of Co-Q10 peaks in a person's twenties thereafter declining with increasing age. Cardiomyocytes in heart failure patients are deficient in Co-Q10 (17, 18) and low myocardial and/or circulating levels are associated with worse symptoms (19-21) and poorer heart function (22) although there is inconsistency of effect on prognosis.(22-24) A common but infrequently recognized feature of heart failure is micronutrient deficiency.(25)

It has been shown that oral Co-Q10 supplementation (up to 300mg per day) leads to increased serum and myocardial levels (21) but it is uncertain whether this increase in level translates to clinical benefit. Co-Q10 is not available on prescription in the UK but can be bought over the counter.

Statins and Co-Q10

Statins block the production of both cholesterol and Co-Q10 and there is some evidence that statin use reduces serum levels of Co-Q10.(26, 27) Whilst younger and healthier statin users appear to tolerate this depletion, it has been suggested that when this happens in CHF patients it worsens myocardial function. Should this be the case, patients using statins may face competing risks/benefits and have a greater capacity to benefit from Co-Q10.

There is divided opinion on the effectiveness and potential role of Co-Q10 in treating CHF. At one extreme it has been suggested that adjunctive Co-Q10 is essential for those receiving statins and that this should be noted in US black box labelling.(28) In contrast current NICE guidance actively lists this as a 'do not do': Do not offer coenzyme Q10 or vitamin D to increase adherence to statin treatment.(6) Existing research evidence is inconclusive.

Existing clinical trial and systematic review evidence

Early uncontrolled studies suggested beneficial effects on ejection fraction (EF), exercise tolerance and symptoms at a variety of doses.(25, 29, 30) Most randomised trials of Co-Q10 have been small, reported surrogate outcomes and results have been mixed. Recent systematic reviews (SR) of single Co-Q10 supplementation have been limited by nature and incompatibility of reported data.

A SR reported by Fotino *et al* in 2013 (31) which included 13 RCTs and 395 participants reported a 3.7% mean net increase in EF (95% CI 1.60% to 5.74%) and -0.3 mean change in New York Heart Association (NYHA) class (95% CI -0.66 to 0.06). A 2014 Cochrane review (32) including 7 RCTs and 914 participants was able to analyse only EF and exercise capacity owing to incomplete reporting in trial publications. It found no clear effects, concluding "*there is no convincing evidence to support or refute the use of Co-Q10 for heart failure"*. Neither of these reviews included the more recently published Q-SYMBIO trial (33) (420 participants), which reported halving of all cause risk of death (HR 0.51 95% CI 0.30 to 0.89). A recent SR published in July 2017 of 14 trials and 2149 participants included Q-SYMBIO. It reported a significant reduction in mortality (RR 0.69 95% CI 0.50 to 0.95) and an improvement in exercise capacity, but reported that owing to limitations further trials were needed.(34) None of these SRs were able to explore potential effect modifiers such as use of statins.

Brief initial searches have identified 5 RCTs of Co-Q10 in combination with other micronutrients, including one published by project team member Witte.(35) Given that CHF patients are generally deficient in micronutrients (25) it is reasonable to question whether any new trial should look at Co-Q10 administered as a single supplement or as part of a multi-micronutrient supplement, or indeed whether a three arm or adaptive design would be appropriate. We will therefore evaluate the randomised evidence for both single-agent and combination approaches.

Rationale for a new systematic review with IPD meta-analysis

Despite a long history and therapeutic promise there is considerable uncertainty about the effectiveness of Co-Q10 in CHF. Most trials have been small and standard SRs have been limited by incomplete reporting and data limitations. As Co-Q10 is classed as a nutritional supplement and is not subject to the same regulatory processes as pharmaceuticals, some trials have not undergone the same independent scrutiny as licensed medicines. Publication bias may be substantial. It is therefore essential that any new evidence synthesis is able to carry out a robust and detailed evaluation of existing trial datasets.

IPD-MA provides an opportunity to seek unpublished trials and updated follow-up, collect unreported outcomes and data from participants excluded from published analyses.(36) Data underlying published results can sometimes be 'unpicked' to enable synthesis of data that could not otherwise be combined. A main advantage of IPD is that it supports time-to-event analyses (37) which is particularly relevant to the cardiac and mortality outcomes to be examined here. Importantly, IPD enables exploration of potential effect modifiers, including co-morbidities such as diabetes and mainstay treatments such as statins and ACE-inhibitors; aiming to identify subpopulations that may benefit more or less from intervention - which could lead to more personalised approaches to guidance and treatment. Access to IPD allows investigation of washout and carryover in crossover trials. This might be especially important in the case of Co-Q10 where there is a lag in Co-Q10 serum and tissue levels responding to starting and stopping supplementation. Where available, baseline levels and patterns of withdrawal can be examined carefully.

Robust independent scrutiny of existing evidence and thorough investigation of potential bias should give confidence in and credibility to project findings.

AIMS AND OBJECTIVES

1. To undertake a high-quality systematic review and individual participant data meta-analysis to assess the effectiveness of co-enzyme Q10 in preventing chronic heart failure.
2. To develop an economic model evaluating cost-effectiveness based on current evidence.
3. To undertake a value of information analysis that will quantify the value of undertaking a new trial to address key uncertainties.

The IPD-MA will compare Co-Q10 (on its own or in combination with other micronutrients) with placebo or no supplementation. Short and long-term benefits and harms will be considered. A main aim will be to undertake detailed exploration of clinical heterogeneity, investigating whether there are particular types of individual who experience greater benefit (or harm) from the intervention. This will help resolve existing uncertainty and provide vital information to inform the development of a linked economic model and value of information analysis.

The economic and VOI analyses will address whether Co-Q10 should be used in CHF based on existing evidence, considering both health outcomes and cost. The VOI analysis will assess whether additional research would be valuable in supporting decisions about the use of Co-Q10 in CHF.

The IPD-MA and the economic evaluation and VOI analyses will be undertaken as two separate but interlinked projects. The IPD meta-analysis will focus on clinical effectiveness and have international relevance. The economic evaluation and VOI will take a UK and NHS perspective.

Separating the synthesis of clinical data from the economic evaluation will allow any international trial investigators who do not want to be involved in research that involves consideration of cost-effectiveness to contribute only to considerations of clinical effectiveness.

Protocol development and registration

This initial draft protocol has been registered on PROSPERO (registration number CRD42018106189**)** A full draft protocol that includes a provisional list of eligible trials (to whom the protocol will be circulated with an invitation to participate in the IPD meta-analysis) will be produced when searching and screening activities are completed. This will then be refined during the project development phase with input from an advisory group and PPI partners and feedback from trial investigators. To safeguard against perception of undue influence or academic bias, a log of feedback will be maintained and any changes will be reflected in audited changes to the PROSPERO record.

To ensure transparency, the final full protocol will be reported in accordance with the Preferred Reporting Items for Systematic review and Meta-analysis Protocols (PRISMA-P) 2015 statement (40) and submitted for publication in an open access journal.

METHODS

Inclusion/Exclusion Criteria

We will aim to include all relevant trials irrespective of whether they are published or unpublished, where they have been carried out, or which language they have been managed and reported in. We will aim to include any trial that completed recruitment before June 2017 (allowing trial investigators approximately 18 months between trial completion and closure of the IPD-MA data collection to complete their own analyses). More recent trials will be identified and logged for potential inclusion in any future IPD-MA updates.

Inclusion and exclusion criteria

- **Population** Adult patients (> 18 years) with diagnosed CHF. Paediatric trials will be excluded. Mixed population trials will be eligible, but only data from relevant individuals (adults with CHF) will be included
- **Intervention** Trials of Co-Q10 (singly or as part of a multi micronutrient supplement), given as an adjunct to co-treatment (e.g. statins) or other routine care
- **Comparator** Placebo given as an adjunct to co-treatment (e.g. statins) or other routine care
- **Outcomes** Trials that measure at least one of the IPD-MA pre-specified outcomes (see below)
- **Study design** Randomized controlled trials including parallel and cross-over designs

Search strategy and screening

Full bibliographic searches of MEDLINE and MEDLINE in Process, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and Science Citation Index will be developed by an experienced information specialist and carried out during the protocol development phase of the project (this is usual for IPD meta-analyses). Update searches will be re-run towards the end of the project to identify any new trials for which IPD have not been sought. An example draft MEDLINE search strategy is provided in Appendix 1.

Trial registers (ClinicalTrials.gov, ISCTRN, the WHO ICTRP portal and OpenTrials.net) will also be searched to identify any unpublished and/or on-going trials. We will also contact manufacturers of Co-Q10 for details of any clinical trials that they have undertaken or sponsored. Authors of included trials will be asked to identify any unpublished trials of which they are aware. We will issue an open call for evidence and use social media and our clinical, patient and research networks to seek information about unpublished trials.

Two researchers will independently screen all titles and abstracts retrieved from electronic database and other searches and full paper publications will be obtained for potentially relevant trials. Where no full paper exists and/or trial eligibility is uncertain, study authors will be asked to provide further information (prior to inviting them to participate in the project). Any discrepancies in screening decisions will be resolved by consensus and discussion with a senior team member as required.

'Near miss' studies that do not meet all of the inclusion criteria and have therefore been excluded will be tabulated and their bibliographic details listed with reasons for exclusion in the final project report and PRISMA diagram.

Data collection

Trial investigators will be invited to supply data in a standardised format using standardised coding that will be developed for the project. However, data will be accepted in any reasonable format and re-coded as necessary by the research team. Data will be requested for all randomised participants, including any who were excluded from the original trial analyses. Trial protocols, forms and ethical approval documents will also be collected.

Data should have all names and identifying numbers removed. Individuals will either be labelled with numbers known only to the original trial team or numbered sequentially with trial investigators keeping a record of these numbers. This will safeguard privacy but enable any data queries to be traced back to the appropriate individual.

Data storage and confidentiality

IPD will be received via secure online transfer or by encrypted email. All data will be anonymous and held in a password-protected area of the CRD server. No attempt will be made to re-identify participants and in the unlikely case of re-identification, confidentiality will be maintained. Access will be limited to staff working directly on the project. Copying data to laptop computers or memory sticks will be prohibited.

Data checking and assessment of risk of bias

Critical appraisal and assessment of data quality will be based on assessment of trial design features described in trial protocols and publications (with clarification from trial investigators as necessary) and through IPD checking. All IPD will be checked on receipt. Data will be examined for internal consistency and integrity of randomization (e.g. temporal distribution of randomisations, baseline balance of important prognostic factors). Patterns of missing data will be examined. Baseline data will be tabulated and compared with the trial publication and any inconsistencies noted. One researcher will run data checks, which will be independently checked by a second person. Findings of all data checking will be discussed with senior members of the research team. Each individual trial will be analysed (primary outcomes only) and compared with corresponding published analyses (bearing in mind that there may be reasonable discrepancies, if for example previously excluded participants have been reinstated in the analyses, or additional follow up provided). Any problems, uncertainties or queries will be passed back to the responsible trial investigator for explanation and discussion.

Risk of bias will be undertaken independently by two researchers using the Cochrane Risk of Bias tool (RoB).(41) Any disagreements will be discussed with a senior member of the team. Results of data checking may up- or down-weight implications of RoB assessments. For example, data checks may show that there is no evidence that risk of bias arising from the method of randomisation has been realised. Any datasets that are judged to be of insufficient quality or completeness will be excluded from the analyses. This may be for the trial as a whole or for particular outcomes or analyses, depending on the nature of the problem.

Care will be taken to avoid availability bias whereby the IPD provided are unrepresentative of the body of evidence (e.g. if only trials with positive results provide data). Monitoring and mitigation (e.g. continued efforts to secure data from all eligible trials with emphasis on the value of data irrespective of results) will therefore be important. Sensitivity analyses supplementing the IPD with published aggregate data for unavailable trials, will be done where feasible.

Data analysis

A statistical analysis plan (SAP) will be developed in advance of commencing analyses, which will set out analytic methods in detail. Analyses will be intent–to-treat. Single and multi-micronutrient trials will be initially analysed separately and if there is no clear evidence of difference these will be combined.

Two-stage models

Initial two-stage analyses will estimate effect (risk ratio, mean difference, hazard ratio) for each trial and then combine these in meta-analyses. This will generate forest plots enabling results across trials to be compared visually, heterogeneity investigated and differences across subgroups visualized. All of these will be essential in fully understanding the underlying dataset, and in motivating the choice of more complex one-stage models. Heterogeneity will be quantified using the I^2 statistic.

One-stage models

One-stage models, (37, 42) will pool IPD from all trials in one step, while accounting for the clustering of participants within trials, using a generalized linear mixed model framework. We will fit linear mixed models for continuous; logistic mixed models for dichotomous; and (if the proportional hazards assumption is reasonable) Cox models for time to event outcomes. Initial examination of potential effect modifiers will be by meta-analysis within subgroups. More formal analysis will then use one-stage models with treatment-covariate interactions added to existing models for treatment effect. If feasible, depending on availability of trials, we will perform an IPD network meta-analysis to compare single Co-Q10 to multi-nutrient combinations and combination treatment with statins.

Outcomes

Short and long-term outcomes will be evaluated. Crossover trials will contribute to assessment of short-term outcomes only. Emphasis will be placed on patient focused outcomes.

- All-cause and cardiovascular mortality (time to event)
  (death from MI, stroke, HF, sudden cardiac death)
- Major cardiovascular events (time to first event)
  (non-fatal MI, non-fatal stroke, re-vascularisation procedures)
- Hospitalisation related to heart condition (any, number and duration of stays)
- Composite outcome
  (any cardiovascular event as above, death or any hospitalisation)
- Hospitalisation related to heart condition (any, number and duration of stays)
- Quality of life measures using validated instrument e.g. EQ5D
- NYHA functional class (or equivalent)
- Adverse effects/side effects
- Left ventricular ejection fraction
- Exercise testing e.g. change in six minute walk test (6MWT) over a defined period

Outcome measures

Dichotomous outcomes will be analysed by calculating the risk ratio for the effect of Co-Q10 compared to placebo. Odds ratios may be used where risk ratios cannot be computed. For continuous outcomes mean differences between treatment arms will be reported. Hazard ratios will be calculated for time-to-event outcomes.

Potential effect modifiers (subgroups)

The impact of trial and patient-level characteristics on treatment effect (that is, treatment-covariate interactions) will be examined. For trial-level covariates the trials will be divided into groups according to the characteristic, and meta-analyses performed within each subgroup. The more formal analysis of interactions will use one-stage models, where treatment covariate interactions will be added to existing one-stage models for treatment effect.(43) This will enable us to take account of multiple participant characteristics when comparing Co-Q10 with placebo or usual care (stratified by trial) and will also enable exploration of potential treatment interactions in a multivariable way. Models will be

compared in terms of goodness of fit and parsimony using the Bayes information Criterion (BIC). Evaluation of potential effect modifiers will include:

Trial level covariates

- Trials specifically comparing Co-Q10 + statin vs statin alone /other trials
- Single or multi-micronutrient supplement
- Parallel or cross-over design

Patient level covariates

- Patients with diabetes at baseline
- Co-treatment, including concomitant or prior use of statins, ACE inhibitors, beta-blockers and diuretics
- Severity of functional class II/III/IV
- Age (as a continuous variable)
- Sex
- Smoker at baseline

Network meta-analysis

If sufficient suitable data are available, a network meta-analysis will compare single and multi-micronutrient supplements containing Co-Q10 and to compare Co-Q10 alone to Co-Q10 in combination with statins or other concomitant treatments. Analyses will be conducted for the main outcomes listed earlier. Two statistical models will be used: first, the Bayesian models of Lu and Ades, (44) which are the most commonly used methods for network meta-analysis. The one-stage meta-analysis models described above will also be extended to include multiple treatment arms. The results of the two approaches will be compared. Both approaches will use random effects to account for heterogeneity. Potential network inconsistency will be investigated by comparing results to results from direct pairwise meta-analyses. If there is evidence of differences node-splitting models will be used to investigate inconsistency further.

Unavailable trials and missing data

Every effort will be made to minimize the amount of missing data, including requesting information for any randomized participants that were excluded from the original trial analyses. Where IPD cannot be obtained for a trial, and where possible, aggregate data will be extracted from publications and combined with the IPD-MA results in sensitivity analyses. Where data are missing for some participants a complete case analysis will be used in the first instance (i.e. excluding patients with missing data). If there are substantial missing data (around 10%) multiple imputation within each trial will be used to generate missing covariates, where this is computationally feasible. Sensitivity analyses based on best and worst-case scenarios will assess the impact of missing outcome data. Trials that have not recorded particular outcomes or particular covariates will not contribute to those analyses. An evaluation at 12 months will confirm whether sufficient IPD have been pledged to enable credible analyses.

Software

All analyses will be performed at CRD using the R software package.(45) Two-stage analyses will additionally use the meta and metafor libraries.(46) One-stage models will be fitted via the lme4 library, and one-stage Cox models will use the coxme library. Forest plots will be produced using in-house R code. For the network meta-analysis, WinBugs and the GeMTC package in R will be used. https://www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-winbugs/.

Relative and absolute differences

Absolute differences will be calculated by applying the resulting risk ratios or hazard ratios to appropriate baseline incidences (calculated from suitable meta-analyses across the trial control arms). Numbers needed to treat and numbers needed to harm will similarly be calculated for a range of plausible baseline measures.

Economic modelling and value of information analysis

Economic modelling and value of information analysis (VOI) will address i) whether Co-Q10 should be used in CHF based on existing evidence; and ii) whether additional research would be valuable.

We will develop an economic analysis to link the IPD-MA outcomes to quality-adjusted life years (QALYs) and costs, in order to determine the cost-effectiveness of the use of Co-Q10. A probabilistic decision analytic model will be developed using a lifetime horizon from the perspective of the NHS and Personal Social Services. Uncertainty will be fully characterised (47) and the value of further research assessed using a VOI analysis.(48)

VOI analysis quantifies the expected health benefits arising from further research by estimating, in health terms, the value of reducing uncertainty in decisions.(48, 49) The importance of this uncertainty is indicated by the scale of health consequences and the likelihood of them occurring. VOI aggregates probability-weighted consequences to yield a net health impact of uncertainty for each alternative intervention.(48)

Overview of cost-effectiveness analysis

A review of cost-effectiveness studies will update our previous work carried out when developing NICE Clinical Guidelines CG108 for CHF (6) and will provide an overview of previous approaches to modelling the clinical pathway of adult patients with CHF. A scoping search has identified several economic evaluations of CHF interventions in a UK setting, including one by co-applicant Rothery (née McKenna), which compares two pharmacological interventions for CHF post-MI.(50) A recent study by Cowie et al (2017) estimates the cost-effectiveness of real-time pressure measurement for treating CHF.(7) These and other identified studies will be reviewed in full and findings used in conjunction with guidance from clinical and patient experts to inform the development of an economic model.

Model structure

We anticipate that the model will include a short-term element capturing the period immediately after starting treatment with Co-Q10 and a long-term component, where patients move between discrete health states over time based on the clinical pathway of CHF patients. The primary events of interest are hospitalisations for major cardiovascular events and all-cause and cardiovascular mortality. These will be informed by the outcomes of the IPD-analysis on clinical effectiveness. The short-term outcomes will be linked to a long-term Markov model that examines the progression of CHF over a patient's remaining lifetime, i.e., reflecting the likelihood of future CV events and mortality, and the implications for NHS resources and patient outcomes.

Linking the short-term and long-term components of the model and capturing the long-term prognosis for CHF patients are expected to be the central challenges for the economic modelling. To ensure that these are captured appropriately, we will incorporate epidemiological evidence including, from registers or patient cohorts on the long-term prognosis of patients with CHF. We will consult with clinical experts at all stages of this work and use their expertise to identify potentially relevant data sources.

Intervention and comparators

The model will explore the addition of Co-Q10 to current standards of care for patients with CHF in line with the IPD-MA. We may present separate analysis for single and multi-micronutrient supplementation, if the findings from the IPD-MA allow an appropriate and robust analysis to be undertaken. Co-Q10 will be compared against placebo or no supplementation since it is proposed as an adjunct rather than as an alternative to current standards of care for CHF.

Key parameters and populating the model

- *Clinical effectiveness:*
  Clinical effectiveness data for Co-Q10 will be drawn from the IPD, and is expected to include all-cause and cardiovascular mortality (death from MI, stroke, HF, sudden cardiac death, and rates of major cardiovascular events (non-fatal MI, non-fatal stroke, re-vascularisation procedures or cardiovascular death). These will be linked to medium and long-term outcomes based on epidemiological evidence. The safety profile of Co-Q10 will also be considered, if found to be relevant.

- *Health-related quality of life:*
  The period of time for which the average patient is alive within the model will be adjusted to QALYs using an appropriate utility or preference score. QoL will be an outcome of the IPD-MA and, if relevant data are identified, this will be used in the model. Alternatively, a targeted review of utility scores will be undertaken to identify appropriate values for major CV events and health states. Initial searches have identified a study that estimated QoL based on the number of re-hospitalisations for CV causes, which could be used to inform our analysis.(51) QoL will be adjusted to reflect both the existence of CHF and the decreases in QoL associated with aging.

- *Resource use and unit costs:*
  Short and long-term costs associated with non-fatal CV events and routine management of HF over time will be included. Resource utilisation data will be identified from published sources, including national surveys and previously published economic analyses, and through consultation with clinical experts and service providers. Unit costs will be obtained from published sources and UK based mainstream retailers of micronutrient supplements and applied in UK pounds sterling, for the financial year 2017–2018 (or appropriate year).

- *Time horizon and discounting of future outcomes:*
  The model will take a lifetime horizon to ensure that all costs and benefits of Co-Q10 supplementation are captured. In economic evaluations, the value of costs and benefits incurred in the future are adjusted to the "present value" to reflect society's preference for the timing of these outcomes. The model will incorporate a discount rate of 3.5% per annum for costs and health benefits, in line with NICE Guidance.(52)

Modelling uncertainty

Uncertainty in the data used to populate the economic model will be characterised using a probabilistic analytic approach, with each input entered as an uncertain parameter with an assigned probability distribution representing its uncertainty. Monte Carlo simulation will use this distribution to take account of and reflect parameter uncertainty in the overall results. This ultimately helps decision makers understand that, in choosing whether or not to provide patients with Co-Q10, there is a likelihood of making an incorrect decision, i.e. decision uncertainty. This will be presented using cost-effectiveness acceptability curves, which show the probability that each intervention is cost-effective conditional on a range of threshold values which NHS decision makers attach to an additional QALY (e.g., £20,000 - £30,000 per additional QALY as used by NICE). Scenario analysis will be used to test the robustness of the cost-effectiveness results to changes in the structural assumptions of the model. Sensitivity analyses will also be used to evaluate the impact of key methodological assumptions on the cost-effectiveness results.

Sub-group analysis

Heterogeneity in cost-effectiveness will be investigated according to the clinical subgroups identified in the IPD-MA, for example, concomitant or prior use of statins or other types of co-treatment, and by severity functional class/other patient characteristics. For each subgroup, separate incremental cost-effectiveness ratios (ICERs) will be presented.

Value of information (VOI) analysis and identifying key sources of uncertainty

As part of the economic evaluation, we will undertake a VOI analysis to establish the value of undertaking further research to resolve decision uncertainty and to identify the key sources of uncertainty in the decision problem. VOI analysis allows us to quantify the expected benefits of further research by estimating the value of reducing uncertainty in decisions. The importance of this uncertainty is indicated by the scale of the health consequences and the likelihood of them occurring. The consequences of making an incorrect decision due to uncertainty can be compared to the costs of conducting new research (e.g. a clinical trial) in order to establish the value of the new research. The expected value of perfect information (EVPI) places an upper bound on the value of research to resolve uncertainty. The expected value of perfect information about parameters (EVPPI) identifies the key sources of uncertainty and indicates the type of evidence required. If further research is worthwhile, information on the fixed costs of a trial and the marginal sampling costs of enrolment into the trial can be used to inform sample size of the trial. This will help inform recommendations for primary research and determine whether a new trial is a good investment.

Economic modelling and value of information analysis will be undertaken only if there are sufficient IPD pledged for meaningful analysis and the project proceeds to phase 2. Of necessity, some initial planning of the economic analyses will need to be done during phase 1.

DISSEMINATION AND PROJECTED OUTPUTS

Direct engagement with the clinical trials community

Results will be presented at a dedicated meeting of the collaborative group with discussion informing the interpretation of results and development of the final report. This discussion will involve key opinion leaders who are able to promote and cascade knowledge generated and can be an important step towards consensus, if opinions are divided.

Academic channels

The IPD-MA is registered in PROSPERO and the full protocol will be published in an open access journal. A full report will be published in the HTA Journal. This will cover all aspects of the project, report drawing on the wider discussion at the trial investigators' meeting, the advisory group and PPI to contextualise findings and reflection on the process of obtaining data to highlight challenges and opportunities for new trials and other follow-on research.

IPD-MA results will be published in an academic journal in the name of the collaborative group and in accordance with PRISMA-IPD(53) and presented at a relevant national or international clinical academic conference.

Results of the economic evaluation will also be published separately in an academic journal by the research team, with full acknowledgement of the IPD-MA and trial investigators.

Other dissemination channels

With PPI partners, we will develop plain language summaries of findings, tailored to relevant public audiences. These will be made available on the Pumping Marvellous Foundation website and offered to other support groups and charities as a resource. We will use social media such as twitter to disseminate key findings and, if warranted, will issue a press release. We plan to produce a short video film for a patient and public audience describing the project and its findings. This will be disseminated through the PMF website and YouTube channel PMTV Live. We also plan a 'live stream' event presenting findings and interacting directly with a public audience.

A project webpage will provide a focus for activity and may include blog posts or video snips and progress reports.

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Appendix 1: Draft MEDLINE search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1 exp Heart Failure/ (108499)
2 (heart adj2 failure$).mp. (180407)
3 (cardiac adj2 failure$).mp. (14388)
4 (myocardial adj2 failure$).mp. (2905)
5 1 or 2 or 3 or 4 (189661)
6 Ubiquinone/ (8215)
7 ubiquinon$.mp. (11732)
8 ubiquinol.mp. (1773)
9 ubidecarenone.mp. (66)
10 quinone.mp. (19514)
11 neuquinon$.mp. (0)
12 bio-quinone Q10.mp. (2)
13 co-enzyme Q$.mp. (120)
14 coenzyme Q$.mp. (5370)
15 COQ10.mp. (1459)
16 COQ 10.mp. (329)
17 Q10.mp. (6310)
18 Q 10.mp. (2278)
19 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (34214)
20 5 and 19 (304)
21 randomized controlled trial.pt. (476988)
22 controlled clinical trial.pt. (96146)
23 randomized.ab. (417587)
24 placebo.ab. (194961)
25 drug therapy.fs. (2045786)
26 randomly.ab. (289174)
27 trial.ab. (438850)
28 groups.ab. (1782381)
29 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (4222639)
30 exp animals/ not humans.sh. (4531946)
31 29 not 30 (3650505)
32 20 and 31 (190)

Appendix B: Data items to be collected for IPD-MA

Trial level data items to be collected

- Trial registration number, if available
- Method of randomisation
- Trial location(s)
- Date trial started
- Date trial closed
- Control arm details
- For each treatment arm
    - Whether single or multi-nutrient supplement
    - Any other nutrients or active ingredients in treatment compound
    - Intended dose and duration of supplement
- Details of planned co-interventions/intervention policy
- Details of how cause of death was verified

Individual-level data items to be collected

Baseline data

- Participant unique ID (does not include participant name or identifier)
- Date of randomization
- Age at randomization
- Sex
- Ethnicity
- Diabetes
- NYHA Functional class (or equivalent) at baseline
- Left ventricular systolic dysfunction confirmed in last 6 months (Y/N)
- Left ventricular ejection fraction at baseline
- Smoker
- Previous cardiac event (and type)
- Angina (Y/N)
- Aetiology (IHF/non-ischaemic)
- Previous MI (Y/N)
- Previous hospitalisation for heart failure (Y/N)
- Use of co-treatments
    - Statins
    - ACE inhibitors
    - Beta-blockers
    - Diuretics
    - Others
- Use of medical devices (with type)
- Serum level of Co-Q10
- Tissue level of Co-Q10

Outcomes

- Dead or alive at last follow up
- Date of death or last follow up
- Cause of death (if appropriate)

- Myocardial infarction (Y/N)
- Date of MI (if appropriate)
- Stroke (Y/N)
- Type of stroke (TIA, ischaemic, haemorrhagic) (if appropriate)
- Date of stroke (if appropriate)
- Other cardiac events (and type)
- Date of other cardiac event (if appropriate)
- Re-vascularisation procedures (Y/N)
- Type of re-vascularisation procedure (if appropriate)

- Number of hospitalisations related to heart related problems (inpatient)
    - Total duration of hospital stay for heart related problems
    - Total duration of any admission to ICU
- Number of hospitalisations for other problems (inpatient)
    - Total duration of hospital stay for other problems
    - Total duration of any admission to ICU

- NYHA functional class (or equivalent)
- Date NYHA functional class measured
- Left ventricular ejection fraction (and date measured)
- Outcomes of exercise testing e.g. six minute walk test (6MWT) with dates or time points of measurement(s)
- Quality of life measures using validated instrument e.g. EQ5D with dates or time points of measurement(s)
- Adverse effects/side effects (type and date)
- Whether participant were excluded from trial analysis (Y/N)
- Reason for exclusion (if appropriate)

Version	Description	Date
V1.1	Draft for NIHR project start	20 Aug 2018