University of York
Centre for Reviews and Dissemination

CHOICE

Co-enzyme Q10 for **H**eart failure **O**bjective **I**nternational **C**ollaborative **E**valuation (**CHOICE**)

Evaluation of Coenzyme Q10 (Co-Q10) in Chronic Heart Failure (CHF): A systematic review and meta-analysis, economic evaluation and value of information (VOI) analysis

PROSPERO registration number: CRD42018106189

Protocol v2.1

April 2020

Funded by NHS National Institute for Health Research

PROTOCOL VERSION 2.1

The CHOICE project was designed as a systematic review with individual participant data (IPD) meta-analysis, which would also inform the development of an economic model and value of information analysis, as set out in version 1 of the CHOICE protocol. However, after 18 months trying to secure access to patient-level data from eligible clinical trials, in March 2020 we reluctantly concluded that insufficient data were available for IPD meta-analysis. Aims and methods have therefore been amended to enable us to complete the project using aggregate data (constructed from IPD where received, or from aggregate data supplied by trial investigators, or from data extracted from trial publication). These methods are set out here, in version 2 of the CHOICE protocol. The original methods for the IPD meta-analysis are available in version 1.2 of the protocol.

ORGANISATIONAL DETAILS

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

Funding

This research is funded by the NIHR Health Technology Assessment programme. Views expressed in this protocol are those of the research team and do not necessarily reflect 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 an independent clinical expert, an independent methodologist and two patient experts/PPI partners including Nick Hartshorne-Evans (who is part of the project team).

Advisory group members include Mark Dayer, Consultant Cardiologist, Taunton and Somerset NHS Trust, Nick Hartshorne-Evans, Chief Executive, The Pumping Marvellous Foundation, Bruce Kilroy, PPI representative, and Jayne Tierney, Professor of Evidence Synthesis, University College London. This group will provide advice and guidance over the course of the project.

Approval by ethics committee

CHOICE will use existing data provided by contributing trials, and address 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 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 contextualising project findings. Both 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 CHOICE will be published in an academic journal, authorship will include trial investigators who provide individual level data for analysis, all members of the meta-analysis research team and all members of the advisory 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 collaborative group and additional authors as appropriate and defined by contribution.

Results meeting

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

Methods

We will search carefully for trials that have compared Co-Q10 with placebo, given alongside standard treatments, such as statins or ACE-inhibitors. We will look for published and unpublished trials and collect data about the patients that they included (for example their average age and proportions of men and women) the treatments used and patient outcomes including cardiovascular events such as a heart attack, admissions to hospital and length of survival.

We will also develop an economic model that will consider the benefits and costs of giving Co-Q10 alongside statins and other usual medicines in the NHS. We will also 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 healthcare systems. 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.

CHF patients are generally deficient in micronutrients (25) and use of Co-Q10 in practice may be as a single supplement or as part of a multi-micronutrient supplement. We will therefore evaluate the randomised evidence for both single-agent and combination approaches. Brief initial searches have identified 5 RCTs of Co-Q10 in combination with other micronutrients.

Rationale

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.

IPD meta-analysis would have provided opportunity to collect unreported outcomes and data from participants excluded from published analyses(36), support time-to-event analyses (37) and model covariate treatment interactions, as well as enabling robust independent scrutiny of the existing trial evidence. However, despite considerable effort, insufficient data were available from trial investigators to support IPD meta-analysis.

There is nonetheless considerable value in completing the meta-analysis and building an economic model using aggregate data. Although previous systematic reviews exist, these can be improved on by bringing them up to date, incorporating additional aggregate data derived from the IPD that were obtained, and by completing additional analyses, including comparing estimates of effectiveness in people taking statins and people not taking statins.

Aims and Objectives

1. To undertake a high-quality systematic review and meta-analysis to assess the effectiveness of co-enzyme Q10 in the management of 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.

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

Protocol development and registration

The original draft protocol was registered on PROSPERO (registration number CRD42018106189) on 06/08/2018 and amended 03/04/2020 to reflect the change to analyse aggregate data.

Methods

Inclusion and 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. Ongoing trials will be identified and logged for potential inclusion in any future updates.

- **Population** Adult patients (> 18 years) with diagnosed CHF. Paediatric trials will be excluded. Mixed population trials will be eligible, if data from relevant individuals (adults with CHF) are available separately. Studies conducted specifically in patients with preserved ejection fraction (HFpEF) form a different population and will be excluded.
- **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 meta-analysis pre-specified outcomes (as below)
- **Study design** Randomized controlled trials including parallel and cross-over designs

Outcomes

Short and long-term outcomes will be evaluated with emphasis 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)
- Any cardiovascular event as above, death or any hospitalisation
  (Composite outcome)
- 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
- B-type natriuretic peptides (BNP)/NT-proBNP level
- Peak oxygen consumption

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. Update searches will be re-run towards the end of the project to identify any new trials. 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.

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. 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.

For trials where investigators do not supply data, we will extract all possible data from all publications of that trial. This will include, where feasible, extracting data from figures such as Kaplan-Meir plots, for re-analysis.

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.

Risk of bias

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 third member of the team. For the trials supplying IPD, 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.

Data analysis

A statistical analysis plan (SAP) was developed for the originally intended IPD meta-analysis, which set out analytic methods in detail. This existing SAP will be followed, as far as is feasible, for this published data meta-analysis. 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.

Meta-analysis

Initial 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. Heterogeneity will be quantified using the I^2 statistic.

Crossover and parallel group trials

The initial analysis will keep crossover and parallel group trials separate, as the two trial designs may not give comparable results. If the two trial designs produce broadly consistent results they will be pooled using two-stage meta-analysis models, as described above.

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, or standardised mean differences if trials use different measurement scales for the same outcome. Hazard ratios will be calculated for time-to-event outcomes.

Network meta-analysis

If sufficient suitable data are available, a network meta-analysis will compare single and multi- micronutrient supplements containing Co-Q10 and 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. Exact methods used will depend on the available trial designs, and whether combining crossover and parallel group designs is justified. Two statistical models will be considered: 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. other 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.

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. Meta-regression will be used for continuous covariates (such as coQ10 dose).

Examination of **individual-level covariates** will be by meta-analysis within subgroups, where feasible, or using meta-regression. 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

In the absence of supplied IPD we will also consider the following:

- CoQ10 dose
- Duration of treatment/trial
- Mean baseline value of outcome
- Year of publication

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 NYHA functional class (or equivalent)
- Age (as a continuous variable)
- Sex
- Smoking history
- Heart failure with preserved ejection fraction

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)], 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 effectiveness 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.

Economic 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 meta-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 meta-analysis 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:
  Where possible, the model will use outcomes from the meta-analysis. This is likely to include all-cause mortality and quality of life. A preliminary review suggests that there are insufficient reported data to inform on cardiovascular morbidity (e.g. MI, stroke, revascularisation). As such, it is likely that these inputs will be obtained from Q-SYMBIO, a large trial which reports outcomes for CV morbidity and mortality. 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. Quality of life (QoL) will be an outcome of the meta-analysis 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 2019–2020 (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

If sufficient data allow, heterogeneity in cost-effectiveness will be investigated according in line with the clinical subgroups investigated in the meta-analysis, 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 if applicable.

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.

Dissemination and projected outputs

Direct engagement with the clinical trials community

Results will be presented at a virtual meeting that includes the project advisory group and the trial investigators that did provide IPD for analysis. Discussion will inform the interpretation of results and development of the final report.

Academic channels

The IPD-MA was registered in PROSPERO and the record updated to reflect that collection of IPD was not possible and completion using aggregate data. A full report will be published in the HTA Journal. This will cover all aspects of the project, report drawing on the wider discussion with the advisory group including PPI members to contextualise findings, and will reflect on the process of obtaining data to highlight challenges and opportunities for new trials and other follow-on research.

The systematic review and meta-analysis results will be published in an academic journal 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.

Other dissemination channels

With PPI partners, we will develop plain language summaries of findings, tailored to relevant public audiences. These will be made available to the Pumping Marvellous Foundation and 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 presentation suitable for a patient and public audience describing the project findings. This will be disseminated through the PMF website and YouTube channel PMTV Live. We planned a ‘live stream’ event presenting findings of the IPD meta-analysis and interacting directly with a public audience. This may still be possible.

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Appendix 1: Eligible trials

Tables 1 to 3 present a provisional list of trials potentially eligible for inclusion in CHOICE. This list will be updated as new trials are identified by further bibliographic searches and from other sources.

Table 1 Trials of Co-Q10 as single micronutrient

Trial	Country	N*	Participants	Intervention	Outcomes	Design
Belardinelli 2005	Italy	21	NYHA class II or III CHF	100mg daily for 4 weeks	LVEF	RCT cross-over 3-arm
Berman 2004	Israel	32	End-stage HF awaiting heart transplantation	60mg twice daily for 3 months	NYHA class, QoL, exercise testing (6 min walk)	RCT parallel group
Davini 1992	Italy	63	NYHA class II-IV CHF with dilative, valvular or ischemic cardiopathy	100mg daily for 4 months	NYHA class, exercise tolerance	RCT parallel group
Hofman-Bang 1995	Sweden	79	NYHA class II-III CHF	100mg daily for 3 months	NYHA class, exercise testing, ejection fraction (EF), QoL	RCT cross-over 2-arm
Keogh 2003	Australia	39	NYHA class II-III HF	150mg daily for 3 months	NYHA, exercise testing (6 min walk), HF clinical outcomes, re-admission, transplantation, death	RCT parallel group
Khatta 2000	USA	55	NYHA class III-IV HF	200mg daily for 6 months	LVEF	RCT parallel group
Kukharchik 2016	Russia	120	Class II-III CHF, MI history	120 mg/day for 3 months	LVEF	RCT parallel group (open label)
Langsjoen 1985	USA	19	NYHA class III-IV with myocardial disease	33.3mg 3 times daily for 12 weeks	LVEF	RCT cross-over
Ma 1996	China	36	NYHA II-IV, dilated cardiomyopathy	20mg times daily for mean 16 months	All-cause mortality	RCT parallel group
Mareev 2017	Russia	148	NYHA I-IV HF, LVEF< 45%	Q10 nasal drops 90mg/day (eq.	NYHA, Exercise testing (6 min	RCT

Trial	Country	N*	Participants	Intervention	Outcomes	Design
				225mg/day) for 24 weeks	walk), clinical status	parallel group
Mazzola 1987	Italy	20	Mild-moderate HF and chronic stable angina	60mg daily for 4 weeks	HF score, anginal symptoms, exercise testing, cardiac output	RCT cross-over 2-arm
Morisco 1993	Italy	641	NYHA III-IV CHF	50mg 2 or 3 times daily for 1 year	NYHA, length of hospital stay, cardiac asthma, pulmonary oedema	RCT parallel group
Morisco 1994	Italy	6	NYHA class II-IV CHF	50mg 3 times daily for 4 weeks	LVEF, stroke volume, cardiac output, exercise testing	RCT cross-over
Mortensen 2014 (Q-SYMBIO) (ISRCTN94506234)	International (Europe, Asia, and Australia)	420	NYHA class III-IV CHF	100mg 3 times daily for 2 years	NYHA, exercise testing, LVEF Long-term: MACE NYHA class, mortality	RCT parallel group
Munkholm 1999	Denmark	22	NYHA II-III HF	100 mg twice daily for 12 weeks	LVEF, NYHA class	RCT parallel group
Nakanishi 1988	Japan	16	NYHA II, III dilated cardiomyopathy	45mg daily for 5 months	LVDF, LVSF	RCT parallel group open label
Permanetter 1992	Germany	25	NYHA I-III dilated cardiomyopathy	33.3mg three times daily for 4 months	LVEF, NYHA class, exercise testing	RCT cross-over
Poggesi 1991	Italy	20	NYHA II-III, LVEF 30-50%, dilated cardiomyopathy	50mg twice daily for 60 days	LVEF	RCT cross-over
Pourmoghaddas 2014	Iran	62	NYHA II-IV HF	100mg twice daily for 4 months (+ atorvastatin 10mg daily)	EF, NYHA class	RCT 2-arm
Watson 1999	Australia	30	CHF, LVEF <35%	33 mg 3 times daily for 12 weeks	LVEF, QoL	RCT cross-over 2-arm
Zhao 2015	China	102	NYHA II-IV HF, LVEF <40%	30mg daily for 12 months	LVEF	RCT 2-arm open-label

* Number randomised. LVEF: left ventricular ejection fraction, EF: ejection fraction, QoL: Quality of Life, NYHA: New York Heart Association, HF: heart failure, LVDF: left ventricular diastolic function, LVSF: left ventricular systolic function, MACE: major adverse cardiovascular event, RCT: randomised controlled trial, CHF: chronic heart failure

Table 2 Trials of multiple micronutrients

Trial	Country	N*	Participants	Intervention	Outcomes	Design
Alehagen 2013 (NCT01443780)	Sweden	443 (33 with LVEF<40%)	Elderly individuals, NYHA II-III (47%), LVEF<40% in 7.6%)	200 mg/day+200 µg/day of organic selenium yeast tablets	All-cause and cardiovascular mortality, NYHA class, LVEF	RCT parallel group
Fumagalli 2011	Italy	67	NYHA II-III CHF LVEF ≤ 35%	16mg od CoQ10 + 170 mg creatine	Exercise testing, HRQL	RCT Parallel group
Garakyaraghi 2015 (IRCT2013020512371N1)	Iran	64	NYHA II-III HF, LVEF ≥35%	90 mg of CoQ10 and 200 µg of selenium daily for 3 months	NYHA class, LVEF	RCT parallel group
Kumar 2007	India	62	NYHA II-IV CHF	270 mg ubiquinol +2250mg L-carnitine daily) for 12 weeks	NYHA class, QoL, exercise testing (6 min walk)	RCT parallel group
Witte 2005	UK	32	CHF, LVEF ≤35%	calcium, magnesium, zinc, copper, selenium, vitamin A, thiamine, riboflavin, vitamins B6, B12, C, D, E, folate, and co-Q10 (150mg), daily for 9 months	LVEF, QoL Exercise testing (6 min walk)	RCT parallel group

* Number randomised. LVEF: left ventricular ejection fraction, EF: ejection fraction, QoL: Quality of Life, NYHA: New York Heart Association, HF: heart failure, RCT: randomised controlled trial, CHF: chronic heart failure

Table 3 Ongoing/unpublished studies

Trial	Country	N*	Participants	Intervention#	Outcomes	Design	Registration/status	Funding
Satoaki 2017 Unpublished	Japan	40 (target)	NYHA class II-IV with pacemaker or ICD	100mg three times daily for 6 months	Heart failure indices (OptiVol or CorVue), physical activity score	RCT parallel group	JPRN-UMIN000027248 Registered: 01/10/2017, recruiting	Kyoto Prefectral University of Medicine, Japan

* Number randomised. LVEF: left ventricular ejection fraction, EF: ejection fraction, QoL: Quality of Life, NYHA: New York Heart Association, HF: heart failure, RCT: randomised controlled trial, CHF: chronic heart failure, , ICD: Implantable cardioverter defibrillator

Appendix 2: 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 3: 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
(where possible corresponding aggregate data will be extracted for trials that did not provide IPD)

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
- Smoking history
- Aetiology (IHF/non-ischaemic)
- Angina (Y/N)
- Previous MI (Y/N)
- Previous stroke (Y/N)
- Previous revascularisation procedure (Y/N)
- Other CHF event requiring hospitalisation (Y/N)
- Use of co-treatments
  - Statins
  - ACE inhibitors or ARBs
  - Beta-blockers
  - Diuretics
  - Digoxin
  - Nitrates
  - Amiodarone
- Use of implanted medical devices (with type)
- Serum level of Co-Q10
- BNP/NT-proBNP level

Outcomes

- Date or timing of last follow up
- Dead or alive at last follow up
- Date or timing of death
- Cause and timing of death (if appropriate)
- Myocardial infarction (Y/N)
- Date or timing of MI (if appropriate)
- Stroke (Y/N)
- Type of stroke (TIA, ischaemic, haemorrhagic) (if appropriate)
- Date or timing of stroke (if appropriate)
- Re-vascularisation procedures (Y/N)
- Type of re-vascularisation procedure (if appropriate)
- Date or timing of re-vascularisation procedure (if appropriate)
- Number of hospitalisations related to CHF (inpatient)
    - Total duration of hospital stay for CHF-related problems
    - Total duration of any admission to ICU
- Number of hospitalisations for any reasons (inpatient)
    - Total duration of hospital stay for any reasons
    - Total duration of any admission to ICU

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

Where dates cannot be supplied, timing of events may be provided as number of days after randomisation

Version	Description	Date
V1.1	Draft for NIHR project start	20 Aug 2018
V1.2	Draft for circulation to trial investigators	
V2	Updated to reflect that IPD meta-analysis was not possible	15 April 2020