NHS
Health Research Authority

QUACS
Quality of life after cardiac surgery

a national multicentre observational study

Protocol Version 3.0 Date 09/09/19

RESEARCH REFERENCE NUMBERS – 19/WA/0123
IRAS Number: 260891

SPONSORS Number: PO2500

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

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

For and on behalf of the Study Sponsor:

Signature: Date:
...../...../.....
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Name (please print):

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Position:
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Chief Investigator:

Signature: Date:
..../...../.....

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Statisticians :

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Sofia Villar

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Yi-Da Chiu

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LIST of CONTENTS

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Funder	The J.P. Moulton Charitable Foundation
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STUDY SUMMARY

Study Title	**Quality of life after cardiac surgery**
Internal ref. no. (or short title)	QUACS
Study Design	Observational
Study Participants	8004
Follow up duration (if applicable)	1 year
Planned Study Period	3 years

PROTOCOL CONTRIBUTORS

Name	**Role**	**Organisation**
Mr Stephen Large Cardiac Surgeon	Advise on clinical and relevance, participate in trial management group and result dissemination the results nationally.	Cardiothoracic Surgery Papworth Hospital
Mrs Christine Mills Project Manager	Oversee trial and sites, ensure recruitment to time and target, write progress, TSC and DMC reports research governance.	Trials Unit Collaboration Papworth Hospital
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Dr Yi-Da Chiu Statistician	Statistical analysis, preparing TSC and DMC Reports. Conducting the analysis with senior statistician.	Trials Unit Collaboration Papworth Hospital
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Mr Peter Braidley Cardiac Surgeon	Local recruitment, participate in trial management group meetings, promote the study nationally.	Cardiothoracic Surgery Northern General Hospital
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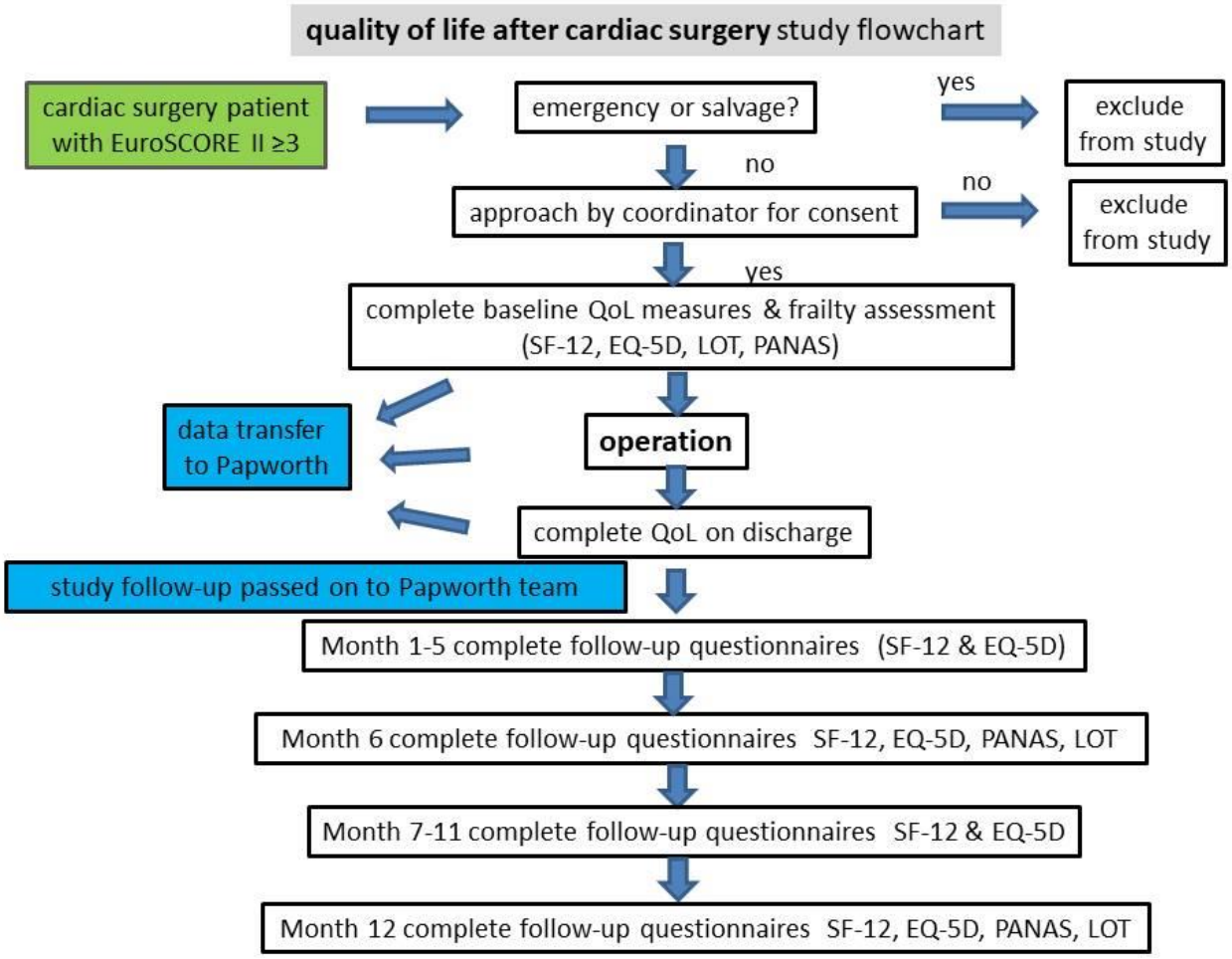
Mr Shakil Farid Cardiac Surgeon	Local recruitment, participate in trial management group meetings, promote the study nationally.	John Radcliffe Hospital Oxford

STUDY FLOW CHART



1 BACKGROUND

Every year, around 40 000 patients undergo open heart surgery in the UK. During the last twenty years heart surgery has become much safer. As a result, the number of patients having heart surgery has steadily increased, and more frail and elderly patients are being offered increasingly complex open heart surgery for various heart problems.

For most patients, heart operations improve both survival and quality of life (QoL). Unfortunately, this is not true for all. In a small percentage of patients, a heart operation can abruptly shorten life, and in some patients, QoL may be adversely affected in the long term. When dealing with the important outcome of survival, we can measure the risk to life from having a heart operation and the risk to life from not having one quite precisely in most heart conditions and for most patients. However, we have very little idea about the impact of heart operations on QoL for individual patients, which is the outcome that many patients care about most of all.

At present, we are unable to provide patients with robust information on how an operation will affect their QoL. This research project will provide this information, so that patients are able to give evidence-based informed consent when they are contemplating a major heart operation.

Heart operations that improve neither survival nor QoL are harmful to patients and a drain on NHS resources. This study seeks to identify them with a view both to improve decision making by patients and doctors and to help eliminate ill-advised resource use in the NHS.

2 RATIONALE

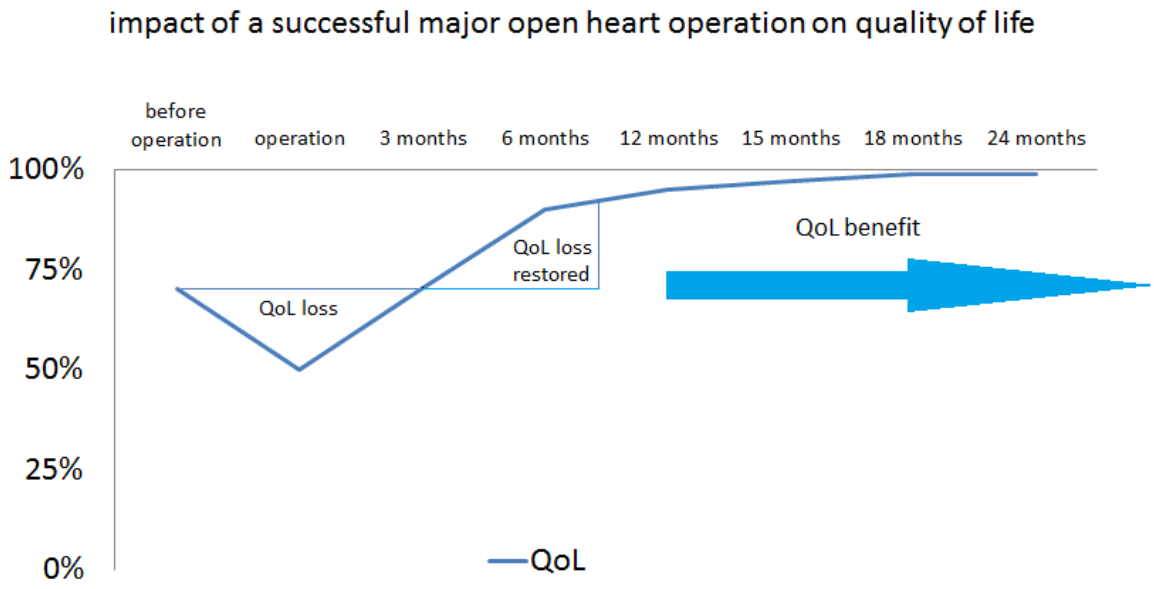
In cardiac surgery, as in all branches of medicine, we treat patients so as to achieve two objectives:

- to improve quality of life (QoL)
- to improve survival

Deciding on an operation to improve survival is now easier due to sophisticated tools (EuroSCORE II [5] & Tute [6]) that measure and compare the risk to life of an operation with the risk to life from not having an operation. No such tool exists for QoL which is often the most important outcome for the patients.

Although some studies of cardiac surgery have included QoL as an outcome measure, no study has ever analysed the changes in QoL over time in the postoperative period and no study has ever analysed the relationship between individual patient and operation characteristics and the QoL outcome.

We know that most patients having heart surgery have symptoms (such as pain and breathlessness) which affect their QoL, and they submit to surgery in the hope of achieving relief from these symptoms and thus improving their QoL. We also know that, immediately after surgery, QoL is actually worse for all patients because postoperative pain, hospitalisation and functional limitation all have an impact. The normal scenario thereafter is that QoL then begins to improve, reaches the level it was before the operation and then hopefully exceeds it so that there will come a time when any QoL lost through surgery is 'paid back' by QoL gained. From that point onwards, the patient truly begins to benefit from having had the operation. The changes in QoL as a consequence of a typical major heart operation over time are graphically illustrated in the figure.



This is true for most patients, but not for all. A few will die from the operation. Some never regain the preoperative level of QoL, and some may not achieve a subsequent QoL improvement that matches or exceeds the QoL loss that occurs after the operation. Previous work[1] indicates that between 8-19% of patients will experience a fall in QoL that does not recover.

When patients consent to major intervention, such as cardiac surgery, they need to know two things:

1) the risk to life of having an operation compared with the risk of not having an operation
2) the impact of an operation on QoL compared with the impact of not having an operation

Currently, we are able to provide detailed individualised information on the first so that we can identify those patients likely to benefit in terms of survival. We do not have such individualised information for QoL. We know that, overall, there is a net benefit in QoL after heart surgery, but we also know that in a sizeable minority of patients, QoL may not improve and may actually worsen after heart surgery, yet we do not have the tools that allow us to identify the patients who will lose in QoL terms. This study will address this knowledge gap.

We shall use existing tools to measure QoL in patients having major heart surgery. QoL will be measured before the operation and monthly afterwards for 12 months in order to answer the following questions:

1) How does having heart surgery affect the QoL immediately after the operation?
2) How long does it take patients to return to the same QoL they had before the surgery, if they ever do?
3) How long does it take patients to regain any loss of QoL due to the operation? Does QoL improve thereafter? And to what extent?
    a) In other words will surgery 'add value' to their QoL?
    b) If so, when?
4) What proportion of patients will achieve a net benefit in QoL?
5) Are there features that can predict who will benefit in terms of QoL and who will not?

Based on the above findings we intend to create a risk model to predict the following:

1) who will experience QoL net improvement and who will not within 12 month of surgery.
2) what is the net gain/loss of QoL that an operation may produce, and for which patients?
3) how long before a patient having a heart operation begins to benefit in terms of QoL

We will use the data to develop an electronic calculator to enable quick and robust evaluation of the impact of heart surgery on the QoL of individual patients. The calculator will be tested by patients and their feedback will be used to refine it so that the final version made available in the clinical setting will function in an accessible, user-friendly and understandable way. Patients will then be in a position to decide if they wish to proceed to surgery based on a full knowledge of *both* surgical risk and the potential impact on QoL.

When completed, the study will:

1) improve the process of informed consent by patients
2) improve the process of medical decision making by doctors
3) as a result of 1 and 2 above, reduce the harm done to patients by unnecessary or ill-advised operations and estimate the cost of such operations to the NHS

4) pioneer a model by which other specialties can measure their own QoL outcomes

3 RESEARCH QUESTION/AIM(S)

1) who will experience QoL net improvement and who will not within 12 month of surgery
2) what is the net gain/loss of QoL that an operation may produce and for which patients
3) how long before a patient having a heart operation begins to benefit in terms of QoL

3.1 Objectives

From answering the above questions we will be able to :

1) improve the process of informed consent by patients
2) improve the process of medical decision making by doctors
3) as a result of 1 and 2 above, reduce the harm done to patients by unnecessary or ill-advised operations and estimate the cost of such operations to the NHS

4 Investigational Plan

4.1 Design

1) The proposed study will be a multi- centres prospective observational study to assess in patients with a EuroSCORE II of 3 or greater undergoing cardiac surgery who will experience QoL net improvement and who will not within 12 month of surgery.

4.2 Setting and Investigators

Nationally all acute NHS cardiac surgical centres will be invited to participate in this study with Royal Papworth as the lead centre.

4.3 Study Population

Eligible patients will be elective cardiac surgery patients with a EuroSCORE II of 3 or more undergoing cardiac surgery.

Inclusion criteria

EuroSCORE II ≥ 3% or EuroSCORE logistic of ≥ 6%

Patients undergoing routine/ urgent cardiac surgery

Patients must have the ability to provide informed consent

Exclusion criteria

Patients undergoing salvage or emergency operations.

Patients having transcatheter aortic valve implantation or TAVI

5. RECRUITMENT AND SAMPLING

5.1 Sampling

The study will recruit a total of 8004 patients over two years and follow them up for 12 months. This sample size was derived as follows: according to Abah et al[1] the percentage of people expected not to regain QoL after heart surgery and after 12 months is between 8-19%. Additionally, there is a 4% predicted mortality rate for heart surgery in the UK in the higher risk population which is the subject of this study. Therefore, a conservative estimate is that 12% of patients in this study would not regain QoL. Assuming the 12% rate as a reference value, with a minimum of 6670 patients we would be powered to produce a predictor tool with a sensitivity of at least 0.75 (or true positive rate to identify those patients that do not regain QoL after surgery) and a 3% error (0.75 ± 0.03) at the 95% confidence level[2.] Anticipating a non-response rate of 20%, we will recruit an additional 1334 patients to compensate for this, giving a total of 8004. Based on the above, the study will estimate the proportion of patients who do not regain QoL after 12 months with a 95% confidence of ± 0.7% (for a rate of 8%) and ± 0.8% (for a rate of 12%) with 6670 patients.

Recruitment and drop-out rates will be continuously monitored by the trial steering committee (TSC). To recruit 8004 patients, we plan to approach all 36 cardiac centres in the UK. Assuming only 30 centres take part (a feasible number based on our NIHR ETTAA study) and a two-year recruitment period, there will be 20000 patients with a EuroSCORE II ≥ 3 who would be eligible for the study over two years. Our sample size calculation requires that 40% of the eligible patients consent over the two-year period. This translates into no more than 134 patients per centre per year, a recruitment target that is conservatively achievable. Based on our original approach to 5 centres, the recruitment rate will average 192 patients per centre per year, so that the required 134 patients per centre per year is achievable and will be carefully monitored by the project management team and the TSC as described in the section 9.4 of this protocol.

5.2 Recruitment

All patients undergoing cardiac surgery at enrolled centres will be invited to consent to the study.

5.3 Patients

Very low-risk patients are highly likely to go through cardiac surgery with few or no adverse events and thus easily achieve both survival and QoL benefits. This study will therefore focus on medium-risk and high-risk patients as being the ones more likely to yield useful information on failure to achieve QoL benefits. The best model for risk-stratifying cardiac surgical patients is EuroSCORE II and we aim to recruit patients whose risk is double the UK national average or higher (EuroSCORE II ≥ 3%). This accounts for about a third of all cardiac surgery patients, approximately 13,000 patients a year.

Cardiac surgical patients (excluding, transcatheter aortic valve implantation or TAVI patients, emergency and salvage patients) will be recruited to this study nationally, and all cardiac centres will be invited to participate (we have already approached 5 key cardiac surgery centres and all have expressed enthusiastic support for the

study and willingness to participate). After initial recruitment, the management of patient follow-up will be conducted centrally from Royal Papworth Hospital.

5.4 Identifying, informing and consenting patients

Informed consent will be obtained prior to the participant undergoing any activities that are specifically for the purposes of the study. Patients will be provided with an information leaflet and consent for approved by the Research Ethics Committee. The procedure for informing and consenting patients will be the same in all centres and devised to accommodate local variations in the patient pathway.

Patients will be identified by a member of their clinical care team on acceptance to the surgical waiting list. Patients will be provided with a copy of the ethically approved patient information sheet and consent form. Patients will be allowed sufficient time to read, understand and ask questions regarding the study to be able to fullyconsider participation. Patients will have the opportunity to ask questions through the consent process and continuously throughout the study. The standard of care will not change whether or not a patient chooses to participate. Patients are free to withdraw at any time.

If patients do not possess the mental capacity to consent they will not be included in the trial due to the burden of having to complete monthly QoL questionnaires. Patients not fluent in English will be unable to participate as the scales are not validated for translation.

5.5 Statistical analysis

All statistical analyses and reporting will comply with CONSORT guidelines [(13)] where possible.

Two single measures for QoL will be used for data analysis. The primary one is the mapping utility value of EQ-5D-5L; the other (as an alternative) is the SF-6D utility value mapped from SF12. An additional combine measure will be considered in case of considerable conflict in those two measures. This will be discussed formally in the statistical analysis plan.

Six outcomes will be used in all the analyses. The three primary outcomes will be defined as: (1) a continuous variable of a difference in the single measure of QoL between the baseline stage and a follow-up stage, this is a measure of the net QoL benefit ; (2) a binary variable of whether the post-surgery QoL has regained to the level at baseline; (3) a binary variable of whether the total sum of the first primary outcome over the follow-up time period where it is positive is larger to the period in which is negative, this is an indicator variable showing if a patient has achieved positive net QoL benefit. All the three primary outcomes will be based on EQ-5D-5L; the other three secondary outcomes derived from SF12 with the same definitions as (1), (2) and (3).

Three work packages will be designed to answer the aforementioned research questions of interest:

1. Perform descriptive statistics on (a) the first primary outcome at the stage immediately post-surgery; (b) the follow-up time (months) if the second primary outcome indicates the first occurrence of regaining (point estimate and confidence intervals); (c) the average trend of the first primary outcome over time; (d) the third primary outcome.

2. Perform inferential statistics on statistical testing to investigate the significance of variables in PANAS, LOT and patient frailty on the third primary outcome.

3. Develop a risk model on the third primary outcome by logistic regression or multilevel logistic regression.

In addition, the sensitivity analysis will be carried by doing the above three work packages replacing the primary outcomes with the three secondary outcomes based on SF12. The robustness of estimates and conclusions will be assessed. If a conflict exists, we may create a single measure of QoL by combing EQ-5D-5L and SF12 and do the same work packages.

6. DATA COLLECTION

6.1 Methods

The data will be collected on to a web-based system designed and coordinated by the Trial Manager and Data Administrator at Royal Papworth Hospital. They will be responsible for training researchers to use the system and will conduct initiation visits.

QoL will be measured using the SF-12 and EQ-5D-3L at:

- baseline
- on hospital discharge
- at 1 month
- and every month for 12 months

Previous work[3] has shown that, as a general rule, routine patients undergoing a routine cardiac operation are likely to have made a full recovery within 3 months if there are no complications and within 6 months if there are complications. To allow additional time for a return to preoperative QoL level, exceed it and achieve QoL benefits that reverse any QoL loss from surgery, QoL assessment will continue up to 12 months postoperatively, at which time patients who have not regained baseline QoL are unlikely to demonstrate any further significant QoL benefit.

6.2 Baseline & Discharge data collection

The Researcher at each centre will enter the baseline and discharge data directly on to the OpenClinica database or alternatively enter the data on to a printed form until such time as it can be entered directly.

The baseline QoL questionnaires should be completed independently by the patient this can be completed either electronically if the recruiting site can support this or on paper based and entered manually by the researcher onsite.

Data collected at baseline will include overall risk stratification, EuroSCORE II which already records data on a number of factors and co-morbidities known to be associated with QoL: age, sex, cardiac disease and complexity, cardiac function, diabetes, neurological and musculoskeletal function, respiratory function and

renal function. To this, we shall add factors not included in EuroSCORE II but known to be correlated with QoL:, patient outlook (objectively assessed by the *Life Orientation Test* and the *Positive and Negative Affect Scale*), socio-demographic status and assessment of frailty . Frailty will be assessed by the Essential Frailty Toolset by Afilalo (a4 item scale encompassing lower extremity weakness, cognitive impairment, anemia and hypoalbuminemia.)

6.3 Follow up questionnaires

After the discharge information is provided by the recruiting hospital the follow up of patients will return to the central Papworth team. Patients will be asked to complete the QoL questionnaires monthly. Patients will be able to use their own devices to enter QoL data directly into an electronic system, allowing for collection of high-quality, timely data in a convenient way. Patients will be notified when they are due to complete a questionnaire by email or text message; an underlying audit trail will provide evidence that the participants completed the forms in the timeframe dictated by the protocol

Patients who are not able to enter their data electronically will be provided with paper questionnaires, which will be scanned directly into an electronic database. This will forgo the need for any manual data entry, therefore reducing significantly reducing cost and errors.

7. MANAGEMENT & GOVERNANCE

The Clinical Project Manager (CPM) and the Trial Manager (TM) (who are based at Royal Papworth) will work directly with the other centres to coordinate all aspects of the study and ensure that the study is conducted according to ICH-GCP standards. They will be responsible for any necessary training.

7.1 Sponsorship

Royal Papworth Hospital NHS Foundation trust has assumed the responsibility of Sponsor. The respective responsibilities of the sponsor, investigator and Trial Manager will be identified and delegated at the start of the study.

7.2 Study project team

The study project team will include the chief investigator, statisticians, data manager, trial manager, project manager. This group will provide daily oversight of the initiation and subsequent progress of the trial. Meetings will be at Papworth and will be frequent (monthly) during the start-up and early recruitment phases and less frequent (3-6 monthly) subsequently. E mail or teleconferencing will be used for input from collaborators at other centres.

7.3 Trial Steering Committee

A Trial Steering Committee (TSC), consisting of at least two independent members, a patient representative and the Chief Investigator will be convened and meet once a year. This committee will monitor the progress of the trial in relation to the stated milestones and the interim and overall objectives and instigate any remedial actions

7.4 Monitoring and Audit

Recruitment of patients and collection of data will be monitored by the Papworth Trial manager on a regular basis.

The recruitment process will be monitored from 6 months since the study commences, this is when we expect centres to be fully functioning and contributing to recruitment. The first interim monitoring is based on the predictive model proposed by Anisimov[9] and the successive recruitment will be evaluated regularly and reported in data monitoring committee and trial steering committee. If the recruited number is below the expected lower boundary, incentive measures will be discussed and implemented after and a TSC meeting will be call upon to discuss this.

8. ETHICAL AND REGULATORY CONSIDERATIONS

Before the start of the study, a favourable opinion will be sought from a REC & HRA for the study protocol, informed consent forms and other relevant documents.

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place and an initiation has been conducted.

All patients will be given sufficient time to consider and discuss the study the investigator will ask them to provide written consent. As part of the trial design patients will be asked to provide consent for their name, contact phone number and email to Royal Papworth Hospital. This will be fully explained in the patient information sheet and consent form.

8.1 AMENDMENTS

All substantial amendments must be approved the REC and the individual Trusts (via their R&D departments)

before being implemented in the individual centres.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study.

9. DATA PROTECTION AND PATIENT CONFIDENTIALITY

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

With patient consent personal information will be collected and provided to Papworth Hospital. This information will be transferred securely through Openclinica our electronic data capture system. The patient identifiable information will be coded and access will only be granted to the individual staff members completing the study follow ups. Data will be collected using the Enterprise version of OpenClinica, the system is fully validated and GCP + CFR21 compliant. OpenClinica Optimized Hosting has numerous features to ensure the security and privacy of data. All data transfer between the OpenClinica system and users is encrypted using SSL/TLS. Access to OpenClinica within the Trust is controlled by the Data Management lead. Each user has their own account to access OpenClinica which requires a strong password. A robust audit trail within OpenClinica tracks all changes to the data and retains a history for each variable, including old and new value, date and time of the change and who made it.

All data used in the formulation of reports to investigators, the sponsor, funder or ethics will only contain anonymised data. The Data Management lead will ensure confidentiality of data is preserved when the data is transmitted to sponsors and co-investigators.

Patient identifiable information will be stored until the end of the study at 3 years; the data will remain stored for 15 years as per the Trust policy. The study data will be exported from OpenClinica and archived locally on Papworth servers. Mr Samer Nashef will act as custodian for the data.

10. FINANCE & INSURANCE

This study is funded by the J.P. Moulton Charitable Foundation. Clinical Trial Agreements will be agreed with all participating sites. Normal NHS indemnity will provide indemnity and/or compensation for negligent harm. NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm. However the normal National Health Service complaints mechanisms will still be available to participants.

The study team will be applying for the Clinical Research Network portfolio adoption for this study. If accepted, sites are able to apply for service support costs for screening and consent time.

11. PATIENT & PUBLIC INVOLVEMENT

Patients and the public are represented by lay members of the Trial Steering Committee. Both the electronic and paper versions of data collection are currently being tested by our patient research ambassadors who will help refine the method to ensure it is user-friendly.

As a preliminary exploration, we approached a series of patients attending cardiac surgical clinics to consider surgery for their cardiac condition. They were shown the TUTE calculator (which predicts their likely benefit in terms of survival) and were asked if they would consider a similar tool predicting QoL outcomes useful to them. The response was invariably positive.

Throughout the course of the study we shall hold yearly patient events to discuss the construction of the QoL prediction tool and in particular the way patients would want this information presented to them so it will be understandable and of value. During the patient events we shall also ask previous cardiac patients what information they would have found useful in aiding them to make the decision to undergo surgery. This development will help design the end product that would be made available to patients and doctors.

Once data collection is completed, a descriptive report will outline the pattern of QoL loss and gain over time after cardiac surgery. The data will then be analysed by logistic regression to identify the factors predictive of loss and gain in QoL outcomes. A full analysis of factor interactions will be carried out. The data will be divided into a development dataset and a validation dataset. The development dataset will then be used to construct a number of risk models to predict the extent and likelihood of any QoL benefit or loss from cardiac surgery. All the models will then be tested for calibration and discrimination against the validation dataset to identify the most useful and robust model. The chosen model will then be developed into a QoL outcome calculator (QoLculator) which will be offered for testing and external validation, following which the calculator will made available on-line and as a mobile phone app for patients and doctors.

12. ACCESS TO THE FINAL STUDY DATASET

The Chief investigator, statisticians, trial manager and data management team will have access to the full anonymised dataset. Investigators at participating sites can apply to access the full dataset in a formal request describing their plans in writing to the steering group.

13. DISSEMINIATION POLICY

13.1 Dissemination policy

On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared. The findings of this research will be disseminated in a variety of ways:.

1. The work will be submitted to international clinical and scientific meetings such SCTS

2. We will aim to publish the outputs of the research in an international peer-reviewed journal that is compliant with the policy on open access.

3. The Trial Steering Committee will agree a formal publication policy for the study.

14 REFERENCES

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9. Anisimov V. Predictive modelling of recruitment and drug supply in multicenter clinical trials. Proc. of Joint Statistical Meeting. Aug. 2009: 1248-1259.

15. APPENDICIES

15.1 Appendix 1- Required documentation

List here all the local documentation you require prior to initiating a participating site (e.g. CVs of the research team, Patient Information Sheet (PIS) on headed paper etc.).

15.2 Appendix 2 – Schedule of Procedures

Procedures						
	Screening	**Baseline**	**Discharge**	**Monthly for 12 months**	**At 6 Months**	**At 12 Months**
Informed consent	X					
Demographics		X				
Frailty assessment – Essential Frailty Toolset by Afilalo		X				
Baseline QoL SF_ 12 EQ-5D LOT PANAS		X				
Discharge Qol SF_ 12 EQ-5D			x			
Discharge Data collection			x			
Qol follow up SF_ 12 EQ-5D				x		
PANAS LOT					x	x

15.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2	24th July	C.Mills	Minor amendment to REC notifying of study sites
2	3		C.Mills, S Nashef	Clarification of inclusion creteria, addition of LOT and PANAS at 6 months & 1 year.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC.