Optimising Cardiac Surgery ouTcOmes in People with diabeteS

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FUNDER

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Protocol Information

This protocol describes the OCTOPuS study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non-study participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This study will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, in accordance with current Data Protection Regulations and all other regulatory requirements, as appropriate.

LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IDSG	Intervention Development Steering Group
ISF	Investigator Site File
ITU	Intensive Treatment Unit
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCTU	Southampton Clinical Trials Unit
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

KEYWORDS
Diabetes, Intervention, Cardiac, Cardiothoracic, Surgery, Out-patient

STUDY SYNOPSIS

Short title/Acronym:	OCTOPuS
Full title:	Optimising Cardiac Surgery ouTcOmes in People with diabeteS

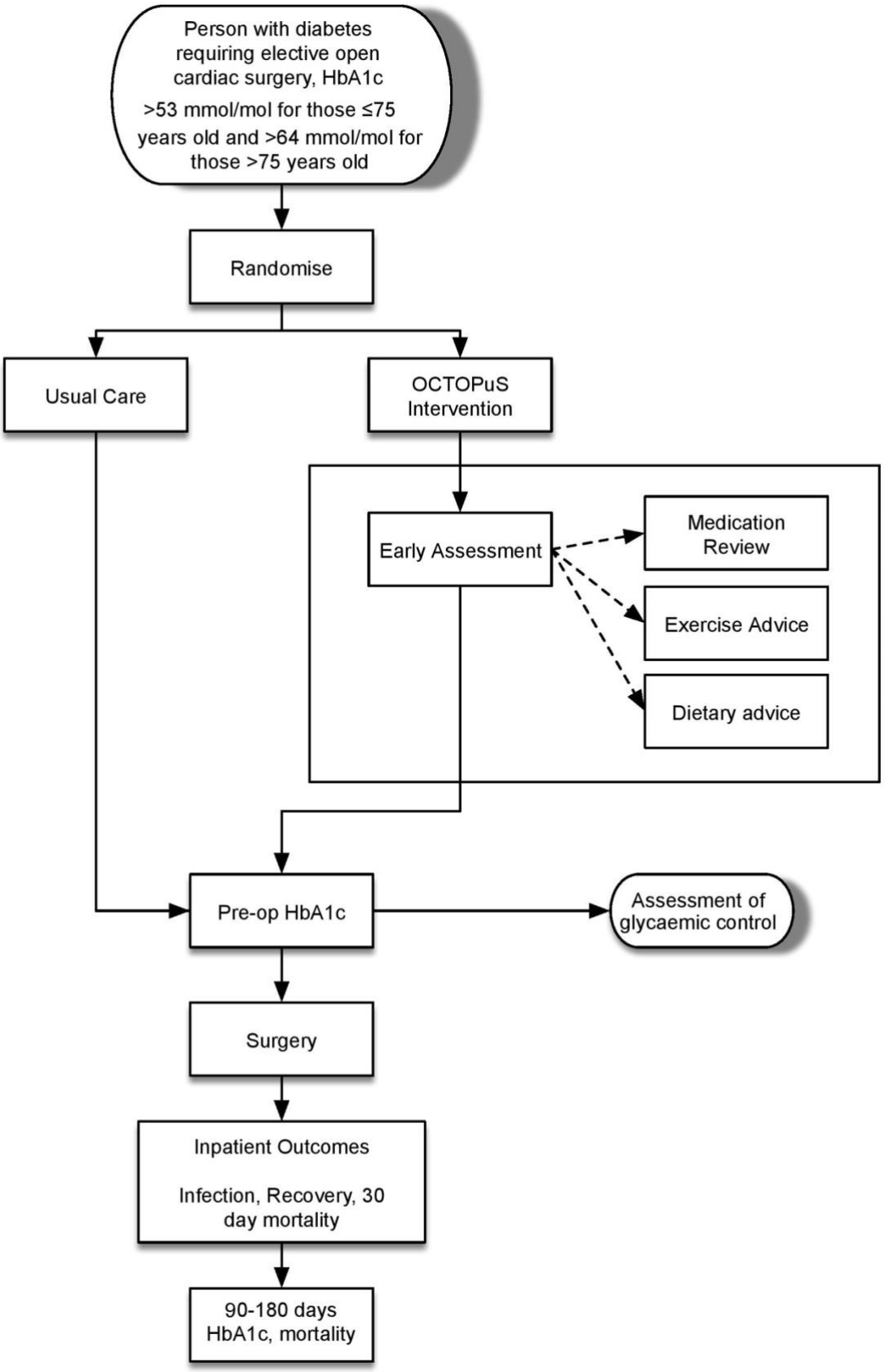
Study Phase:	III
Population:	Adults (≥18 yrs) with sub-optimally controlled type 1 or type 2 diabetes (HbA_{1c} >53 mmol/mol if aged 18-75 years or HbA_{1c} >64 mmol/mol if aged >75 years) undergoing elective cardiac surgery, who are clinically able to wait at least 2 months for their surgery.
Primary Objective:	To investigate whether an outpatient intervention, delivered in the weeks prior to elective major cardiac surgery, can improve outcomes for people whose diabetes is sub-optimally controlled.
Secondary Objectives:	• Through qualitative and psychosocial research, assess patients' and clinicians' experience of receiving and delivering the intervention, respectively. • Health economic evaluation of the intervention
Rationale:	There are currently two important uncertainties in the management of people with sub-optimally controlled diabetes undergoing intermediate and major surgery; • how to improve diabetes management in the weeks leading up to an elective procedure, and • whether that improved management is reflected in improved outcomes post-surgery. We have previously assessed the feasibility of the OCTOPuS intervention, an outpatient intervention delivered to people with sub-optimally controlled diabetes before elective cardiac surgery. The present study will assess whether this intervention can reduce HbA_{1c} levels and improve post-surgery clinical outcomes.
Study Design:	A multicentre, parallel group, single-masked, individually randomised trial incorporating a pre-planned futility analysis comparing time from surgery until clinically fit for discharge in adults with sub-optimally controlled type 1 or 2 diabetes undergoing elective surgery between the OCTOPuS intervention and usual care.
Sample size :	426
Treatment/Intervention:	An outpatient based intervention delivered over approximately 8-12 weeks prior to surgery

URL for Database:	https://www.imedidata.com

Primary Study Endpoints:	Time from surgery until clinically fit for discharge.
Secondary Study Endpoints:	• Actual time from surgery to discharge from hospital • Days alive and either out of hospital or judged as clinically fit for discharge • Pre-operative mortality • 30 day mortality

	• 90 day mortality • Time on ITU • Time on a ventilator • Sternal Infections • Leg wound infections, in participants who provide donor vein • Chest infections • Urinary tract infections • Acute myocardial infarction • Change in weight between randomisation and surgery • Effect on post-operative renal function and incidence of acute kidney injury • HbA_{1c} immediately preoperative, and at between 90 and 180 days post operation. • Change in HbA_{1c} between baseline and immediately preoperative, and change from preoperative to between 90 and 180 days post operation • Frequency and severity of self-reported overall, minor, severe and nocturnal hypoglycaemia • Operations permanently cancelled for sub-optimal glycaemic control • EQ-5D at baseline, 7 days, 90 days and (if found feasible and effective) 30 days post-surgery. • Cost effectiveness of intervention – Use of NHS lifestyle improvement programs and diabetes services – Use of medication – Time spent by practitioners for a) training, b) delivering the intervention and c) liaising with local services – HbA_{1c} point-of-care and blood glucose monitoring costs • Psychosocial questionnaires at baseline and 90 days post surgery using: – Problem areas in diabetes (PAID) – Brief illness perception questionnaire (BIPQ) – Diabetes empowerment scale (DES5) – Summary of diabetes self-care activities (SDSCA) – Patient health questionnaire 2 (PHQ-2)
Total Number of Sites:	Approximately 15

STUDY SCHEMA



SCHEDULE OF OBSERVATIONS AND PROCEDURES

Visit:	Screening	Consent	Baseline	Intervention	Support calls[1]	Pre-Surgery assessments	Surgery	Discharge	Surgery +7 days	Post-discharge support call[2]	Surgery +30 days	Surgery +90 days	End of study
Notes review	X												
Informed Consent		X											
Eligibility evaluation (incl. pregnancy test where appropriate)	X	X	X										
Medical History (incl. smoking status, diabetes and current medications)			X			X							
Physical Exam (incl height, weight and waist circumference)			X[3]			X							
Vital Signs (incl. BP)			X			X							
Biochemistry (incl HbA_{1c}, blood glucose and renal function)			X			X		X[4]				X[5]	
Hypoglycaemia			X		X	X							
Infections and surgical complications								x			x	X	
Mortality						x					x	x	x
Intervention				X									
Intervention support phone call (incl. review of diary card and					X					x			

[1] Every 2 to 6 weeks until surgery.
[2] One to 3 weeks after discharge.
[3] Please note: 'Height' will only be recorded at 'Baseline'.
[4] Only serum creatinine and renal function will be measured to capture acute kidney failure.
[5] This can be completed between 90 and 180 days post-surgery.

Visit:	Screening	Consent	Baseline	Intervention	Support calls[1]	Pre-Surgery assessments	Surgery	Discharge	Surgery +7 days	Post-discharge support call[2]	Surgery +30 days	Surgery +90 days	End of study
components of intervention utilised)													
Practitioner time (cost-effectiveness)			X	X	X					X			
NHS resource use questions (cost-effectiveness)						X							
Surgery (inc. time on ventilator/ITU)							X						
Blinded assessment								X					
Adverse Events			X	X	X	X			X	X	X	X	X
EQ-5D 5L			X						X		x[6]	X	
Participant qualitative interview			X[7, 8]									X[7]	
Psychosocial questionnaires			X									X	

The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).

Key health professionals involved in the delivery of the intervention will be interviewed once around 12 months after the start of trial in their centre but as the timing is independent from the study visits and will vary for each site, these interviews are not included in the above table.

[6] Only if feasible and effective (see section 7.5).

[7] For those randomised to intervention.

[8] Interviews will be conducted with 50 participants within 6 weeks of surgery.

1 INTRODUCTION

1.1 BACKGROUND

There are approximately 4 million people living with diagnosed and undiagnosed diabetes mellitus in the UK (1). Since 1996, the number of people diagnosed with diabetes has increased from 1.4 million. Diabetes increases the risk of cardiovascular disease by approximately 2-fold after adjustment for other cardiovascular risk factors. Ischaemic heart disease is by far the leading cause of death in people with diabetes accounting for approximately two thirds of all deaths in those aged >65 years. Coronary heart disease tends to be more diffuse and progresses more rapidly in people with diabetes which may explain why up to 35% of those presenting for elective cardiac revascularisation have diabetes (2). Sub-optimal glycaemic control increases the risk of wound and chest infections, renal impairment and death, especially following cardiac surgery (3-7).

The increasing number of people with diabetes will increase the demand for cardiac surgery in the future. These patients have longer lengths of hospital stay and higher re-admission rates, placing a large financial burden on the NHS. If the pre-operative intervention is successful in improving glycaemic control, this may reduce the complication rate and improve the clinical outcomes. It may also prove cost effective and even cost saving.

The Joint British Diabetes Societies for in-patient care provided recommendations to improve the management of adults with diabetes undergoing surgery (3). As sub-optimal peri-operative glycaemic control is associated with an increased risk of all surgical complications, the guidelines recommend improving glycaemic control to optimise surgical outcomes.

Since 2011, the diabetes team at the Royal Bournemouth Hospital have worked to optimise the surgical experience of people with diabetes. Using a nurse-led outpatient intervention, delivered around 3 months before surgery to people with sub-optimally controlled diabetes, they achieved a reduction in HbA_{1c} from 85 mmol/mol at first referral to 74 mmol/mol on admission for surgery. This has been associated with a reduced length of stay from a mean of 5.9 days to a mean of 3 days, while the length of stay for those without diabetes remained constant at 5 days. Other work has shown the practicality of improving HbA_{1c} over a period of weeks in primary care (8).

The OCTOPuS project was established to address whether a pre-operative out-patient healthcare professional delivered intervention to improve diabetes management improves cardiac surgical outcomes for people with diabetes. The project is divided into two parts:

1. Intervention Development
2. Randomised Controlled Trial to evaluate the effectiveness and cost effectiveness of the intervention developed in part 1

The Intervention Development part of the study was covered by a separate ethics application and protocol (18/SC/0508) and is summarised below. The rest of this protocol refers explicitly to the OCTOPuS Randomised Controlled Trial, hereafter referred to as the OCTOPuS study.

1.2 OCTOPUS INTERVENTION DEVELOPMENT

1.2.1 Feasibility study

1.2.1.1 Aims

A feasibility study was conducted to assess whether the intervention is acceptable for people with diabetes and clinicians and can be delivered in a multicentre randomised controlled trial.

More specifically we explored (1) whether any changes needed to be made to the first draft of the manual and (2) if there are any potential barriers in the process that could inform the main trial.

1.2.1.2 Methods

Participants were recruited through 5 cardiac surgery outpatient clinics at University Hospital Southampton NHS Foundation Trust since March 2019 using the same process anticipated for the main trial. In brief, clinic lists were screened several weeks prior to the clinic for potential participants. They were contacted by letter and follow-up phone call to assess their willingness to take part in the study. On the day of their clinic visit, if they were listed for cardiac surgery, they were recruited to the study if they fulfilled the inclusion/exclusion criteria. After providing informed written consent, the participants receive their first OCTOPuS consultation from a diabetes specialist healthcare professional (OCTOPuS practitioner) either on the day of their outpatient appointment with the surgeon or at a dedicated weekly OCTOPuS clinic established explicitly for the study. A formal diabetes management was agreed to help prepare the participant for surgery. Participants were then contacted by an OCTOPuS practitioner, initially at least fortnightly, to assess their diabetes management and to provide on-going encouragement and support to help the participant achieve their diabetes goals. The precise format of this contact was driven by the OCTOPuS intervention manual. Feedback from the participants experiencing the intervention and clinicians delivering the intervention was obtained using semi-structured interviews with the aim of refining and finalising the manual in preparation for the main trial.

1.2.1.3 Process evaluation

We evaluated the recruitment and intervention delivery process throughout the study to ensure the fidelity of the intervention when scaled up. The main barriers and measures we took to mitigate are presented below:

Challenge	Solution
Recruiting participants on the same day as their outpatient appointment	Dedicated OCTOPuS clinic every Thursday afternoon
Small number of potential candidates when recruiting from one cardiac surgery clinic	Expansion to all 5 UHS clinics
Large number of people >75 years old who were excluded only on the basis of age and could benefit from the intervention	Recruiting participants aged >75 years old. We used a higher HbA_{1c} threshold of >64 mmol/mol to reduce the risk of iatrogenic hypoglycaemia

1.2.1.4 Results

Overall, the feedback from both participants and clinicians was positive and both groups were more focused on pre-operative diabetes management after taking part in the OCTOPuS trial. Participants reported that taking part in the trial improved their health prior to surgery, and felt supported and satisfied with the care they had received. High levels of anxiety relating to the prospect of cardiothoracic surgery were reported by some participants. As the OCTOPuS intervention provided an opportunity to alleviate some of these fears, we added clarifications to the OCTOPuS manual regarding the impact of diabetes on cardiac surgery.

From the practitioners' point of view, participants seemed happy after surgery and were less likely to need referral to inpatient diabetes services after surgery. For them, the main challenge was how to fit the time-commitment to the study within NHS normal practice. Establishing the dedicated OCTOPuS clinic allowed much better time management and was easier for the OCTOPuS team.

Most of the OCTOPuS manual performed well and only minor changes to the manual were needed during the intervention development. However, further changes may be required once all the qualitative feedback has been analysed. Preliminary analysis demonstrated a reduction in HbA_{1c} between baseline and surgery but the sample size was too small to draw conclusions about the magnitude of this effect.

It is envisaged that the manual will be a dynamic document and will be updated as appropriate in response to changes in clinical practice during the main trial.

1.2.1.5 The OCTOPuS training package

A training package will be developed at the end of the intervention development including the final OCTOPuS manual as well as details on how to run the study. This training will be provided to all study sites prior to the commencement of the study at each site.

1.3 THE OCTOPUS SURVEY

In parallel to assessing the feasibility of the OCTOPus intervention, we developed and distributed a survey to understand the current practice for management of people with diabetes in cardiac surgery centres in the UK. The results of this survey will inform how the OCTOPuS study can fit into current NHS clinical practice.

2 RATIONALE & OBJECTIVES

There are currently two important uncertainties in the management of people with sub-optimally controlled diabetes undergoing intermediate and major surgery;

1) how to improve diabetes management in the weeks leading up to an elective procedure, and
2) whether that improved management is reflected in improved outcomes post-surgery (9).

Practice is therefore varied, with current UK guidelines recommending a delay to elective surgery to allow for improved diabetes management if HbA_{1c} is above 69 mmol/mol (where it is safe to do so); in contrast, the USA guidance recommends considering a delay to if the HbA_{1c} is above 53 mmol/mol. The current NICE guidelines recognise this as an evidence gap (10), as do the Joint British Diabetes Societies (3).

The Intervention Development part of the OCTOPuS study demonstrated that an outpatient intervention delivered to people with sub-optimally controlled diabetes before elective cardiac surgery is acceptable by people with diabetes and clinicians. The study demonstrated the feasibility of the recruitment process within the NHS routine pathway.

The present study aims to investigate whether the OCTOPuS intervention is both clinically and cost-effective at improving outcomes for people with sub-optimally controlled diabetes in a large-scale multi-centre Randomised Controlled Trial (RCT) involving approximately 15 cardiothoracic UK centres.

Specifically:

- We will assess whether the intervention can improve clinical outcomes following cardiac surgery.

- We will test whether the intervention can reduce HbA_{1c} levels in people awaiting cardiac surgery compared with usual care.
- Through qualitative and psychosocial research, we will explore the patient experience of receiving the intervention.
- We will undertake a health economic evaluation of the intervention.

3 STUDY DESIGN

OCTOPuS is a multicentre, parallel group, single blind, individually randomised trial incorporating a pre-planned futility analysis. It will compare time from surgery until an individual is clinically fit for discharge in adults with sub-optimally controlled type 1 or 2 diabetes undergoing elective surgery (as defined as an HbA_{1c} >53 mmol/mol for those ≤75 years old and > 64 mmol/mol for those > 75 years old) between the OCTOPuS intervention and usual care.

3.1 PRIMARY ENDPOINT

Time from surgery until clinically fit for discharge, as judged by the surgical team. Teams will be blinded to pre-hospital diabetes management allocation. This primary outcome was chosen because reduced time in hospital (though not at the expense of safety) is valued by people with diabetes, clinicians, and commissioners.

3.2 SECONDARY ENDPOINTS

- Time from surgery to actual discharge from hospital – this recognises that discharge can be delayed for non-clinical reasons
- Days alive between surgery and either out of hospital or judged as clinically fit for discharge
- Pre-operative mortality
- 30 day mortality
- 90 day mortality
- Time on ITU
- Time on a ventilator
- Sternal Wound Infections, defined as below according to the NICE guidance and the CDC criteria (19, 20):
  - Superficial Sternal Wound Infection, which involves skin, subcutaneous tissues and/or pectoralis fascia only without bone involvement
  - Deep Sternal Wound Infection, which involves the bone or mediastinum
- Leg wound infections, in patients who provide donor vein are graded according to the Centers for Disease Control and Prevention definitions of surgical site infections. Any sternal or leg wound infection occurring within three months after surgery will be considered as postoperative wound infections (21).
- Chest infections, defined as a change in typical chest symptoms (cough, increase respiratory rate, shortness of breath) in conjunction with a fever or inflammatory markers.
- Urinary tract infections, defined as ”clinically-diagnosed and treated, whether or not results from a urine culture are available’’
- Acute Coronary Syndrome, referring to any of these conditions leading to a hospital admission:
  - stable angina
  - unstable angina requiring or not nitrates infusion
  - non-ST elevation myocardial infarction
  - ST-elevation myocardial infarction (21)

- Change in weight between randomisation and surgery
- Effect on post-operative renal function and incidence of acute kidney injury as assessed by measurement of serum creatinine and calculation of estimated glomerular filtration rates
    - Acute Kidney Injury is defined as an increase in serum creatinine 1.5 -1.9 times the baseline level or serum creatinine increase ≥26.5 µmol/l within seven days after surgery (21).
- HbA_{1c} immediately preoperative, and at between 90 and 180 days post operation.
- Change in HbA_{1c} between baseline and immediately preoperative, and change from preoperative to between 90 and 180 days post operation
- Operations cancelled for sub-optimal glycaemic control
- Frequency and severity of self-reported overall, minor, severe and nocturnal hypoglycaemia assessed at Baseline, during the Support Contact and Pre-surgery according to the following definitions:
    - Overall hypoglycaemia is defined as any self-reported hypoglycaemia confirmed by a self-monitored capillary or interstitial glucose of <4 mmol/L
    - Minor hypoglycaemia is defined as any self-reported hypoglycaemia confirmed by a self-monitored capillary or interstitial glucose of <4 mmol/L when this was treated by the participant
    - Severe hypoglycaemia is defined as any self-reported episode of hypoglycaemia that required external assistance for treatment
    - Noctural hypoglycaemia is defined as any self-reported hypoglycaemia confirmed by a self-monitored capillary or interstitial glucose of <4 mmol/L that occurred between 0000 and 0600 (22).
- EQ-5D at baseline, 7 days and 90 days post-surgery. In the first phase of the trial, the utility of collecting EQ-5D at 30 days post-surgery will be explored. This has the potential for providing an extra data point, but the increased participant burden may risk the loss of completeness of the survey at 90 days.
- Psychosocial questionnaires at baseline and 90 days post-surgery to explore the impact of the intervention on factors important to quality of life and any changes to participants' diabetes self-management (see 7.6.2).
- Cost effectiveness of intervention
    - Use of NHS lifestyle improvement programs and diabetes services
    - Use of medication
    - Time spent by practitioners for a) training, b) delivering the intervention and c) liaising with local services
    - HbA_{1c} point-of-care and blood glucose monitoring costs

3.3 DEFINITION OF END OF STUDY

The last visit will be 180 days post-surgery for the last study participant who has a trial operation. The end of trial is defined as the date after the last patient has their last visit and when all data points required to answer the research question are captured and verified.

4 SELECTION AND ENROLMENT OF PARTICIPANTS

4.1 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Written informed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected.

After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Participants will be asked to consent for long-term follow-up using routine data. We anticipate exploring (not as part of the current funding contract) outcomes such as 5 and 10 year mortality, and effect on longer term glycaemic control.

Cardiac surgery clinic lists will be scrutinised by the clinical cardiac surgery team to identify potentially eligible individuals who will be sent study information and receive a telephone call to discuss the study. Potential participants will have the opportunity to ask questions prior to their outpatient cardiac surgery appointment allowing at least 24 hours to consider the trial before their outpatient appointment.

A similar approach has been used by Foss et al (12), who demonstrated that people receiving telephone-based counselling about a trial showed similar levels of comprehension to those being counselled face-to-face. In the present study, potential participants will also have the opportunity to discuss the study face-to-face with the research nurse after their appointment with the cardiac surgeon and before consent is sought. See section 5.1 below for screening and consent procedures.

Upon completion of the informed consent form, a copy will be given to the participant, a copy stored in the participant's medical notes, a copy sent to the Southampton Clinical Trials Unit (SCTU) and the original filed in the Investigator Site File. The SCTU copy should be emailed to uhs.sctu@nhs.net using a secure nhs.net email address to allow for central monitoring.

4.2 INCLUSION CRITERIA

1. Aged ≥ 18 years old with type 1 or type 2 diabetes
2. Sub-optimally controlled diabetes defined as an HbA_{1c} > 53 mmol/mol for those ≤ 75 years old and an HbA_{1c} > 64 mmol/mol for those > 75 years old[9], measured using a near patient test at the cardiac surgery outpatient appointment where the decision to proceed to surgery is made.
3. Awaiting elective open-heart cardiac surgery
4. Anticipated delay before surgery of at least 2 months.
5. Surgery will take place at one of the hospitals participating in the trial
6. Ability to give informed consent.
7. Ability to interact with the study documentation and processes.

4.3 EXCLUSION CRITERIA

1. Active malignancy that would preclude engagement with OCTOPuS intervention[10]
2. Pregnancy
3. Previous cardiac surgery
4. Known haemoglobinopathies that affect the measurement of HbA_{1c}

[9] The higher cut-off in older people is designed to minimise the risk of iatrogenic hypoglycaemia in this population (17).

[10] Active malignancy is defined as malignancy which is currently being treated by chemotherapy, surgery or radiotherapy or is likely to cause death within 6 months

5. Other illnesses or conditions that would preclude engagement with the OCTOPuS intervention
6. Surgery taking place outside one of the participating hospitals, e.g. at a private hospital

4.4 SCREENING FAILURES

Screen failures will be recorded on the 'patient screening log'. This is completed for all individuals who have been considered for the study and is faxed or emailed monthly to the OCTOPuS Trial Team on 0844 774 0621 or octopus@soton.ac.uk.

4.5 REGISTRATION/RANDOMISATION PROCEDURES

After consent, a web-based remote randomisation system, maintained by Southampton CTU, will allocate participants to either the OCTOPuS intervention, or the control condition.

Participants will be randomised between the arms in a 1:1 ratio and stratified by centre, age (≤75 years old and >75 years old) and baseline HbA_{1c} (< 69 mmol/mol and ≥69 mmol/mol as per [3]), using pre-generated permuted blocks to prevent clinicians anticipating the allocation.

Participants randomised to the OCTOPuS intervention will see a health care professional trained in the OCTOPuS intervention.

4.6 CONTRACEPTION

Although it is not anticipated that there will be many pre-menopausal women in the study, women of child-bearing age will be advised to avoid pregnancy during the study.

5 STUDY OBSERVATIONS AND PROCEDURES

5.1 SCREENING PROCEDURES

Outpatient cardiac surgery appointment clinic lists will be scrutinised by a member of the cardiac surgery clinical team (or research nurse where he/she is a member of the clinical team) ahead of appointments, to identify those who may meet the study eligibility criteria. For people who appear eligible for the OCTOPuS study, an information sheet explaining the trial will be sent by post or email as appropriate. Before the outpatient appointment a member of the site trial research team will contact the prospective participant to discuss the study, allowing sufficient time for reflection and discussion (at least 24 hours) before the outpatient appointment. The information sheet will also include contact details to opt out if the person does not want to be contacted about the trial. This will allow those who are eligible for the study to be randomised immediately after the outpatient appointment, and where applicable receive their first OCTOPuS consultation, on the same day.

At the outpatient appointment where a decision to proceed to surgery is made, the treating surgeon will remind eligible patients about the trial. If the participant wishes to take part, a more detailed interview with a research nurse will follow, where the study can be discussed in depth according to the needs of the individual, and final exclusion criteria checked (e.g. pregnancy status) and written consent given.

Patients whose medical records cannot be accessed prior to the appointment to determine eligibility (e.g. patients from another hospital), will be given information about the study on the day of their outpatient appointment and will be offered the opportunity to come on another

day to discuss their participation in the trial. Where possible, the OCTOPuS visit will be scheduled for the same day to reduce the number of times that any individual has to travel to the trial centre.

The reason for this method of recruitment is because many cardiothoracic centres provide care to people living in a diverse geographical area and this will reduce the number of visits and length of time needed for travel to the trial centre.

5.2 STUDY PROCEDURES

Participants who are randomised to receive the OCTOPuS intervention will have an initial consultation with an OCTOPuS trained health professional (OCTOPuS Practitioner), who may be a doctor, nurse, pharmacist, or other appropriately trained person. In this consultation the participant's diabetes management will be discussed, as well as the likely benefits that improved glycaemic control will provide in the run up to surgery. The practitioner and participant will agree a number of actions, tailored to the individual needs and ability. These are likely to include:

- A graded exercise regimen. This may be completely self-delivered, or alternatively by joining a local appropriate exercise scheme – such as a 'health walk'. There is a general consensus amongst cardiac surgeons that limited exercise can be allowed prior to surgery. This needs to be individualised for each person and should not provoke symptoms of angina or breathlessness. The usual format of exercise suggested is walking on the flat, for short, frequent, episodes.
- Dietary advice, supplemented by a consultation with a dietitian if needed
- Medication review, which may lead to the introduction of insulin or other diabetes medications for people with type 2 diabetes.
- Specific advice about managing expectations, understanding facilitators to achieve change and overcoming barriers to improve medical and psychosocial outcomes

The exact process for this discussion and the treatment options are set out in the OCTOPuS intervention manual.

Participants will receive regular review with the OCTOPuS practitioner, probably by telephone, at least once a fortnight until the patient's diabetes management is optimised or no further changes are needed. After this, the frequency of the calls can be reduced at the discretion of the OCTOPuS practitioner to a minimum of every 6 weeks until surgery. This will be an opportunity to offer encouragement and support and address any issues which have arisen for the participant. One more support contact will be made between 1 and 3 weeks after discharge to ensure the continuity of the intervention beyond surgery. Although this final contact will not affect the primary outcome of the study, it was added following feedback from the participants in the intervention development study, who requested a final consultation before the diabetes management returned to their usual setting.

Where necessary the OCTOPuS practitioner will liaise with local services, e.g. the participant's GP or a dietitian, to facilitate delivery.

Participants in the control arm will receive usual care in the cardiac surgery centre attended by the individual. This is likely to contain brief advice from the patient's surgeon to pay attention to their diabetes in the run up to surgery. Some people may act on this advice, either on their own or in conjunction with their GP.

The study will document 'usual care' at all recruiting centres and explore with participants in the control arm as part of the qualitative work what actions were taken in response to advice received.

Discharge assessment: This should be completed by the surgical team who are blinded to the participant's pre-hospital diabetes management allocation.

5.3 FOLLOW UP

Following surgery all participants will be followed up at discharge, 7 days, 30 days and 90-180 days post-surgery. Also, as explained above a support call will be conducted between 1 and 3 weeks post-discharge. See 'SCHEDULE OF OBSERVATIONS AND PROCEDURES' for the information to be collected at each follow-up.

Most of the outcome measures will be collected in hospital, with the exception of 30 and 90 day mortality, which will either be collected through in-patient note review, or where possible using adult cardiac surgery databases (e.g. the SCTS National Adult Cardiac Surgery Audit).

Any of the following approaches can be used to obtain the 90-180 day HbA_{1c}.

- Many people have 3 – 6 monthly blood tests; for these individuals, the research team will ask for the copy of the result.
- For those attending cardiac surgery or cardiology outpatients in this window, the results of any outpatient clinic blood test result will be requested.
- The research team will contact the participant's GP to establish whether they have died, and if so the date of their death. If the person is still alive, they will be sent a capillary HbA_{1c} testing kit, which can be returned by post.

5.4 DEVIATIONS AND SERIOUS BREACHES

Any study protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and /or the study protocol will immediately be reported to the regulatory authorities and other organisations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

5.5 STUDY DISCONTINUATION

In consenting to the study, participants have consented to the study intervention, follow-up and data collection. Participants may be discontinued from the study procedures at any time.

Participants may be discontinued from the study in the event of:

- Permanent cancellation of surgery or postponement beyond 6 months of the original planned date of surgery
- Clinical decision, as judged by the Principal Investigator or Chief Investigator
- In the event the trial is discontinued due to the interim analysis (as outlined in Section 7.3)

Full details of the reason for study discontinuation should be recorded in the eCRF and medical record.

5.6 WITHDRAWAL

The participant / legal representative is free to withdraw consent from the study at any time without providing a reason.

Investigators should explain to the participants the value of remaining in study follow-up and allowing these data to be used for trial purposes. Where possible, those who have withdrawn from study treatment should remain in follow-up as per the trial schedule. If participants additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. It would remain useful for the study team to continue to collect standard follow-up data and unless the participant explicitly states otherwise, follow-up data will continue to be collected.

Details of study discontinuation (date, reason if known) should be recorded in the eCRF and medical record.

5.7 PROHIBITED AND RESTRICTED THERAPIES DURING THE STUDY

There are no prohibited or restricted therapies during this study.

5.8 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

Due to the nature of the interventions in this trial it will not be possible to blind the participants or investigators, with the exception of discharge. Every attempt will be made to keep the surgical team assessing fitness to discharge blinded to the treatment allocation. As this assessment does not depend on treatment allocation, it will not be necessary to unblind the surgeons.

6 SAFETY

6.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a participant or clinical study participant which does not necessarily have a causal relationship with study treatment or participation.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment or participation (regardless of causality assessments).

Serious Adverse Event (SAE) is any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening***
- **Requires hospitalisation, or prolongation of existing hospitalisation****
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- Other important medical events***.

*‘life-threatening’ in the definition of ‘serious’ refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE. Prolongation of hospitalisation is considered to be the case from >30 days post-cardiothoracic surgery i.e. hospitalisation for surgery and up to 30 days is not considered an SAE.

***Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Note: It is the responsibility of the PI or delegate to grade an event as 'not serious' (AE) or 'serious' (SAE).

6.2 SERIOUSNESS

A complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

All adverse events that fulfil the criteria definition of 'serious' in protocol section 6.1, must be reported to SCTU using the Serious Adverse Event Report Form – Non-CTIMP. Specific exceptions to this (as listed below) should be recorded as AEs rather than SAEs.

All SAEs must be reported immediately by the PI at the participating centre to the SCTU.

6.2.1 Exceptions:

For the purposes of this study, the following SAEs **do not** require reporting to SCTU using the Serious Adverse Event Report Form – Non-CTIMP:

- Hospitalisations for elective treatment of a pre-existing condition

Also, the following SAEs **do not** require reporting to SCTU using the Serious Adverse Event Report Form – Non-CTIMP if they occur between 'Surgery' and 'Discharge':

- Arrhythmia, including atrial fibrillation
- Immediate postoperative surgical bleeding
- Pneumonia

6.3 CAUSALITY

A complete assessment of the causality must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists the local investigator should inform the SCTU who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

Relationship	Description	Event Status
Unrelated	There is no evidence of any causal relationship	Not related to treatment
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study treatment). There is another reasonable explanation for	Not related to treatment

	the event (e.g. the participant's clinical condition, other concomitant treatment).	
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study treatment). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Related and expected SAE/ Related and unexpected SAE
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Related and expected SAE/ Related and unexpected SAE
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Related and expected SAE/ Related and unexpected SAE

In terms of event status; **Not related to treatment** would highlight that the SAE is not related to the trial treatment. **Related and expected** SAE would signify that the SAE is related to the trial treatment and is expected (according to the list of expected events listed in the protocol). **Related and unexpected SAE** would be classified as an SAE which is related to the trial treatment and is unexpected in terms of the events listed in the protocol.

In the case of discrepant views on causality between the Investigator and others, SCTU will classify the event as per the worst case classification and where applicable the Ethics Committee will be informed of both opinions within the required timelines.

6.4 EXPECTEDNESS

Expectedness assessments are made against the list of expected events below:

6.4.1 Expected Adverse Events:

- Minor musculoskeletal aches and pains
- Myocardial infarction
- Respiratory tract infection

The nature or severity of should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available then the AE should be recorded as 'unexpected'.

6.5 REPORTING PROCEDURES

All adverse events should be reported until the End of Study as defined in 3.3.

Depending on the nature of the event, the appropriate reporting procedures below should be followed. A flowchart will be provided to aid in the reporting procedures.

6.5.1 Reporting Details

A SAE for Non-CTIMPs Form should be completed for all SAEs and faxed to SCTU within 24 hours of site becoming aware of the event.

Complete the SAE form and fax or email a scanned copy of the form with as many details as possible to the SCTU together with anonymised relevant treatment forms and investigation reports.

Or
Contact the SCTU by phone for advice and then fax or email a scanned copy of the completed SAE form.

SAE REPORTING CONTACT DETAILS

Please email or fax a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

Fax: 0844 774 0621 or Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 4138 (Mon to Fri 09:00 – 17:00)

Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

6.5.2 Follow Up and Post- study SAEs

The reporting requirement for all AEs and SAEs affecting participants applies for all events occurring up to 90 days following cardiac surgery.

All unresolved adverse events should be followed by the investigator until resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to this study.

6.5.3 Pre-existing Conditions

Medically significant pre-existing conditions (those which are present prior to informed consent) should not be reported as an AE unless the conditions worsens during the trial. The condition, however, must be reported on the Medical History eCRF. Any adverse events which occur after informed consent taken should be recorded on the AE eCRF as per safety reporting section.

6.5.4 Serious Adverse Events

All SAEs should be reported within 24 hours of the local site becoming aware of the event. The SAE Non-CTIMP Form asks for nature of event, date of onset, severity, corrective therapies given, outcome, causality (i.e. unrelated, unlikely, possible, probably, definitely) and expectedness. The responsible investigator should assign the causality and expectedness of the event with reference to the events listed in Section 6.4.1. The event term should be in accordance with the latest version of MedDRA and grades given in accordance with the NCI CTCAE v5, Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

6.6 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC

SCTU will notify the necessary competent authorities of all **Related and Unexpected** SAEs occurring during the study within 15 days.

SCTU submit all safety information to the REC in annual progress report.

7 STATISTICS AND DATA ANALYSES

7.1 METHOD OF RANDOMISATION

Participants will be individually randomised between the arms, using a 1:1 allocation ratio. The randomisation will be performed via an online system allowing instant assignment to groups 24 hours per day. The service will be provided by Southampton Clinical Trials Unit with telephone back up during office hours (9am-5pm) on days when the University of Southampton is open. Randomisation will be stratified by centre, age and baseline HbA_{1c} and use permuted blocks.

7.2 SAMPLE SIZE

7.2.1 Futility Assessment – Physiological Effect of Intervention

To demonstrate that a physiological response is plausible we need to show an HbA_{1c} improvement of 5 mmol/mol in the intervention group at pre-surgery compared to baseline. Previous experience shows the mean initial HbA_{1c} in our study population to be around 72 mmol/mol, with a standard deviation of around 15 mmol/mol (13,14). For an expected change in HbA_{1c} from baseline of 5 mmol/mol in the intervention group, and assuming a conservative correlation of 50% between baseline and pre-surgery, a sample size of 50 participants would allow a margin of error of 4.16 below the mean for a 95% confidence interval (CI). This CI width would allow us to exclude a difference of zero if the treatment difference of 5 was observed.

7.2.2 Intervention effectiveness – clinical outcomes

The primary outcome is the time from surgery to when the responsible consultant considers the participant clinically fit for discharge. We will not consider the actual discharge date in the primary analysis, as currently in cardiothoracic surgery many elective patents are kept in hospital longer than clinically indicated due to their social situation. Discussions with clinicians and commissioners suggest that a mean improvement of half a day would be clinically worthwhile.

The current mean duration post-surgery until clinically fit for discharge is 7 days, with a standard deviation of 1.5 days. To demonstrate an improvement of 0.5 days with 90% power and 5% significance with 1:1 randomisation between intervention and control arms would require a total of 382 participants (nQuery v7.0). After listing for surgery, very few patients are lost to follow-up. We will therefore allow for a 5% loss to follow-up, and a further 5% for deaths post randomisation inflating the final target sample size to 426 participants.

7.3 INTERIM ANALYSIS

The futility will be assessed, and there is the potential that the trial could be stopped early in one of two ways:

7.3.1 Recruitment and Delivery

There are several threats to recruitment and delivery of this trial:

- Being unable to recruit and initiate sufficient centres.

- Centres not being able to recruit sufficient participants
- Centres not being able to deliver the OCTOPuS interventions

Therefore throughout the trial phase of the study we will review progress against a number of criteria at three time points, grading trial progress as red, amber, or green each time. Appendix 1, Table 1 sets out the actions to be taken depending on how progress is scored. Appendix 1, Table 2 describes the criteria leading to the scores.

7.3.2 Physiological Effect of Intervention

It is believed that the OCTOPuS intervention will have its clinically relevant effects (such as reducing length of stay, reducing infection and reducing mortality) through improvement of a number of clinical variables, including change in body weight, exercise, lipid profile and blood pressure. However, as the main target of the intervention is to improve glycaemic control, if no physiological effect can be demonstrated on glycaemic measures, continuation of the trial would be futile. After the first 100 participants have had their surgery we will assess the effect of the intervention on pre-operative HbA_{1c} as stated in Appendix 1. If there is no discernible effect (defined as a change of HbA_{1c} of < 5 mmol/mol) we will ask the TSC to review the trial's viability.

7.3.3 Other reasons for stopping the trial early

While previous experience has suggested that in a different clinical group a 3 day saving in length of stay is possible, advice from clinicians, commissioners, and service managers is that a 0.5 day reduction in length of stay would be worthwhile. The trial is therefore powered on a 0.5 day reduction, however, the DMEC will be asked to periodically review the effect being observed and to recommend a change in sample size or stop the trial if appropriate.

7.4 STATISTICAL ANALYSIS PLAN (SAP)

Since this is a parallel group, randomised controlled trial, with a usual care (control) arm, data will be reported and presented according to the revised CONSORT statement (15, 16). A detailed statistical analysis plan will be developed prior to the final analysis of the trial, however, the main features of the plan are discussed below.

Demographics and characteristics of participants at baseline will be summarised and assessed for comparability between the intervention and control arms (16). The primary analysis will be conducted using ANCOVA adjusted for randomisation stratification factors on an intention to treat population. Continuous data will be presented as means and standard deviations and analysed using ANCOVA (or presented as medians and ranges and analysed using Mann-Whitney U tests if data are skewed). Binary data will be reported in terms of odds ratios and analysed using logistic regression modelling. Analysis of time-to-event outcomes will include presenting Kaplan-Meier graphs by arm and analysed using Cox proportional hazards regression (or competing risk regression as discussed below). A two-sided p-value of 0.05 or less will be used to declare statistical significance for all analyses and results will be presented with 95% confidence intervals.

Subgroups will be investigated, including those with HbA_{1c} above or below 69 mmol/mol at presentation; type of diabetes; age above or below 75 years. The cut-off of 69 mmol/mol has been chosen as the level above which the Joint British Diabetes Societies recommend specific

action to improve pre-operative glycaemic control. The cut-off for age has been chosen to reflect the different HbA_{1c} entry criteria for those above and below 75 years.

It is possible that a small proportion of participants will receive the intervention/usual care but will not actually undergo the planned surgery due to death, or clinically directed surgery cancellation. A small proportion may also undergo urgent revascularisation due to myocardial infarction after they have received their allocated treatment. A further group may undergo surgery but die before they are well enough for discharge from hospital and thus not meet the primary endpoint. In total, it is expected that these events will occur in no more than 5% of participants. In this case, these individuals will be excluded from the primary analysis but the prevalence of each of these outcomes will be monitored and recorded by treatment arm separately and presented to the DMEC for their guidance if there is any indication that there is an excess of any of these outcomes in either treatment group. A sensitivity analysis will be considered, looking at a competing risks model, where any of these outcomes and functional recovery are competing risks. This sensitivity analysis will also be performed if the total prevalence of these events is more than 5%. The analysis plan for the psychosocial questionnaires is detailed in section 7.6.2 below.

7.5 ECONOMIC EVALUATION

Within-trial analysis, with longer term modelling, will be used to estimate the cost-effectiveness of the intervention compared with usual care. The analysis will follow a NICE 'reference case', with costs estimated from a healthcare perspective and outcomes quantified using Quality Adjusted life Years (QALYs).

The 'within-trial' analysis will be conducted using data on healthcare use, mortality and health-related quality of life ('utility'); covering the period from randomisation to 90 days post-surgery. Utility will be measured with the patient-reported **EQ-5D-5L questionnaire**, at baseline, 7, 30 and 90 days post-operative. After the first 100 patients have been recruited, it will be examined whether an EQ-5D-5L taken at 30 days post-surgery is both useful and a reasonable patient burden. If so, we will continue to collect EQ-5D-5L at this timepoint.

Intervention costs will be estimated, including: practitioner training time; practitioner time for delivery of the initial consultation, telephone follow-up and liaison with local services (also see 'Study Observations and Procedures' table). Participants in both groups will be asked about use of related NHS services before surgery, including changes to medication for diabetes, consultations with GP, dietitian or other clinicians, and participation in lifestyle interventions, such as exercise referral schemes (also see 'Study Observations and Procedures' table). It is important to collect this information for both study groups, to estimate the net cost to the NHS of delivering the intervention. Hospital care or treatment for any surgical complications will be collected in the CRF. For study efficiency, and to minimise burden on the participants, post-discharge data will not be collected on healthcare use from participants, although total NHS costs will be estimated in the modelling approach described below. Unit costs for all staff and services will be obtained from routine national sources (NHS Reference Costs, PSSRU estimates and BNF or Drug Tariff for medications).

Methods of analysis for the economic trial data will be pre-defined alongside the statistical analysis plan. QALYs will be estimated from EQ-5D-5L and mortality data, using the area-under-the-curve method. Similarly, costs will be estimated at the patient level. Mean between-group differences in QALYs and costs will be estimated using a regression-based approach, including adjustment for baseline covariates and interaction terms for pre-defined sub-groups, and allowing for clustering at hospital and/or practitioner level. Results will be presented as an

Incremental Cost-Effectiveness Ratio (ICER) if appropriate. Non-parametric bootstrapping will be used to estimate confidence intervals around estimated cost differences and ICERs.

A simple modelling approach will be also be used to estimate the costs and health impacts of surgical complications over a lifetime horizon. This long extrapolation is necessary to reflect any mortality or lasting quality of life decrement associated with surgical complications. There will be no attempt to estimate the long-term impact of improved diabetes management related to the intervention, as it will be difficult to predict the duration over which any improvements will be maintained. This is likely to be a conservative assumption that will under-estimate the QALY gain and cost-effectiveness of intervention if it proves to be effective. Model parameters will be estimated from the trial and from other published sources. Long-term resource use, mortality and utility decrements associated with key surgical complications, will be identified by systematic review of HTAs, NICE guidelines and published literature.

Permission to use the EQ-5D measure has been granted by the EuroQol Research Foundation.

7.6 QUALITATIVE & PSYCHOSOCIAL OUTCOMES

In addition to the descriptive, biomedical and physiological data collected and analysed, qualitative interviews and validated psychosocial measures will be used to understand and explore:

- Participants' experiences of the intervention and health professionals' views about delivering it.
- The perceived benefits of the intervention from participants' and health professionals' perspectives; and, their recommendations for future refinements.
- Any changes participants make to their diabetes self-management practices and treatment goals after receiving the intervention and 90 days after surgery, and why.
- Whether there are any site-specific differences in how participants self-manage their diabetes after receiving the intervention, and why.

7.6.1 Interviews

Qualitative interviews with participants, those who decline to participate/drop out and healthcare professionals will explore perceptions and experiences of the intervention and how it might be improved. Treatment fidelity will be maintained by including all content to be covered on checklists, assessed by intervention access/usage and examining any diversions from the protocol.

7.6.1.1 Participant interviews

Fifty participants receiving the intervention will be recruited across all participating sites. Purposive sampling will be used so that there is diversity in terms of age, gender, diabetes duration, treatment type and occupation in the final sample. Baseline interviews will take place within 2 weeks of participants' commencing the intervention and will explore their experiences; any changes made to their diabetes self-management practices, and why; short- and long-term treatment goals and the reasons for these; and perceived barriers and facilitators to achieving these goals. These interviews will also include detailed exploration of participants' historical diabetes management practices; previous contact with health professionals and diabetes management programmes; and, their everyday work and family lives. After the first 3-4 interviews have been conducted, these interviews will be reviewed so that revisions can to be made to the topic guide if these are required.

After all baseline interviews have been completed, the team will undertake an interim analysis and then meet to: (a) discuss preliminary findings; (b) agree on a coding frame; and (c) develop and agree on a topic guide for the follow-up interviews.

The follow-up interviews will be conducted with the same participants at 90 days post-surgery to explore whether, how and, why, their diabetes self-management practices and treatment goals have changed in the intervening period; and, any perceived barriers to achieving future changes and goals. The interviews will also explore participants' information and support needs and whether, and in what ways, the intervention and follow-up care could be changed or improved.

Both interviews may be audio-recorded and brief quotations may be included in study reports. Nobody will be able to identify any participant in these reports. Audio-recordings and subsequent transcripts of the interviews will be stored for up to 15 years after the end of this study for research review purposes and will be held securely.

7.6.1.2 Health professional interviews

Key personnel involved in the delivery will be interviewed once around 12 months after the start of trial in their centre[11]. Interviews will explore: previous experiences; perceived benefits as compared to routine care; experiences of, and views about the intervention; barriers and facilitators to intervention delivery; perceived impact of the intervention on participants' diabetes self-management practices; and, any suggested improvements for future use.

Data analysis will commence as soon as data collection begins. Regular meetings will be held between the team to discuss preliminary findings, make refinements to the topic guides if required and to agree on a coding frame. A thematic approach will be used to analyse the data, the purpose of which is to look for, and understand, patterns and experiences which cut across different people's accounts and the reasons for these. Key aspects of the analysis will include: (a) comparisons between participants' baseline and follow-up interviews to identify changes in their perceptions, experiences and diabetes self-management practices over time, and the reasons for these; (b) comparison of participant and health professional accounts to identify similarities and differences in their understandings and any impact on diabetes self-management practices; (c) cross-comparison of participants' accounts to identify common issues and experiences as well differences in diabetes self-management practices between subgroups of participants (e.g. men versus women, participants of different ages etc.), and the reasons for these.

7.6.1.3 Quality procedures

Several quality procedures will be used to increase the validity and credibility. Procedures to be used are for instance: using a member check, the use of several data collection methods (triangulation), using a reflexive diary, doing the analyses by two researchers and the use of 'thick descriptions'.

The data from both the participant and health professionals interviews will be collected outside of the study database and will be analysed by qualitative researchers who are part of the study team.

[11] Please note: as the timing is independent from the study visits and will vary for each site, the health professional interviews are not included in the 'Schedule of Interventions and Procedures'.

7.6.2 Psychosocial Questionnaires

The following questionnaires will be completed by participants at baseline and at 3 months post-surgery to explore the perceived benefits of the intervention, any changes to participants' diabetes self-management and associations between psychosocial factors and the primary endpoint:

- **Diabetes Empowerment Scale (short form)**: an 8 item questionnaire assessing diabetes-related psychosocial self-efficacy. License (to be) purchased by Mapi Research Trust.
- **PAID5**: a 5 item self-reported measure of diabetes related distress with high internal consistency. Accessed from McGuire et al. (2010), permission obtained from main author.
- **Patient Health Questionnaire (PHQ-2)**: ultra-brief depression screener, variant of PHQ-9. It is not used to establish a final diagnosis or to monitor depression severity but rather to screen for depression as a 'first step' approach. Adapted from PHQ9, freely available from the public domain.
- **Brief Illness Perception Questionnaire (B-IPQ)**: a 8 item measure assessing cognitive illness representations, emotional representations, illness comprehensibility and perceived causal factors for illness. Accessed from the website, permission obtained from Elizabeth Broadbend. The final item of the B-IPQ is qualitative and will not be collected in this study.
- **Summary of Diabetes Self-Care Activities scale (SDSCA)**: a 15-item self-report questionnaire of diabetes self-management that includes items assessing the following aspects of the diabetes regimen: general diet, specific diet, exercise, blood-glucose testing, foot care, and smoking. It is a brief yet reliable and valid self-report measure of diabetes self-management that is useful both for research and practice. Permission was obtained by Oregon Research Institute.

The analysis of the questionnaire responses will aim to answer the following questions:

1. What effect does baseline score (categorised as high/low etc. as appropriate) have on study outcomes, i.e. days until considered fit for surgery?
2. What effect does the study intervention have on change in score assessed as a continuous variable from baseline to 90 days post-surgery?
3. Does the treatment work better or less well in people depending on their baseline score (categorised)?

8 REGULATORY

8.1 CLINICAL TRIAL AUTHORISATION

This study is not considered to be a clinical trial of a medicinal product, so clinical trial authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) is not applicable.

9 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the recommendations for physicians involved in research on human participants included in the WMA Declaration of Helsinki, as amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the study should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the study without giving reasons must be respected.

After the participant has entered the study, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the study for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and study follow-up without giving reasons and without prejudicing their further treatment.

9.1 SPECIFIC ETHICAL CONSIDERATIONS

Our proposal to randomise participants on the same day as the decision to proceed to surgery is unusual. However, it is believed that this is entirely justified as (i) this is a pragmatic approach, which reflects how the intervention would be used in routine practice, (ii) it is more convenient for the participants, relieving them on an additional journey to a potentially remote hospital, (iii) this approach to consent has been used previously within the European Union (12), and (iv) this approach was feasible and acceptable to participants during the intervention development study. All participants will have an opportunity to discuss the study face-to-face with a clinician before randomisation, and will able to withdraw should they change their mind.

Participants will be reassured that all personally identifiable data collected during the course of the research will be kept strictly confidential, and non-identifiable data will be shared in accordance with the University of Southampton policies. All participant data will be anonymised and stored on a database in accordance with current Data Protection Regulations. We will also seek the participant's permission to inform their general practitioner that they are taking part in this study. Documentation relating to clinical trials managed by Southampton CTU is retained for 15 years after notification of the trial's end.

9.2 ETHICAL APPROVAL

Ethical approval for this study protocol will be sought by from Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

9.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a study and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the study and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the patient information leaflet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the study with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

9.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the study. The investigator must ensure that participant's anonymity will be maintained and that their identities are

protected from unauthorised parties. On CRFs participants will not be identified by their names, but by an identification code.

10 SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the study sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

10.1 INDEMNITY

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

10.2 FUNDING

This study is funded by the National Institute for Health Research Health Technology Assessment Programme (16/25/12).

10.2.1 Site payments

The payments assigned to the study sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

This study is automatically eligible for the NIHR portfolio. This enables Trusts to apply to their comprehensive local research network for service support costs, if required.

10.2.2 Participant payments

Participants will not be paid for participation in this study but reasonable travel expenses will be refunded for trial related activities.

10.3 AUDITS AND INSPECTIONS

The study may be inspected and audited by UHS (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

11 STUDY OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group, the Trial Steering Committee and the Data Monitoring and Ethics Committee.

11.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the study.

The OCTOPuS TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

11.2 TRIAL STEERING COMMITTEE (TSC)

The TSC acts as the oversight body on behalf of the Sponsor and Funder. The TSC will meet twice a year. The majority of members of the TSC, including the Chair, should be independent of the study.

The OCTOPuS TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

11.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC) / DATA MONITORING AND ETHICS COMMITTEE (DMEC)

*(**NB** for the purposes of this protocol, IDMC and DMEC refer to the same committee, and these terms can be used interchangeably).*

The aim of the IDMC is to safeguard the interests of study participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study.

There is a theoretical risk that the intervention – especially the exercise component - may induce myocardial infarction, and hence possibly death. When participants have a myocardial infarction while on a waiting list for cardiac surgery, the most common outcome is survival with urgent revascularisation. Adverse outcomes will be collected, and the Data Monitoring and Ethics committee will be asked to review myocardial infarction rates and deaths for participants enrolled in the trial. If the DMEC believes that the intervention is causing excessive morbidity and mortality they will recommend stopping the trial.

The OCTOPuS DMEC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the IDMC, including the timing of meetings, methods of providing information to and from the IDMC, frequency and format of meetings, statistical issues and relationships with other trial committees.

12 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data are pseudo-anonymised by assigning each participant a participant identifier code which is used to identify the participant during the study and for any participant-specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Informed Consent Form will specify the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). eCRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The laboratory reports (original or copies) must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the study specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created.

Data queries will either be automatically generated within the eCRF, or manually raised by the study team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the study after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Request will be considered on a monthly basis.

Please note that the qualitative interview data will be not be collected as part of the study database.

12.1 DATA SHARING

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process for results that are available in the public domain. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

13 MONITORING

13.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at SCTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to SCTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

The DMEC also have responsibility for specific central monitoring activities, as described in protocol section 11.3.

13.2 CLINICAL SITE MONITORING

Monitoring will be completed as per the trial monitoring plan.

13.2.1 Source Data Verification

On receipt of a written request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to study staff and departments.

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the study, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the study site.

13.3 SOURCE DATA

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

14 RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure the PI will maintain all source documents and study related documents. All source documents will be retained for a period of 15 years following the end of the study.

Sites are responsible for arching the ISF and participant's medical records. The Sponsor is responsible for archiving the TMF and other relevant documentation.

15 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual investigators may not publish data concerning their participants that are directly relevant to questions posed by the trial until the Trial Management Group (TMG} has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

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17 APPENDICES

17.1 APPENDIX 1- PROGRESS GRADING

Table 1 – Actions to be taken depending on progress grade

Grade	Action
Green	Continue trial, keeping an eye on accrual.
Amber	Working with governance committees (TSC, TMG, PPI Committees), seek root cause for under performance. Consider whether these can be mitigated through work with organisations or individuals within the study.
Red	Review the study with governance committees, taking steps as detailed under amber, but also explicitly considering recommending study closure.

Table 2 - Progress grading time points and criteria

Assessment Point	Green	Amber	Red
After 100 patients have had surgery (50 intervention and 50 control)	HbA_{1c} reduction in intervention group > 5mmol/mol	HbA_{1c} reduction in intervention group < 5mmol/mol	HbA_{1c} reduction in intervention group not consistent with physiological effect
6 complete months after 1st recruiting site has opened	≥ 8 centres have recruited at least one participants and ≥ 50 participants have been recruited and At least 10 participants have completed their OCTOPuS intervention and have either received surgery, or have had their surgery cancelled or postponed for either clinical or operational reasons.	One or two criteria in green column met	No criteria in green column met
12 complete months after 1st recruiting site has opened	≥ 12 centres have recruited at least one patient and At least 50 participants have completed their OCTOPuS intervention and have either received surgery, or have had their surgery cancelled or postponed for either clinical or operational reasons.	Only one criterion from green column met	No criteria on green column met
End of month 15 of recruitment	The mean recruitment rate across the trial in months 13, 14, and 15 following the opening of the first recruiting centre is compatible	The mean recruitment rate across the trial in months 13, 14, and 15 following the opening of the first recruiting centre is compatible	The mean recruitment rate across the trial in months 13, 14, and 15 following the opening of the first recruiting centre is not

	with completing recruitment by the end of month 27 of recruitment	with achieving 75% or more of target recruitment by the end of month 27	compatible with achieving at least 75% of target recruitment by the end of month 27

18 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes