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# The Optimising Cardiac Surgery ouTcOmes in People with diabeteS (OCTOPuS) randomised controlled trial to evaluate an outpatient pre-cardiac surgery diabetes management intervention: a study protocol

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## ABSTRACT

**Introduction** Cardiothoracic surgical outcomes are poorer in people with diabetes compared with those without diabetes. There are two important uncertainties in the management of people with diabetes undergoing major surgery: (1) how to improve diabetes management in the weeks leading up to an elective procedure and (2) whether that improved management leads to better postoperative outcomes. We previously demonstrated the feasibility of delivering the Optimising Cardiac Surgery ouTcOmes in People with diabeteS (OCTOPuS) intervention, an outpatient intervention delivered by diabetes healthcare professionals for people with suboptimally managed diabetes over 8–12 weeks before elective cardiac surgery. The present study will assess the clinical and cost-effectiveness of the intervention in cardiothoracic centres across the UK.

**Methods and analysis** A multicentre, parallel group, single-blinded 1:1 individually randomised trial comparing time from surgery until clinically fit for discharge in adults with suboptimally managed type 1 diabetes or type 2 diabetes undergoing elective surgery between the OCTOPuS intervention and usual care (primary endpoint). Secondary endpoints will include actual time from surgery to discharge from hospital; days alive and either out of hospital or judged as clinically fit for discharge; mortality; time on intensive therapy unit (ITU)/ventilator; infections; acute myocardial infarction; change in weight; effect on postoperative renal function and incidence of acute kidney injury; change in $HbA_{1c}$; frequency and severity of self-reported hypoglycaemia; operations permanently cancelled for suboptimal glycaemic levels; cost-effectiveness; psychosocial questionnaires. The target sample size will be 426 recruited across approximately 15 sites. The primary analysis will be conducted on an intention-to-treat population. 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% CIs.

**Ethics and dissemination** The trial was approved by the South Central–Hampshire A Research Ethics Committee (20/SC/0271). Results will be disseminated through conferences, scientific journals, newsletters, magazines and social media.

**Trial registration number** ISRCTN10170306.

## Strengths and limitations of this study

- The Optimising Cardiac Surgery ouTcOmes in People with diabeteS (OCTOPuS) intervention was developed according to the Medical Research Council (MRC) framework for complex interventions and successfully piloted in a single cardiothoracic surgical centre.
- This is the first trial to assess whether early contact with a specialist diabetes team in the weeks leading up to surgery improves cardiothoracic surgical outcomes and reduces the excess morbidity and mortality experienced by people with diabetes.
- Hospital length of stay is an important clinical and economic measure of the success of surgery.
- The sample size and number of sites will mean that the results are sufficiently generalisable to the remaining cardiothoracic centres across the UK.
- The start of the study will likely be delayed by COVID-19 because of the effect of the pandemic on elective surgery.

## INTRODUCTION

The prevalence of cardiovascular disease is increased approximately twofold in people with diabetes after adjustment for other cardiovascular risk factors.[1] It affects approximately a third of all people with type 2

diabetes and contributes to over 50% of deaths.[2] As coronary heart disease in people with diabetes tends to be more diffuse affecting multiple vessels, coronary artery bypass grafting is often the preferred method for revascularisation. Approximately 30%–40% of all people undergoing open cardiac surgery have diabetes.[3]

Surgical outcomes are worse in people with diabetes, with an up to threefold higher risk of postoperative complications which include poor healing, wound complications and renal dysfunction.[4 5] These complications are associated with longer hospital stay and higher readmission rates. The reasons underlying the poorer outcomes include hyperglycaemia, dyslipidaemia and obesity. Although national and international groups have published detailed guidelines to improve surgical outcomes in people with diabetes, many people with diabetes are poorly prepared for surgery.[6–8] In the European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG) study, 54% of people with type 2 diabetes treated with non-insulin medications and 67% of those with insulin-treated diabetes had an $HbA_{1c}$ above 53 mmol/mol (7.0%) prior to cardiac surgery.[5]

There are two important uncertainties in the management of people with suboptimally managed diabetes undergoing major surgery: (1) how to improve diabetes management in the weeks leading to elective surgery and (2) whether that improved management is reflected in better surgical outcomes. To address these gaps, the overarching aim of the Optimising Cardiac Surgery ouTcOmes in People with diabeteS (OCTOPuS) project is to develop and test whether a preoperative outpatient intervention to improve diabetes management improves cardiac surgical outcomes.

The development of the intervention is described in detail elsewhere (Holt *et al*,[9] Under review). In summary, the prototype OCTOPuS intervention was based on a nurse-led outpatient intervention that has been used in Royal Bournemouth Hospital for 7 years and incorporated the findings of two rapid literature reviews. A feasibility study conducted in 17 people with diabetes undergoing cardiothoracic surgery at the University Hospital Southampton showed that it is possible to develop a clinical pathway to deliver the OCTOPuS intervention to improve glycaemic management prior to admission that was acceptable for people with diabetes and clinicians.

The present study will be a multicentre randomised controlled trial (RCT) in cardiothoracic centres across the UK to assess the clinical and cost-effectiveness of the intervention.

## METHODS AND ANALYSIS

### Study design

OCTOPuS is a multicentre, parallel group, single blind, individually randomised controlled trial incorporating a preplanned futility analysis. It will compare time from surgery until an individual is clinically fit for discharge in adults with suboptimally managed type 1 diabetes or type 2 diabetes undergoing elective cardiothoracic surgery between the OCTOPuS intervention and usual care. The provisional planned trial recruitment dates are 1 September 2021–31 August 2023. These are contingent on the reopening of elective cardiothoracic surgery and research capacity following the latest national COVID-19 lockdown.

### Eligibility

#### Inclusion criteria

1. Aged ≥18 years old with type 1 diabetes or type 2 diabetes.
2. Suboptimally managed diabetes defined as an $HbA_{1c}$ >53 mmol/mol (7%) for those ≤75 years old and an $HbA_{1c}$ >64 mmol/mol (8%) for those >75 years old. The higher $HbA_{1c}$ criterion for older people is to minimise the risk of iatrogenic hypoglycaemia.[10] $HbA_{1c}$ will be measured using a near patient test at the cardiothoracic 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 a hospital participating in the trial.
6. Ability to give informed consent.
7. Ability to interact with the study documentation and processes.

#### Exclusion criteria

1. Active malignancy, where the malignancy is currently being treated by chemotherapy, surgery or radiotherapy or is likely to cause death within 6 months.
2. Pregnancy.
3. Previous cardiac surgery.
4. Known haemoglobinopathies that affect the measurement of $HbA_{1c}$.
5. Other illnesses or conditions that would preclude engagement with the OCTOPuS intervention.
6. Surgery taking place outside the participating hospitals, for example, at a private hospital.

### Recruitment

#### Screening and consent

Outpatient cardiac surgery appointment clinic lists will be scrutinised ahead of appointments and an information sheet explaining the trial will be sent by post or email as appropriate to people who appear eligible (including contact details to opt out if the person does not want further contact about the trial). Before the outpatient appointment, a researcher will contact the prospective participant to discuss the study at least 24 hours before the appointment allowing time for reflection and discussion. This will permit eligible individuals to be randomised immediately after the outpatient appointment, and where possible receive their first OCTOPuS consultation, on the same day. The treating surgeon will remind eligible patients about the trial if a decision to proceed

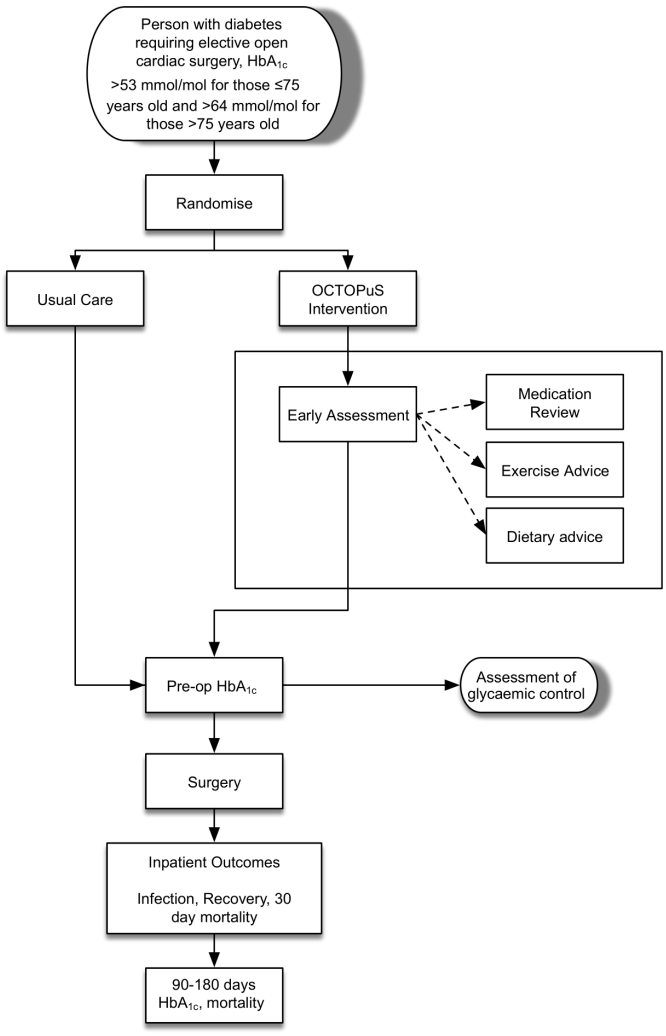


**Figure 1** OCTOPuS (Optimising Cardiac Surgery ouTcOmes in People with diabeteS) study flowchart.

to surgery is made. If the person wishes to participate, he or she will have the opportunity to discuss the study face-to-face with a research nurse before they give written consent. Final eligibility criteria will be checked prior to recruitment. Patients whose medical records cannot be accessed prior to the appointment to determine eligibility (eg, patients from another hospital) will be given information about the study on the day of the appointment and will be offered the opportunity to attend another day to discuss participation.

### Randomisation

Participants will be individually randomised in a 1:1 ratio, stratified by centre and age (≤75 and >75 years old), using permuted blocks. The study flow is illustrated in figure 1.

## Study procedures

### Baseline measurements

After randomisation, the following data will be collected on participants in both arms: medical history and examination; vital signs; biochemistry; self-reported episodes of hypoglycaemia.

### The OCTOPuS intervention

#### *Initial consultation*

Participants randomised to receive the OCTOPuS intervention will have an initial consultation with an OCTOPuS practitioner, who may be a doctor, nurse, pharmacist or other appropriately trained healthcare professional. In this consultation, the participant's diabetes management will be discussed, as well as the likely benefits of improved glycaemic management prior to surgery. The practitioner and participant will agree actions, tailored to the individual needs and ability, including the following:

- A graded exercise regimen. This may be completely self-delivered, or alternatively by joining a local appropriate exercise scheme, such as a 'health walk'.
- 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 and the treatment options are set out in the OCTOPuS intervention manual (online supplemental material 1).

#### *Support calls*

After the initial consultation, participants will receive regular review with an OCTOPuS practitioner, usually by telephone, at least once a fortnight until the participant's diabetes management goals have been reached and no further changes are needed. After this, the frequency of the calls can be reduced at the discretion of the OCTOPuS practitioner and participant to a minimum of every 6 weeks. This contact 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 1–3 weeks after discharge to ensure the continuity of diabetes management beyond surgery. Where necessary, the OCTOPuS practitioner will liaise with local services, for example, the participant's GP or a dietitian, to facilitate delivery.

### Control arm

Participants in the control arm will receive usual care in the cardiac surgery centre attended by the individual. This is likely to contain standardised brief advice from the surgeon to pay attention to their diabetes prior 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.

### Follow-Up visits

After participants are randomised to either the intervention or control arm, data will be collected from them at the following timepoints: presurgery; discharge; 7 days postsurgery; 30 days postsurgery; and at their next routine diabetes care visit between 90 and 180 days postsurgery. In addition to the baseline measures, information about the surgery, infections and surgical complications, mortality and adverse events will be collected (table 1). Presurgery, surgery and discharge data will be collected in hospital. After discharge, data will be collected remotely, for example, over the phone, by post, through inpatient note review or where possible using adult cardiac surgery databases (eg, the SCTS National Adult Cardiac Surgery Audit).

## Endpoints

### Primary endpoint

Time from surgery until clinically fit for discharge, as judged by the surgical team. Teams will be blinded to prehospital 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.

### Secondary endpoints

- Time from surgery to actual discharge from hospital—this recognises that discharge can be delayed for nonclinical reasons.
- Days alive between surgery and either out of hospital or judged as clinically fit for discharge.
- Preoperative mortality; 30-day mortality; 90-day mortality.
- Time on ITU.
- Time on a ventilator.
- Sternal wound infections, defined according to the National Institute for Health and Care Excellence (NICE) guidance and the Centers for Disease Control and Prevention (CDC) criteria.[11 12]
- Leg wound infections, in those who provide donor veins; graded according to the CDC definitions of surgical site infections.[13]
- 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.[13]
- Change in weight between randomisation and surgery.
- Effect on postoperative renal function and incidence of acute kidney injury as assessed by measurement of serum creatinine and calculation of estimated glomerular filtration rates.[13]
- $HbA_{1c}$ 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 suboptimal glycaemic management.
- Frequency and severity of self-reported overall, minor, severe and nocturnal hypoglycaemia assessed at baseline, during the Support Contact and Pre-surgery.[14]
- EQ-5D at baseline, 7, 30 and 90 days postsurgery.
- Qualitative interviews and psychosocial questionnaires at baseline and 90 days postsurgery to explore participants' experiences and perceived benefits of the intervention and any changes to their diabetes self-management.
- Cost-effectiveness of intervention, including use of NHS lifestyle improvement programmes and diabetes services; use of medication, time spent by practitioners for training, delivering the intervention and liaising with local services; $HbA_{1c}$ point-of-care and blood glucose monitoring costs.

## Sample size

### Futility assessment: physiological effect of intervention

To demonstrate that a physiological response is plausible, we need to show an $HbA_{1c}$ reduction of 5 mmol/mol in the intervention group presurgery compared with baseline. Previous experience shows the mean initial $HbA_{1c}$ in our study population is approximately 72 mmol/mol, with a SD of 15 mmol/mol.[15 16] For an expected change in $HbA_{1c}$ from baseline of 5 mmol/mol in the intervention group, and assuming a correlation of 50% between baseline and presurgery, a sample size in the intervention group of 50 participants would allow a margin of error of 4.16 below the mean for a 95% CI and would, therefore, allow us to exclude a difference of zero if the treatment difference of 5 was observed.

### 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 many elective cardiothoracic surgical patients remain 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 postsurgery until clinically fit for discharge is 7 days, with an SD 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 V.7.0). We will allow for a 5% loss to follow-up, and 5% for deaths post randomisation inflating the final target sample size to 426 participants. Participants will be recruited across approximately 15 UK cardiothoracic centres.

**Table 1** Summary of data collection during the OCTOPuS study at various timepoints

| Timepoint | Screening | Consent | Baseline | Intervention | Support calls (every 2–6 weeks post-op) | Presurgery assessments | Surgery | Discharge | Surgery +7 days | Post-discharge support call | 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 examination (incl. height, weight and waist circumference) | | | X (height will only be recorded at baseline) | | | X | | | | | | | |
| Vital signs (incl. BP) | | | X | | | X | | | | | | | |
| Biochemistry (incl. $HbA_{1c}$, blood glucose and renal function) | | | X | | | X | | X (only serum creatinine and renal function to capture acute kidney failure) | | | | X (between 90–180 days post-op) | |
| 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 components of intervention used) | | | | | X | | | | | x | | | |
| Practitioner time (cost-effectiveness) | | | X | X | X | | | | | X | | | |
| NHS resource use questions (cost-effectiveness) | | | | | | X | | | | | | | |
| Surgery (incl. time on ventilator/ITU) | | | | | | | X | | | | | | |
| Blinded assessment | | | | | | | | X | | | | | |
| Adverse events | | | X | X | X | X | | | X | X | X | X | X |

Continued

**Table 1** Continued

| Timepoint | Screening | Consent | Baseline | Intervention | Support calls (every 2–6 weeks post-op) | Presurgery assessments | Surgery | Discharge | Surgery +7 days | Post-discharge support call | Surgery +30 days | Surgery +90 days | End of study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EQ-5D-5L | | | X | | | | | | X | | X | X | |
| Participant qualitative interview | | | X | | | | | | | | | X | |
| Psychosocial questionnaires | | | X | | | | | | | | | X | |

BP, blood pressure; ITU, Intensive therapy unit; NHS, National Health Service.

## Interim analysis

Futility will be assessed, and the trial could be stopped early for one of two main reasons:

### Recruitment and delivery

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

- Being unable to recruit and initiate sufficient centres.
- Centres being unable to recruit sufficient participants.
- Centres being unable to deliver the OCTOPuS intervention.

Therefore throughout the trial, we will review progress against criteria at three timepoints, grading trial progress as red, amber or green each time (online supplemental material 2).

### Physiological effect of intervention

It is believed that the OCTOPuS intervention will have its clinically relevant effects through improvement of clinical measures, including change in body weight, exercise, lipid profile and blood pressure. However, the main target of the intervention is to improve glycaemic management; if no physiological effect can be demonstrated on glycaemic measures, continuation of the trial would be considered futile. After the first 100 participants have had their surgery, we will assess the effect of the intervention on preoperative $HbA_{1c}$. If there is no discernible effect (defined as a change of $HbA_{1c}$ of <5 mmol/mol), we will ask the trial steering committee to review the trial's viability.

## Statistical analysis

Baseline participant demographics and characteristics will be summarised between the two arms.[17] The primary analysis will be conducted using analysis of covariance (ANCOVA) adjusted for randomisation stratification factors on an intention-to-treat population. Continuous data will be presented as means and SD 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 ORs 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% CIs. 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 preoperative glycaemic management. 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 fit for discharge and thus not meet the primary endpoint. It is expected that these events will occur in fewer than 5% of participants. 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 to assess if there is an excess of any of these outcomes in either group. A sensitivity analysis will be considered, looking at a competing risks model, where these outcomes and functional recovery are competing risks. This sensitivity analysis will also be performed if the total prevalence of these events exceeds 5%.

## Economic evaluation

Quality-adjusted life years (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 predefined subgroups, 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 CIs around estimated cost differences and ICERs.

A simple modelling approach will also be used to estimate the costs and health impacts of surgical complications over a lifetime horizon. This 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 underestimate the QALY gain and cost-effectiveness of intervention if it proves 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.

## Qualitative and psychosocial evaluation

### Interviews

Fifty participants receiving the intervention will be recruited across all participating sites balanced for age, gender, $HbA_{1c}$, socioeconomic status and ethnicity. Baseline interviews will take place within 2 weeks of participants' starting the intervention and follow-up interviews will be conducted with the same participants at 90 days postsurgery. Key personnel involved in the delivery will be interviewed once around 12 months after the start of trial in their centre.

Interview data analysis will include (1) 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; (2) comparison of participant and health professional accounts to identify similarities and differences in their understandings and any impact on diabetes self-management practices; (3) cross-comparison of participants' accounts to identify common issues and experiences as well differences in diabetes self-management practices between subgroups of participants (eg, men vs women, participants of different ages, etc), and the reasons for these.

### Psychosocial questionnaires

The following questionnaires will be completed by participants at baseline and at 3 months postsurgery:

- Diabetes Empowerment Scale (short form): an 8-item questionnaire assessing diabetes-related psychosocial self-efficacy.
- PAID5: a 5-item self-reported measure of diabetes-related distress with high internal consistency.
- 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.
- Brief Illness Perception Questionnaire (B-IPQ): an 8-item measure assessing cognitive illness representations, emotional representations, illness comprehensibility and perceived causal factors for illness.
- 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.

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, that is, 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 postsurgery?
3. Does the treatment work better or less well in people depending on their baseline score (categorised)?

## SAFETY

Standard definitions and reporting procedures of adverse events, serious adverse events (SAEs), seriousness will be used (online supplemental material 3). For the purposes of this study, the following SAEs will not require reporting to Southampton Clinical Trials Unit:

- Hospitalisations for elective treatment of a pre-existing condition.

Also, the following SAEs will not require reporting if they occur between 'Surgery' and 'Discharge':

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

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

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

## PATIENT AND PUBLIC INVOLVEMENT

The trial has been developed in collaboration with the study patient and public involvement advisory group and local branch of Diabetes UK. The trial includes two patient representatives as a member of the Trial Steering Committee (TSC) and a member of the Trial Management group. Both individuals have been involved in the development of this protocol and have attended meetings regularly. To date, they have had an active role in assessing the study progress to date and both will be involved in resolving any issues that may arise.

## ETHICS

Ethics approval was obtained by the South Central–Hampshire A Research Ethics Committee on 25 August 2020 (20/SC/0271). University Hospital Southampton NHS Foundation Trust will sponsor the study (RHM MED1718). The study is funded by the National Institute of Health Research *Health Technology Assessment* (*HTA*) Programme (16/25/12). The day-to-day management of the trial will be coordinated through the Southampton Clinical Trials Unit and oversight will be maintained by the Trial Steering Committee. The study will be conducted in accordance with WMA Declaration of Helsinki and as revised and recognised by governing laws and EU Directives.

All participants may withdraw at any time without providing a reason. Investigators will explain 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 will revert to standard clinical care. The study team will continue to collect standard follow-up data unless the participant explicitly states otherwise.

## DISSEMINATION

Results will be disseminated through national and international conferences, scientific journals, newsletters, magazines and social media. Target audiences include diabetes specialist teams, cardiac surgeons, primary care team and medical professionals or scientists overall, as well as people with diabetes. This study addresses an important clinical question and is the first to assess whether early contact with a specialist diabetes team in the weeks leading up to surgery improves cardiothoracic surgical outcomes and reduces the excess morbidity and mortality experienced by people with diabetes. We further believe that the sample size and number of sites will mean that the results are sufficiently generalisable to broader cardiothoracic practice across the UK and internationally.

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**Contributors** RIGH is the chief investigator of the OCTOPuS study. He wrote the first draft of the protocol and will act as guarantor for the study. GD and ED will be the trial managers. GD further had significant contribution in editing and finalising the paper. KB-K and LC wrote the qualitative sections of the protocol. KT and AW wrote the statistical and data analysis sections of the protocol. AW was also involved in the original grant application and the design of the study. MP, PN-J and MG were involved in the design of the study. MP will lead the 'clinical' OCTOPuS intervention team and PN-J and MG will be members of the team. HP was involved in the design of the study and intervention. SL and SO were involved in the design of the study from the cardiothoracic perspective. JL wrote the health economics aspects of the protocol. JN is a patient representative on the trial management team and supported the development of the protocol. AC is associate director of the Clinical Trials Unit and was involved in the design of the study. KS was involved in the original grant application and the design of the study. All authors have critically revised the paper for intellectual content and approved the final draft. All authors agree to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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OCTOPuS

Optimising Cardiac Surgery ouTcOmes in People with diabeteS

# OCTOPUS Intervention Manual

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## OCTOPuS Intervention Manual

Welcome to the OCTOPuS Intervention Manual

The OCTOPuS intervention has been designed for people with diabetes who have been listed for cardiac surgery involving a sternotomy. The aim of the intervention is to improve diabetes control in the run up to surgery, with the goal of improving the surgical and post-surgical experience. Although the focus of the intervention is to improve glucose control, the intervention also includes the management of other aspects of diabetes, such as weight, that are known to affect surgical outcomes.

The intervention begins once an individual has been accepted for cardiac surgery and continues until the individual has had their cardiac surgery or the surgery is cancelled. Following discharge or if the surgery is cancelled, an individual's diabetes care will revert to their usual care prior to listing for surgery.

The OCTOPuS intervention will be tested in a randomised controlled trial, funded by the National Institute for Health Research Health Technology Assessment programme.

It is hoped that if the intervention is successful in improving surgical outcomes, it can be implemented in the National Health Service and adapted for other major surgery.



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## Change Control

| Date | Version | Activity | Who |
|---|---|---|---|
| **19th Dec 2018** | 2 | Clarification on how many support calls are required. | Liz Dixon |
| **15th August 2019** | 3 | Clarification on timing of intervention and managing surgical queries. | Liz Dixon |
| **14th October 2019** | 4 | 1. Additional support call post-surgery<br>2. Note regarding retinopathy | Giorgos Dritsakis, Richard Holt |
| **16th January 2020** | 5 | Changes regarding frequency of telephone calls and HbA1c measurement | Richard Holt |
| **9th June 2020** | 6 | Addition of remote initial consultation option | Richard Holt |
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Southampton Clinical Trials Unit

## Contents



## Figures



## Tables





Holt RIG, *et al. BMJ Open* 2021; 11:e050919. doi: 10.1136/bmjopen-2021-050919



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# 1 About OCTOPuS and this manual

## 1.1 What is the OCTOPuS Intervention?

The OCTOPuS intervention is a set of elements, designed to improve the management of a person with diabetes over the weeks preceding scheduled major surgery. The components of the OCTOPuS intervention represent current best clinical practice and are endorsed by NICE or other guidelines. Suitably qualified and trained clinicians will deliver OCTOPuS.

The planned randomised evaluation (see Appendix 1) has been designed to assess the use of the OCTOPuS intervention for people with inadequately controlled diabetes undergoing cardiothoracic surgery, and this manual assumes that setting.

## 1.2 Why is the OCTOPuS intervention needed?

There are approximately 4 million people living with diagnosed and undiagnosed diabetes mellitus in the UK. Since 1996, the number of people diagnosed with diabetes has increased from 1.4 million to around 3.5 million. Diabetes increases the risk of cardiovascular disease by approximately two 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.

The increasing number of people with diabetes will increase the demand for cardiac surgery in the future. These individuals have longer lengths of hospital stay and higher re-admission rates, placing a large financial burden on the NHS.

Poor glycaemic control increases the risk of wound and chest infections, renal impairment and death, especially following cardiac surgery. The Joint British Diabetes Societies for in-patient care has provided recommendations to improve the management of adults with diabetes undergoing surgery. As poor peri-operative glycaemic control is associated with an increased risk of all surgical complications, the guidelines recommend improving glycaemic control to optimise surgical outcomes.

Hyperglycaemia, however, does not wholly explain poorer surgical outcomes of people with diabetes; other important risk factors, such as obesity, hypertension and dyslipidaemia, are also more common in people with diabetes. Furthermore, lack of knowledge and training of the nursing and medical teams might also contribute.

If the pre-operative intervention is successful in improving glycaemic control and addressing other risk factors, this may reduce the complication rate and improve the clinical outcomes. It may also prove cost effective and even cost saving.



Holt RIG, *et al. BMJ Open* 2021; 11:e050919. doi: 10.1136/bmjopen-2021-050919

### 1.3 Who is the OCTOPuS intervention for?

The intervention can be offered to any person with sub-optimally controlled diabetes, which is defined as an $HbA_{1c}$ >53 mmol/mol (>7%) using a point-of-care test at the cardiothoracic outpatient appointment where the decision to proceed to surgery is made.

The intervention described here assumes there is a period of at least 10 to 12 weeks before the scheduled surgery, but patients may derive benefit from a shorter intervention. In some circumstances, surgery may be delayed beyond 12 weeks. In this instance the pre-operative OCTOPuS intervention should continue until the patient is admitted surgery.

OCTOPuS is not suitable for people with malignancy, women who are pregnant or those with other illnesses or conditions that would preclude engagement with the intervention.

### 1.4 When should this manual be used?

The OCTOPuS intervention should begin as soon as possible after an individual has been accepted for cardiac surgery. The intervention continues until the individual has had their cardiac surgery or the surgery is cancelled. Following discharge or if the surgery is cancelled, an individual's diabetes care will revert to their usual care prior to listing for surgery.

### 1.5 About this manual

This manual describes the OCTOPuS intervention. At the time of writing, the intervention is still under development. The latest version of the manual can be obtained from the SCTU website (www.southampton.ac.uk/ctu) or from the OCTOPuS trial manager (octopus@soton.ac.uk).

This section has described the background and justification for the intervention.

Section 2 describes the components of the intervention, with a discussion of how each component might be delivered individually.

Section 3 discusses how these components are brought together and delivered as a coherent intervention.





## 2 The OCTOPuS Intervention

In this section, we describe the individual components of the intervention. How these components are tied together and delivered to the patient is described in section 3.

The OCTOPuS intervention comprises several elements, which are brought together in a systematic way. It is the role of the OCTOPuS practitioner to work with the patient awaiting surgery to decide which elements of the programme are applicable to the individual.

The recommendations in this manual represent the views of the OCTOPuS research team and are presented after careful consideration of the evidence and currently available NICE and international guidelines. When making treatment decisions with the participants, OCTOPuS practitioners are expected to take this manual into account, alongside the individual needs, preferences and values of their trial participants. It is not mandatory to apply the recommendations in the manual, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Given the short duration of the intervention and limited number of contacts, it may not be feasible to implement all actions and changes suggested by this manual. The OCTOPuS practitioner should work with the patient to implement as much as possible, planning to bring the patient to the best clinical status prior to surgery, but not delaying the planned surgical procedure in order to deliver OCTOPuS.

The sections below provide guidance in how to decide which elements might benefit each individual and guide the decision-making process. In general, the management below should follow NICE guidance for the management of diabetes, hypertension, dyslipidaemia and obesity unless specifically described otherwise.

### 2.1 The OCTOPuS practitioner

The OCTOPuS practitioner is a clinically qualified health care worker with expertise in diabetes. They are most likely to be a diabetes nurse specialist, but might, for example, be a pharmacist, dietitian or physician. The OCTOPuS practitioner will receive additional specific training about the OCTOPuS intervention.

Once a plan has been agreed, the practitioner supports the patient through regular contact (at least fortnightly until optimised), encouragement and counselling, signposting, and referral to key services.

Each practitioner will work with several patients awaiting surgery, providing initial advice, then remote telephone follow-up over the 3 months or so until the cardiac procedure. The OCTOPuS practitioner will need to provide advice about medication regimens, direct patients to local services, to advocate on patient's behalf, and to provide a listening ear to the patient.

### 2.2 Glucose Management

All patients eligible for the intervention will have an $HbA_{1c}$ of >53mmol/mol (7.0%) and may benefit from improved glucose control. The challenge is to improve control without inducing episodes of hypoglycaemia, or excessive weight gain. The decision to intensify therapy should be made on an individual basis; for example, a more relaxed target may be appropriate for a

person with significant co-morbidities or where the risk and consequence of hypoglycaemia are high. There is a risk of worsening retinopathy in people with existing retinopathy if there is a rapid decline in HbA1c. The OCTOPuS practitioner should enquire whether the participant has a history of retinopathy and whether their retinal screening is up-to-date. The OCTOPuS practitioner should consider retinopathy when discussing treatment changes.

Improving glucose control may require lifestyle intervention, medication change or a combination of these strategies. How they can be delivered will be determined by local policies and funding. If the OCTOPuS practitioner is able to prescribe then they may undertake any initial changes themselves; otherwise, they should make recommendations to the patient's GP or local specialist diabetes team.

The patient's diabetes management and medication should be considered at every OCTOPuS interaction. The process is outlined in this section and summarised in Figure 1 on page 13. The OCTOPuS practitioner should provide the patient with a Diabetes UK Information Prescription about glycaemic management at each visit, if appropriate, to support glycaemic management.

### 2.2.1 Glucose monitoring

If the patient is not already monitoring their blood glucose, the OCTOPuS practitioner should provide the patient with a capillary glucose monitor and sufficient strips for the duration of the intervention (approximately 100 strips). They should teach the patient how to monitor and interpret their glucose using a standardised education package. All participants with Type 2 diabetes should be given a copy of 'Your Guide to Type 2 Diabetes' education booklet produced by Diabetes UK to keep for their personal reference and use throughout the study. Where applicable, participants should be shown online software management systems such as the Accu-Chek 360° Diabetes Management System. Although glucose monitoring is not usually recommended for routine use in people not using insulin or sulfonylureas, this is an important component of the intervention as short-term improvements in glucose control may not be apparent from changes in $HbA_{1c}$ because of the short duration of the intervention.

In addition to any glucose monitoring that the patient is already undertaking prior to the intervention, patients should be advised to check their glucose levels 4 times a day (before meals and before bed) on the 3 days prior to the next OCTOPuS contact. The OCTOPuS practitioner should provide the patient with a glucose and diet diary so that the results can be recorded prior to the consultation. The OCTOPuS practitioner should encourage the patient to record what they eat in the diary so that any relationship between glucose readings and reported diet can be discussed at the consultation.

As most consultations will be remote, e.g. by telephone or Skype, where possible, the results should be sent to the OCTOPuS practitioner before the consultation, e.g. by email or Diasend (where available).

Following discussion between the OCTOPuS practitioner and patient, the glucose targets should be individualised, taking into account the risk of hypoglycaemia. However, typical glucose targets would be:

- Fasting and pre-meal glucose values: 4.0-6.0 mmol/L
- Post-meal and before bed glucose values: 4.0-7.8 mmol/L (for people using insulin who are prepared to test after meals)

### 2.2.2 Lifestyle modification

Dietary and exercise advice should follow the 2018 Diabetes UK nutritional guidelines (https://www.diabetes.org.uk/professionals/position-statements-reports/food-nutrition-lifestyle/evidence-based-nutrition-guidelines-for-the-prevention-and-management-of-diabetes). Where necessary, a healthcare professional with specific expertise and competencies in nutrition should see the patient.

Encourage high-fibre, low-glycaemic-index sources of carbohydrate in the diet, such as fruit, vegetables, wholegrains and pulses; include low-fat dairy products and oily fish; and control the intake of foods containing saturated and trans fatty acids. Encourage the patients to avoid excessive alcohol consumption.

The following leaflets may be of benefit:

**British Heart Foundation:**
Food labelling guidance: https://www.bhf.org.uk/publications/healthy-eating-and-drinking/this-label-could-change-your-life

**Weight Loss advice:**
https://www.bhf.org.uk/publications/healthy-eating-and-drinking/facts-not-fads---your-simple-guide-to-healthy-weight-loss

**Nutrition and Diet Resource**
Weight loss advice: describes 80kcal portions of different food groups so that the participants can decide how many of each they can have i.e. 1500kcal
https://www.ndr-uk.org/item/81/WeightManagement/Weight-Loss-You-Can-See-with-guidelines.html
This is a paid resource but could be useful for more visual patients

**Carbs and cals – a variety of recipes, carb values, and low calorie meal options:**
https://www.carbsandcals.com/weight-loss/weight-loss

**British Dietetic Association:**
Basic diet sheets for glycaemic index, healthy eating and weight loss
https://www.bda.uk.com/foodfacts/GIDiet.pdf
https://www.bda.uk.com/foodfacts/HealthyEating.pdf
https://www.bda.uk.com/foodfacts/Want2LoseWeight.pdf

For individuals who are overweight or obese, weight loss should be encouraged (see below).

The OCTOPuS practitioner should encourage the patient to become more physically active (see below).

### 2.2.3 Drug therapy for people with type 2 diabetes not currently receiving anti-diabetes medication

Almost all patients will need anti-diabetes drug therapy because of the elevated $HbA_{1c}$ and short window-of-opportunity to improve the glucose control. The OCTOPuS practitioner should use their clinical judgement in the choice of medication, which should be individualised in discussion with the patient. All prescribing advice should be within the drug licence and take account of the individual Summary of Product Characteristics.

In line with NICE and 2018 American Diabetes Association guidance, the first line treatment of choice is standard release metformin, unless contraindicated. Metformin should be used according to its licence. Slow release metformin can be considered if the standard released metformin is not tolerated.

Where the initial $HbA_{1c}$ is ≥75 mmol/mol (9%), consideration should be given to starting dual therapy from the outset as recommended by the 2018 American Diabetes Association guidance.

If metformin is insufficient to achieve adequate glycaemic control (as judged by capillary glucose monitoring described above), a second agent should be added. Because of the short-time scale of the intervention, it is not possible to base treatment changes on the measurement of $HbA_{1c}$ for most patients. As all patients will have existing atherosclerotic cardiovascular disease, in line with the 2018 American Diabetes Association guidance, the first treatment intensification should usually be with a drug that has proven cardiovascular benefit, e.g. an SGLT-2 inhibitor (e.g. empagliflozin or canagliflozin) or a GLP-1 receptor agonist (e.g. liraglutide), unless contraindicated. The second treatment intensification should be the other class of drug (i.e. if an SGLT2 inhibitor was the first intensification then the second should be GLP-1 receptor agonist or vice versa), unless contraindicated. OCTOPuS practitioners will need to take account of drug-specific and patient factors as well as local formulary requirements.

The 2018 American Diabetes Association guidance diverges from current NICE guidance as the latter has not yet been updated in light of the latest cardiovascular outcome trials. However, there is a need to avoid weight gain and hypoglycaemia in this group of patients and there is a need to avoid provoking cardiovascular events as occurred in the ACCORD study.

Where these drugs are contraindicated, alternative agents, such as DPP-4 inhibitors, pioglitazone or sulfonylureas, e.g. gliclazide, can be used according to NICE guidance.

If adequate glycaemic control is not achieved with three non-insulin therapies, insulin should be initiated according to NICE guidance (see below). Where the initial $HbA_{1c}$ is ≥86 mmol/mol

(10%), consideration should be given to starting insulin therapy from the outset as recommended by the 2018 American Diabetes Association guidance.

### 2.2.4 People with type 2 diabetes currently receiving oral anti-diabetes medication

Lifestyle factors, such as diet and physical activity, should be explored but it is likely that drug therapy will need to be intensified.

The OCTOPuS practitioner should explore whether the patient is taking the medication as prescribed. It is known that fewer than 50% of people receiving oral anti-diabetes treatments, antihypertensive agents and statins persist with their medication 2 years after treatment initiation and up to 20% never start treatment. The barriers to adherence should be discussed with the patient.

Where drug therapy intensification is needed, this should be done as described in the previous section 2.2.3. If the individual is on other combinations of oral anti-diabetes agents, the OCTOPuS practitioner should consider whether to change these to treatments with proven cardiovascular benefit.

#### *2.2.4.1 Commencement of Insulin in people with type 2 diabetes*

If adequate glycaemic control (judged by capillary glucose monitoring or presenting $HbA_{1c}$) is not achieved with three non-insulin therapies, insulin should be initiated according to NICE guidance. Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 units per day or 0.1–0.2 units/kg/day, depending on the degree of hyperglycaemia.

As hypoglycaemia is a major risk factor for cardiovascular events, the OCTOPuS practitioner should have a low threshold to initiate insulin analogues instead of NPH insulin because of the lower risk of hypoglycaemia seen with the use of insulin analogues.

The OCTOPuS practitioner will need to liaise with local health services to ensure that the patient is offered sufficient training to use the insulin effectively. Given the urgency of treatment, in many instances, this will need to be outside usual channels.

Intensification of insulin is usually by the addition of prandial insulin or switch to pre-mixed insulin. The options should be discussed with the patient and a management plan agreed with the patient.

### 2.2.5 People with type 2 diabetes already on insulin

The OCTOPuS practitioner should review the current insulin regimen, injection technique and sites with the patient. The OCTOPuS practitioner should offer advice about the doses and types of injection as necessary.

### 2.2.6 People with type 1 diabetes

It is likely that the OCTOPuS practitioner will see people on a variety of insulin regimens, including both multiple daily injection and insulin pump therapy. The OCTOPuS practitioner

should review the current insulin regimen, injection technique and sites with the patient. The OCTOPuS practitioner should offer advice about the doses and types of injection as necessary.

If the patient has not attended a structured education course, this should be offered where possible.

A detailed description of insulin therapy is beyond the scope of this manual and the OCTOPuS practitioner should refer to the NICE type 1 diabetes guidance.

### 2.2.7 Summary of anti-diabetes medication options

The OCTOPuS practitioner should provide the patient with a Diabetes UK Information Prescription about glycaemic management at each visit to support glycaemic management.

Figure 1 summarises the options available to improve glycaemic control prior to surgery. The OCTOPuS practitioner should discuss progress with the patient at every visit or fortnightly phone call and management plan adjusted accordingly.

Southampton Clinical Trials Unit

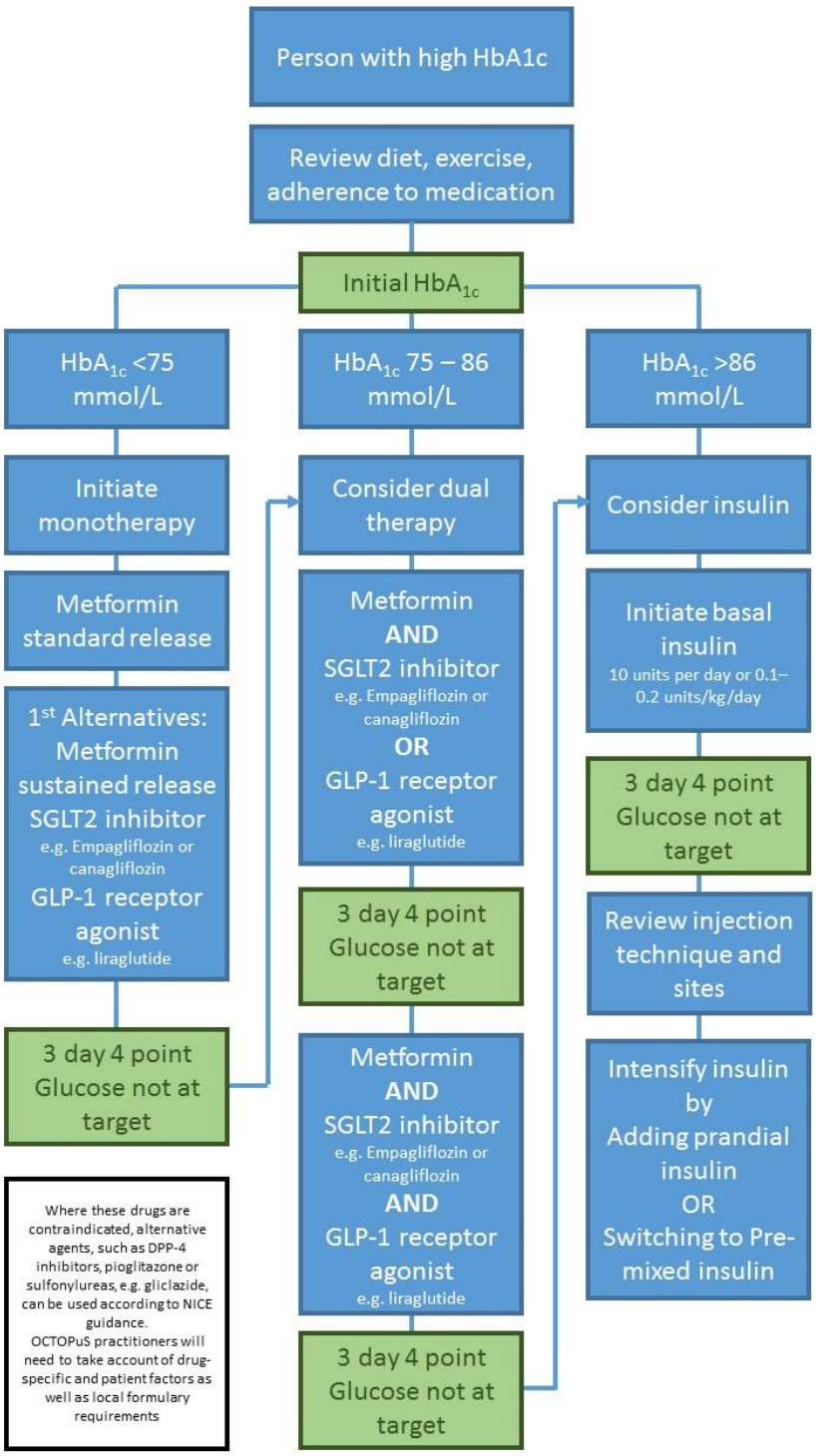


Figure 1 - Diabetes medication flowchart for people with type 2 diabetes; based on the 2018 American Diabetes Association care standards.



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### 2.2.8 Diabetes management during admission for cardiac surgery

The OCTOPuS practitioner will need to provide advice about medication and glucose management when the patient is admitted for surgery. Where possible, the OCTOPuS practitioner should arrange to see the patient after admission but prior to surgery to provide advice about diabetes management during the admission.

The OCTOPuS practitioner may need to liaise with the diabetes in-patient team in the cardiothoracic centre, if not already a member of this team. Local protocols and JBDS guidance should be followed (http://www.diabetologists-abcd.org.uk/JBDS/Surgical_guidelines_2015_full_FINAL_amended_Mar_2016.pdf). There may be specific questions about cardiac surgery or management of diabetes during the operation that the OCTOPuS practitioner is unable to answer. If this is the case, the OCTOPuS practitioner should alert the cardiac surgeon so that the surgical team can answer these questions.

The OCTOPuS practitioner should advise the patient to continue to monitor their glucose, where appropriate. They should warn the patient of the risk of hypoglycaemia during fasting prior to admission. The OCTOPuS practitioner should advise the patient that oral anti-diabetes medications and GLP-1 receptor agonists need to be omitted on the day of surgery. The OCTOPuS practitioner should provide advice about adjustments to insulin doses. Suggested adjustments to insulin doses are as follows:

| **Insulin** | **Day before procedure** | **Day of procedure** |
|---|---|---|
| Once daily (evening) (e.g. Lantus, Levemir, Tresiba, Abasalaglar Insulatard or Humulin I, Toujeo) | Take 80% of usual insulin dose at usual time. | Take 80% of usual insulin dose in the evening after the procedure |
| Once daily (morning) (e.g. Lantus, Levemir, Tresiba, Insulatard or Humulin I) | Take usual time. | Take 80% of usual insulin dose in the evening after the procedure |
| Twice daily (e.g. Novomix 30, Humulin M3, Humalog Mix 25 or 50, Lantus, Levemir) | Take usual time | Omit morning dose |
| Meal time injection | Take usual time | Omit all rapid insulin |
| Insulin pump | Please inform specialist pump team before admission for personalised advice. Continue with usual basal rates and continue to bolus depending on carbohydrate intake | Continue with usual basal rates and continue to bolus depending on carbohydrate intake |

Following surgery but prior to discharge, the OCTOPuS practitioner should see the patient to discuss post-operative diabetes management. In some situations, it may be appropriate to discontinue insulin therapy. Any treatment changes and on-going management plans should be communicated to the patient's GP and specialist diabetes team, if necessary, following discharge after surgery. This information could be included in the discharge summary or communicated separately depending on local arrangements.

### 2.3 Lipid Management

Most patients will already be taking lipid-lowering therapy. However, if they are not taking a statin, the OCTOPuS practitioner should discuss the benefits of statin therapy and recommend that this is initiated if there are no contraindications or the person has previously not tolerated treatment with statins.

For those already taking lipid-lowering therapy, the OCTOPuS practitioner should review the patient's latest lipid profile. If a greater than 40% reduction in non-HDL cholesterol has not been achieved, the OCTOPuS practitioner should discuss adherence and timing of dose, optimise adherence to diet and lifestyle measures and consider increasing the statin dose if the participant is taking less than atorvastatin 80 mg. The OCTOPuS practitioner should consider the addition of ezetimibe. In some circumstances, these measures may be insufficient to control the lipid profile and in this situation, the OCTOPuS practitioner should considering recommending a referral to a specialist lipid clinic for consideration of PCSK9 inhibitors if this is available within the timeframe of the intervention.

Where changes have been recommended, the OCTOPuS practitioner should provide the patient with a Diabetes UK Information Prescription about lipid management.

### 2.4 Hypertension Management

Hypertension and endothelial dysfunction are common in people with diabetes. The OCTOPuS practitioner should measure the blood pressure or record the clinic blood pressure measurement as part of the initial assessment.

Preliminary data suggest that preoperative use of an antagonist of renin-angiotensin system (ACE inhibitor or angiotensin receptor blocker) in people undergoing CABG is associated with decreased in-hospital mortality. Unless contraindicated, the OCTOPuS practitioner should consider an antagonist of renin-angiotensin system (ACE inhibitor or angiotensin receptor blocker) for all patients after discussion with the local cardiothoracic surgical team. The dose should be titrated against the patient's blood pressure, which should be measured in the patient's general practice or by the patient at home. Further agents may be added in accordance with NICE guidance (CG127) as necessary. When an ACE inhibitor or angiotensin receptor blocker is added, the OCTOPuS practitioner should advise the measurement of urea and electrolytes and estimated glomerular filtration rate according to standard clinical

practice. At each contact, the OCTOPuS practitioner should advise the patients to withhold ACE inhibitors or angiotensin receptor blockers from 5 days prior to surgery.

Bear in mind that the surgical team may wish to commence a beta blocker prior to surgery, so if a second line agent is needed the OCTOPuS practitioner should consider commencing a beta blocker. This decision should be discussed with the local cardiothoracic surgical team.

Where changes have been recommended, the OCTOPuS practitioner should provide the patient with a Diabetes UK Information Prescription about blood pressure management.

### 2.5 Weight Management

Obesity and being overweight are associated with poor surgical outcomes. People with a BMI >25 Kg/$m^2$ are therefore likely to benefit from weight reduction, both to improve their diabetes control and surgical outcome.

The OCTOPuS practitioner should measure the patient's height and weight and calculate their BMI.

For recommendations on weight management, see the NICE guidelines on: preventing excess weight gain, weight management, and obesity. For most patients undertaking OCTOPuS, the major element of weight reduction will be through diet. Exercise is discussed in section 2.6 below.

The OCTOPuS practitioner should refer the patient or facilitate referral to a local NHS weight reduction programme or dietitian if this can be accessed quickly enough to achieve a worthwhile effect before surgery (e.g. the programme can be started within 4 weeks).

As described above, Diabetes UK and the British Heart Foundation both produce excellent leaflets about healthy eating and the OCTOPuS practitioner should provide the patient with a copy of these or let the patient know how to access them.

If an NHS option is not available, then other weight reduction options should be explored. This could include commercial programmes, such as Weight Watchers, or a self-managed diet.

### 2.6 Exercise

Physical activity has profound benefits for people with diabetes, including improved fitness, reduced insulin requirement and better glycaemic control, lower cardiovascular risk (lower blood pressure and improved lipid profile) and improved survival. People with diabetes should take at least 150 minutes of exercise per week spread over a minimum of 3 days with a mixture of aerobic exercise and resistance training.

However, care is needed in this group of patients as those awaiting cardiac revascularisation surgery may experience angina on exertion and have a limited capacity to provide oxygenated blood to cardiac muscle. Similarly, those awaiting valve surgery may not have significant capacity to exercise. Therefore, this component of the intervention will require the OCTOPuS practitioner to tailor any recommendation to the capacity of the individual.

It is also important to ascertain whether the individual has diabetes microvascular complications before starting to exercise. People with a history of active foot ulcers should avoid weight-bearing exercise and appropriate footwear should be worn.

However, where possible, the OCTOPuS practitioner should encourage patients to take gentle exercise, such as walking or dancing. The use of pedometers can support a gradual increase in physical activity. The best exercise is the one that the person enjoys. Practical advice should be given to help the person with diabetes find ways to become more physically active.

In the case of Type 1 diabetes, exercise can lead to unstable glucose levels during and immediately after exercise and a later risk of severe hypoglycaemia. Patients should be advised to avoid exercise of this intensity. As prior hypoglycaemia blunts the catecholamine response, people should be advised to avoid exercise within 24 hours of a severe hypoglycaemic episode and 1 hour of a self-treated episode. Exercise should also be avoided if blood ketone levels are increased. The OCTOPuS practitioner should consider whether a referral to a consultant diabetologist is required to address this complex area.

In type 2 diabetes, exercise does not usually cause hypoglycaemia and so carbohydrate supplementation is not required.

### 2.7 Smoking Cessation

All patients should be encouraged and supported to stop smoking, where possible. For recommendations on smoking cessation, see the NICE guidelines on: smoking: brief interventions and referrals, stop smoking services, and smoking: harm reduction.

### 2.8 Involvement of spouses, or other relatives and friends

The involvement of people important in the patient's life may lead to greater adherence to the components of the OCTOPuS intervention. Encouragement and support from friends and family will make the changes in medication, diet, and other activity, more sustainable over the few weeks that the intervention is delivered.

Therefore, if possible friends and relatives should be involved in the initial consultation, and consideration should be given to including them in the fortnightly phone calls.

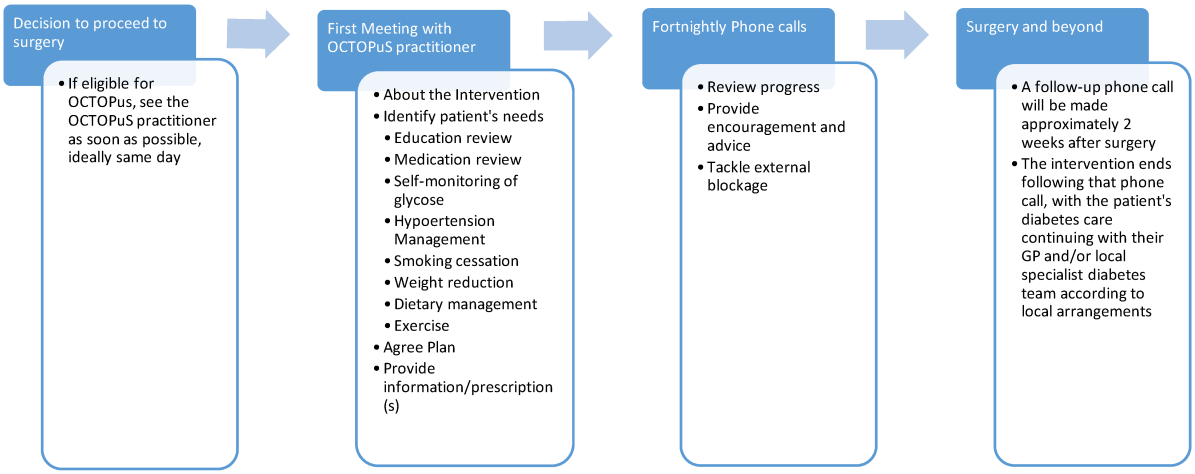
## 3 Delivering the OCTOPuS Intervention

The elements described in section 2 are brought together in the OCTOPuS intervention.

### 3.1 The Schedule of Events

The intervention follows a series of events, shown in Figure 1. At each stage, the practitioner works with the patient to agree a set of goals and actions.

*Figure 1 - A high-level flowchart of the OCTOPuS Intervention*




#### 3.1.1 The Initial Assessment

The initial assessment is key to the OCTOPuS intervention. It is where the practitioner establishes a trust relationship, which will enable the patient to take the greatest advantage of the programme. We anticipate that the initial consultation will be usually be conducted face-to–face. However, alternative remote delivery options (video or telephone consultations) may be considered when these are necessary, for example, when the patient is unable to attend the hospital or to comply with COVID-19 social distancing.

*Table 1 - Framework for Initial Assessment*

| Phase | Activity |
|---|---|
| **Assessment** | Explore the patient's understanding and experience of diabetes.<br>Explore any concerns the patient has relating to diabetes and their prospective surgery.<br>Establish whether there are relevant co-morbidities<br>Establish any significant people in the patient's life who could provide support in the run up to surgery. |
| **Explanation** | Explain the OCTOPuS intervention, and its goals, in the light of information elicited in the assessment phase. |
| **Measurement** | Make any clinical assessments which may be required, that weren't done in the most recent cardiovascular outpatient appointment<br>• $HbA_{1c}$<br>• Blood Pressure<br>• Height, Weight -> BMI |
| **Review** | Review the patient's situation in the areas set out in section 2 of this manual.<br>• Glucose Management<br>• Hypertension Management<br>• Weight Reduction<br>• Smoking Status<br>• Exercise<br>Agree a plan, where appropriate, with the patient for each of these elements |
| **Follow-up** | Schedule the first fortnightly phone call. You may like to schedule multiple calls for the complete period up to the planned surgery date.<br>Obtain permission from the patient to contact their GP or other services to support the patient's action plan. Liaise with local clinical team where necessary<br>Put into place any arrangements needed to support the patient's action plan |

### 3.1.2 The Fortnightly Phone Call

At least every fortnight, the OCTOPuS practitioner will contact the patient until the patient's diabetes management is optimised or no further changes are possible. After this has been achieved, the frequency of the calls can be reduced at the discretion of the OCTOPuS practitioner to a minimum of every 6 weeks. We envisage this being by phone but other methods (face-to-face, Skype etc.) could be used by mutual agreement.

This is an opportunity for the practitioner to review progress against goals, and for the patient to raise any queries they might have.

The OCTOPuS practitioner should ensure that the patient has the contact details of the OCTOPuS team so that they can contact the team if necessary.

*Table 2 - Framework for Fortnightly Phone Call*

| **Phase** | **Activity** |
|---|---|
| **Assessment** | Explore the patient's activity and progress against the goals agreed at the previous initial assessment or fortnightly phone call<br><br>Explore whether there has been any changes health, e.g. infection, that might affect the management plan. |
| **Measurement** | Make any clinical assessments, which may be required. This will generally involve the patients reporting over the phone or by alternative means of communication, such as email, DIASEND, Freestyle Libreview etc.<br>• Recent self-monitoring of blood glucose<br>• Weight<br>• Smoking status |
| **Listen** | To any problems or concerns that the patient raises |

| Phase | Activity |
|---|---|
| **Review** | Review the patient's situation in the areas set out in section 2 of this manual.<br>• Glucose Management – where surgery is delayed beyond 3 months, the OCTOPuS practitioner should arrange for a further HbA1c measurement every 3 months<br>• Hypertension Management<br>• Weight Reduction<br>• Smoking Status<br>• Exercise<br>Agree a plan, where appropriate, with the patient for each of these elements, in the light of the review and listening phases.<br>Liaise with local clinical team where necessary |
| **Follow up** | Schedule the next fortnightly phone call, if not already done. |

### 3.1.3 Surgery and Beyond

Surgery will proceed according to local protocols.

Approximately two weeks after surgery, the OCTOPuS practitioner will contact the patient again. This phone call will follow the framework in Table 2 above. During the final support call, the OCTOPuS practitioner should undertake a review of the elements of the intervention and develop a future diabetes management plan.

All patients who have completed the OCTOPuS intervention and their surgical treatment should then return to routine diabetes care with their GP or local diabetes specialist team.



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## Appendix 1: The OCTOPuS Randomised Controlled Trial

The OCTOPuS trial has been funded by the NIHR HTA programme to evaluate the OCTOPuS intervention, and to determine whether it adds value to patient care.

Approximately 426 people with poorly controlled diabetes undergoing cardiac surgery will be randomised to either the OCTOPuS intervention or to usual care. The outcomes of interest include time from surgery until clinically for hospital discharge, 30 & 90 day mortality, wound infections, chest infections, renal impairment, $HbA_{1c}$ pre-op and, 90 days post op, cost-effectiveness, procedures cancelled due to glycaemic control, quality of life, patient satisfaction & experience.

More information is available at
https://www.journalslibrary.nihr.ac.uk/programmes/hta/162512/#/



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## Appendix 2: Bibliography

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# PROGRESS GRADING

## 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. |

## 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 |



Holt RIG, *et al. BMJ Open* 2021; 11:e050919. doi: 10.1136/bmjopen-2021-050919

**SAFETY CONSIDERATIONS**

**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, i.e. the participant was at risk of death at the time of the event
- Requires hospitalisation (regardless of length of stay), or prolongation of existing hospitalisation (>30 days post- cardiothoracic surgery)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Other important medical events (if they jeopardise the participant or require an intervention to prevent one of the above consequences).

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

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

**Causality & Expectedness**

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. The nature or severity 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'.

**Reporting Procedures**

All adverse events should be reported until the End of Study as defined in 3.3. SAEs should be reported to SCTU within 24 hours of site becoming aware of the event. Additional information should be provided as soon as possible if the event has not resolved at the time of reporting. 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.

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.

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.