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Synopsis

Optimising cardiac surgery outcomes in people with diabetes: the OCTOPuS pilot feasibility study

Richard IG Holt[1,2*] Katharine Barnard-Kelly[3] Mayank Patel[4] Philip Newland-Jones[4] Suvitesh Luthra[5] Jo Picot[6] Helen Partridge[7] Andrew Cook[8] and on behalf of the OCTOPuS Study Group

[1]School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK
[2]National Institute for Health and Care Research Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[3]Barnard Health – Health Psychology Research, Fareham, UK
[4]Diabetes Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[5]Cardiothoracic Surgery Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[6]Southampton Health Technology Assessments Centre, University of Southampton, Southampton, UK
[7]Diabetes Department, University Hospitals Dorset NHS Foundation Trust, Bournemouth, UK
[8]Clinical Trials Unit, Faculty of Medicine, University of Southampton, Southampton, UK

[*]**Corresponding author** r.i.g.holt@soton.ac.uk

Published August 2025
DOI: 10.3310/POYW3311
Volume 29 • Issue 39

Abstract

Background: Surgical outcomes are worse in people with diabetes, in part, because of the effects of hyperglycaemia, obesity and other comorbidities. Two important uncertainties in the management of people with diabetes undergoing major surgery exist: (1) how to improve diabetes management prior to an elective procedure and (2) whether that improved management leads to better post-operative outcomes.

Objective: The Optimising Cardiac Surgery ouTcOmes in People with diabeteS project aimed to assess whether a pre-operative outpatient intervention delivered by a multidisciplinary specialist diabetes team could improve diabetes management and cardiac surgical outcomes for people with diabetes. Although the intervention could be applied to any surgical discipline, cardiothoracic surgery was chosen because 30–40% of those undergoing elective cardiac revascularisation have diabetes.

Methods: The project had three phases: (1) designing the intervention, (2) a pilot study of the intervention and (3) a multicentre randomised controlled study in United Kingdom cardiothoracic centres to assess whether the intervention could improve surgical outcomes. The first two phases were completed, but the COVID-19 pandemic and its subsequent effects on cardiothoracic services and research capacity in the United Kingdom meant that the randomised controlled study could not be undertaken.

Intervention development: Two rapid literature reviews were undertaken to understand what factors influence surgical outcomes in people with diabetes and what interventions have previously been tested. The Optimising Cardiac Surgery ouTcOmes in People with diabeteS intervention was based on an existing nurse-led outpatient intervention, delivered in the 3 months before elective orthopaedic surgery. This intervention reduced pre-operative glycated haemoglobin and reduced length of stay. We undertook a survey of United Kingdom cardiothoracic surgeons, which found limited and inconsistent pre-operative management of people with diabetes awaiting cardiothoracic surgery. A prototype intervention was developed following discussions with relevant stakeholders.

Pilot study: The pilot feasibility study recruited 17 people with diabetes and was undertaken by the diabetes and cardiothoracic surgery departments at University Hospital Southampton NHS Foundation Trust. Biomedical data

This synopsis should be referenced as follows:
Holt RIG, Barnard-Kelly K, Patel M, Newland-Jones P, Luthra S, Picot J, *et al.* Optimising cardiac surgery outcomes in people with diabetes: the OCTOPuS pilot feasibility study. *Health Technol Assess* 2025;**29**(39). https://doi.org/10.3310/POYW3311

were collected at baseline and prior to surgery. We assessed how the intervention was used. In-depth qualitative interviews with participants and healthcare professionals explored perceptions and experiences of the intervention and how it might be improved.
Thirteen people completed the study and underwent cardiothoracic surgery. All components of the Optimising Cardiac Surgery ouTcOmes in People with diabeteS intervention were used, but not all parts were used for all participants. Minor changes were made to the intervention following feedback from the participants and healthcare professionals. Median (interquartile range) glycated haemoglobin fell 10 mmol/mol (3–13) prior to surgery. The median duration of admission for surgery was 7 (interquartile range 6–9) days.
Multicentre randomised controlled study of the United Kingdom cardiothoracic centres: We could not proceed to the multicentre randomised controlled study because of the impact of COVID-19 on the delivery of cardiothoracic surgical services and research capacity.
Conclusion: There remains an urgent need to improve the surgical outcomes for people with diabetes. This project demonstrated that it is possible to develop a clinical pathway to improve diabetes management prior to admission.
Limitations: We could not test the effectiveness of the intervention in a multicentre randomised controlled trial because of the COVID-19 pandemic.
Future work: The intervention is available for future research or clinical implementation.
Funding: This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programmme as award number 16/25/12.
A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/POYW3311.

Introduction and background

Introduction

There are currently more than 4.9 million people living with diagnosed and undiagnosed diabetes in the UK.[1] In the last 15 years, the prevalence of diagnosed diabetes has almost doubled, and the numbers are projected to increase to 5.6 million by 2030. People with diabetes experience poorer surgical outcomes with an up-to-threefold higher risk of post-operative complications. These include poor healing, wound complications and renal dysfunction and are associated with longer hospital stay and higher re-admission rates.[2,3] The reasons underlying the poorer outcomes include hyperglycaemia, dyslipidaemia, obesity and other comorbidities. These patients have longer lengths of hospital stay and higher re-admission rates, which places a large financial burden on the UK's NHS. Although national and international groups, such as the National Institute for Health and Care Excellence (NICE), Joint British Diabetes Societies for Inpatient Care (JBDS-IP), American Diabetes Association (ADA) and International Diabetes Federation (IDF),[4–8] have published detailed guidelines to improve surgical outcomes in people with diabetes, many people with diabetes are poorly prepared for surgery.[2,6]

In response to the call from the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme, 'Poorly controlled diabetes and outcomes of elective surgery' (HTA 16/25), the Optimising Cardiac Surgery ouTcOmes in People with diabeteS (OCTOPuS) project was established to address poor surgical outcomes in people with diabetes undergoing cardiothoracic surgery. The aim of the project was to assess whether a pre-operative outpatient intervention delivered by a multidisciplinary specialist diabetes team could improve diabetes management and improve cardiac surgical outcomes for people with diabetes.

Although the principles of the intervention could be applied to any surgical discipline, cardiothoracic surgery was chosen as an exemplar for several reasons. First, diabetes increases the risk of cardiovascular disease (CVD) by approximately twofold after adjustment for other cardiovascular (CV) risk factors and affects approximately a third of all people with type 2 diabetes.[9] Ischaemic heart disease is a leading cause of death in people with diabetes, and coronary heart disease tends to be more diffuse and progresses more rapidly in people with diabetes, which may explain why up to 30–40% of those presenting for elective cardiac revascularisation have diabetes.[10]

Open-heart surgery constitutes a major operation with long length of stay (LOS); if the pre-operative intervention is successful in reducing the complication rate and improving surgical outcomes, it has the potential to be cost-saving.

Finally, when the project was envisaged, there was a waiting time of 2–3 months between listing for surgery and admission for surgery. We planned to turn this 'vice' into a 'virtue' by using this waiting time constructively to optimise diabetes care in the interim with a view to improving post-operative outcomes.

The project was conceived with three phases: the first was designing the intervention, followed by a pilot study of the intervention and finally a multicentre randomised controlled study in UK cardiothoracic centres to assess whether the intervention could improve surgical outcomes. The first two phases were completed according to the plan, but the COVID-19 pandemic and its subsequent effects on cardiothoracic services and research capacity in the UK meant that the randomised controlled study could not be undertaken.

This synopsis will provide the background to the OCTOPuS project, the three publications that arose from the work and will end by highlighting the lessons learnt and possible future research.

Epidemiology of diabetes

Diabetes mellitus is a complex metabolic disorder characterised by chronic hyperglycaemia due to relative insulin deficiency, insulin resistance or both. In 2021, the IDF estimated that 537 million adults aged 20–79 years (10.5% of the global population) had diabetes, and this number is projected to reach 643 million by 2030 and 783 million by 2045.[11] Diabetes is associated with both short- and long-term complications that reduce quality of life (QoL) and life expectancy, and is associated with major health costs, estimated globally to be US$966B in 2021. Complications include acute metabolic disturbance, macrovascular disease (leading to an increased prevalence of coronary artery disease, peripheral vascular disease and stroke) and microvascular damage causing retinopathy, nephropathy and neuropathy. In the UK, every week, diabetes leads to more than 770 strokes, 590 myocardial infarctions (MIs) and 2300 cases of heart failure.[12] Diabetes was responsible for approximately 6.7 million deaths or 12.2% of all deaths in 2021, outnumbering the combined global deaths from human immunodeficiency virus, tuberculosis and malaria.[11] In the UK, over 14,000 deaths per annum were attributable to diabetes in 2015, with standardised mortality ratios of 2.28 [95% confidence interval (CI) 2.18 to 2.37] and 1.28 (95% CI 1.27 to 1.29) for type 1 diabetes and type 2 diabetes, respectively.[13] The relative risk of death is higher in younger people and in women. Globally, diabetes is among the top 10 causes of mortality.[11]

Classification of diabetes

Diabetes is classified according to whether the diabetes is primary or secondary. Primary diabetes includes type 1 diabetes, type 2 diabetes and hybrid forms that have features of both type 1 diabetes and type 2 diabetes.[14] Secondary diabetes is much less common but occurs when other pathology interferes with insulin secretion or action and includes diabetes that is secondary to single-gene (monogenic) defects or other genetic syndromes, exocrine pancreatic disease, endocrine disease, drugs and chemicals, infection or uncommon forms of immune-mediated diabetes. Gestational diabetes refers to glucose intolerance appearing for the first time in pregnancy.

Type 1 diabetes

Type 1 diabetes is a disease of insulin deficiency caused by the autoimmune destruction of the insulin-secreting β cells in the pancreas.[15] It accounts for 5–10% of all cases of diabetes and has a global prevalence of 5.9 per 10,000 people.[16] The incidence of type 1 diabetes has risen rapidly over the last 50 years and is currently estimated to be 15 per 100,000 people per year.[16] Type 1 diabetes typically presents in childhood and young adulthood, reaching a peak incidence around the time of puberty. In 2021, globally over 1.2 million children and adolescents had type 1 diabetes with approximately 184,100 new cases every year.[11] Type 1 diabetes, however, can present in all age groups, and as people with type 1 diabetes live for many decades after its onset, the overall prevalence of type 1 diabetes is higher in adults than in children.[17] The rates of type 1 diabetes vary dramatically throughout the world, with the highest rates being in populations of Northern European origin and in certain countries in the Middle East and North Africa.[18]

Type 2 diabetes

Type 2 diabetes is the commonest form of diabetes, accounting for around 95% of all cases.[19] It is a heterogeneous disorder that primarily results from the interaction of genetic predisposition and environmental factors that lead to both insulin deficiency and insulin resistance.[20] The prevalence of type 2 diabetes is rising rapidly through a combination of population growth, an ageing population, improved management leading to longer survival with type 2 diabetes, earlier age at onset and better case-finding.[21] Type 2 diabetes is a disease of nutrient excess, and the incidence has increased with the obesity epidemic, poor-quality diet and reduced physical activity.[22]

The prevalence of type 2 diabetes varies markedly across the world, with the highest rates being in the Middle East and Pacific Islands, and the lowest in Africa and Europe.[11] Approximately, three-quarters of those with type 2 diabetes live in low- and middle-income countries, and the most rapid rise in incidence is occurring in countries with rapidly growing economies, such as India and China. Two-thirds of people with diabetes live in urban areas, compared with 54% of the general population.

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Management of diabetes

Aims of diabetes care

For most people, diabetes is a lifelong condition. As only a few hours a year are spent in contact with healthcare professionals (HCPs), the majority of people with diabetes need the skills, motivation and opportunity to look after their condition themselves for most of the time. Optimal diabetes management occurs when the person with diabetes and multidisciplinary diabetes care team actively work together as equal partners to achieve diabetes-related goals.[23] Diabetes management is a balance between short-term optimisation of glycaemic management to prevent acute metabolic emergencies, including hypoglycaemia, and treatment of symptoms, and maintaining QoL while at the same time reducing the risk of long-term complications. Although diabetes management has traditionally focused on glycaemic goals and high-quality randomised trials have proven that improving glycaemic management is associated with a reduction in microvascular complications,[24–27] modern diabetes care is much broader, encompassing CV risk factor management and appropriate psychosocial support and education.[15,28]

Self-management education

Diabetes self-management education has become an important cornerstone of diabetes care.[29] The education needs to be tailored to the individual, and structured educational programmes with a clear philosophy, such as 'Dose Adjustment for Normal Eating' or 'Diabetes Education and Self-Management for Ongoing and Newly Diagnosed', employing trained facilitators using a written curriculum, are seen as the gold standard.[30–32] These programmes improve diabetes knowledge, QoL and glycaemic levels and reduce mortality.[29,33] Education should not be viewed as a 'one-off inoculation', and regular ongoing support and updates will be needed.

Health behaviours

Although diet plays a key role in the management and clinical care of all people with diabetes, no one single diet is effective in managing diabetes and so it is important to adopt an individualised approach, taking into consideration the person's personal and cultural preferences.[34] In general, people should be encouraged to eat more vegetables, fruits, wholegrains, fish, nuts and pulses while reducing the consumption of red and processed meat, refined carbohydrates and sugar-sweetened beverages. For those using intensive insulin regimens, people need to match their insulin dose to the carbohydrate consumed in the meal and so it is important to teach people how to 'carbohydrate count'. Maintenance of a normal body weight also improves glycaemia, and in some circumstances, a 10–15 kg of body weight loss through lifestyle, pharmacological or surgical treatment can lead to diabetes remission.[35,36] Physical activity improves fitness, reduces insulin requirement and improves glycaemic levels, lowers CV risk and lengthens life expectancy.[28,37,38] People with diabetes should be advised to take at least 150 minutes of aerobic exercise and resistance training per week, spread over a minimum of 3 days. Smoking cessation is advised.[15,28]

Medication for diabetes

Insulin

The discovery of insulin has transformed the lives of millions of people with diabetes.[39] Insulin is always indicated in people with type 1 diabetes and is often needed in those with type 2 diabetes as the condition progresses.[15,28] The philosophy of insulin therapy is to mimic the normal physiological secretion of insulin as closely as possible.[15] This frequently involves the use of both long-acting insulin to replicate the basal secretion of insulin and short-acting insulin to cover mealtimes, but many different regimens are used. Insulin is administered subcutaneously by intermittent injection or by insulin pumps (continuous subcutaneous insulin infusion).

Although insulin and the means of administering insulin continue to improve, achieving optimal glycaemic levels is extremely challenging for people living with diabetes for a number of reasons. The amount of insulin needed to reduce glucose levels in the post-prandial state will cause hypoglycaemia in the fasted state. If too little insulin is administered, glucose concentrations rise outside the normal range; while if too much insulin is administered, glucose concentrations fall into the hypoglycaemic range. Insulin requirements are highly variable from one person to another and vary within the same individual within a day and between days.[40] It is, therefore, critically important that people are trained to use their insulin effectively and safely, and this forms a central component of diabetes self-management education for people with diabetes.[30]

Hypoglycaemia Hypoglycaemia (low blood glucose) is the most common side effect of insulin therapy and is the major limitation to what can be achieved with insulin treatment. Most people treated with insulin will experience several episodes of symptomatic hypoglycaemia per week and one to two severe episodes per year when external help is required for recovery. Hypoglycaemia is more common in people with type 1 diabetes, where there is absolute insulin deficiency, but also affects people with type 2 diabetes, particularly with longer duration of diabetes.[41] Hypoglycaemia greatly impairs QoL and

induces fear and anxiety in the person with diabetes, their family and carers.[42] Hypoglycaemia is also associated with a number of long-term medical consequences, including cardiovascular events (CVEs) and falls.[43]

Non-insulin treatments for type 2 diabetes

There has been a revolution in non-insulin therapies for type 2 diabetes over the last two decades. Several new classes of agents have been licensed, increasing the number of treatment options.[28] Several classes, including metformin, sodium-glucose transporter 2 inhibitors (SGLT2 inhibitors or 'flozins') and glucagon-like peptide 1 (GLP-1) receptor agonists, have strong evidence supporting health benefits (such as mortality benefit and reduction of CVD) that extend well beyond their glucose-lowering effects.

Metformin Metformin was introduced into clinical practice in the 1950s, but the precise mechanism of action of metformin remains unclear.[44] It likely involves a range of insulin-dependent and insulin-independent actions that improve insulin sensitivity and reduce blood glucose. Metformin is the best-validated treatment for type 2 diabetes and appears as a first-line pharmacological agent in most type 2 diabetes guidelines.[28] Metformin treatment is associated with a reduction in CVEs compared with treatment with sulphonylureas or insulin.[27]

Sulphonylureas Sulphonylureas were originally derived from sulfonamide antibiotics and act on the β cell to induce insulin secretion.[45] Sulphonylureas can also be used in combination with other oral antidiabetes agents or basal insulin, although they are usually stopped when the individual requires short-acting insulin at mealtimes.

Sodium-glucose transporter 2 inhibitors ('flozins') Sodium-glucose transporter 2 inhibitors are recommended as second-line agents or first-line agents in people with diabetes and established or high risk of atherosclerotic CVD or heart failure because of strong evidence of their cardioprotective and renoprotective effects.[46,47] They act by lowering the renal threshold for glucose, consequently increasing urinary glucose excretion. It is not entirely clear how SGLT2 inhibitors reduce the risk of MI, stroke, CV death and heart failure, but several hypotheses have been proposed, including increased natriuresis leading to fluid loss and small reductions in systolic blood pressure (BP), increased production of ketones, vasodilation and direct protective effects on the heart.[48]

Glucagon-like peptide 1 receptor agonists Glucagon-like peptide 1 receptor agonists are a heterogeneous class of drugs that act by enhancing the incretin effect by activating the GLP-1 receptor.[49] GLP-1 receptor agonists are resistant to cleavage by dipeptidyl peptidase 4 (DPP-4) which prolongs the duration of action and achieves supra-physiological GLP-1 concentrations. They act to increase insulin in a glucose-dependent manner but also decrease glucagon secretion and act on the hypothalamus to reduce appetite and food intake leading to weight loss. Most are given by injection (daily to once-weekly), but semaglutide is available as a daily oral tablet.[50] There is strong clinical trial evidence that GLP-1 receptor agonists reduce the risk of MI, stroke, CV death and heart failure.[47] The GLP-1 receptor agonists may also have reno- and neuro-protective effects and have a major role in the treatment of obesity.

The dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist, tirzepatide, is a once-weekly subcutaneous injection and exerts greater reductions in glycated haemoglobin (HbA1c) and body weight in individuals with type 2 diabetes than GLP-1 receptor agonists.[51] Further dual or triple agonists are in clinical development.

Dipeptidyl peptidase 4 inhibitors or 'gliptins' Dipeptidyl peptidase 4 inhibitors also act on the incretin system by inhibiting the enzyme DPP-4, which prevents the rapid inactivation of GLP-1.[52] They are less effective than GLP-1 receptor agonists and are most effective in the early stages of type 2 diabetes, when insulin secretion is relatively preserved.

Thiazolidinediones or 'glitazones' Thiazolidinediones reduce insulin resistance by interaction with peroxisome proliferator-activated receptor gamma, a nuclear receptor that regulates large numbers of genes, including those involved in lipid metabolism and insulin action.[53] They are used less often because they induce significant weight gain and fluid retention that can precipitate heart failure, but pioglitazone may specifically benefit people with metabolic dysfunction-associated steatotic liver disease, a frequent comorbidity of type 2 diabetes.

Other antidiabetes agents Several other agents are available, including meglitinides, alpha-glucosidase inhibitors, quick-release bromocriptine, colesevelam and amylin analogues, none of which are widely used and some of which are not available in the UK.

Which drug and when?

Type 2 diabetes is characterised by progressive β-cell failure and glucose levels increase over time, meaning a progressive and pre-emptive escalation of diabetes therapy is needed.[54] There is strong evidence of delays in treatment escalation, which exposes the individual with

diabetes to prolonged periods of hyperglycaemia and the risks of complications.[55,56] With the introduction of a wider selection of drugs to treat type 2 diabetes, the choice of which drug and when becomes more and more relevant. Clinicians need to consider specific patient characteristics and factors that will inform discussions with people with diabetes to individualise treatment.[28]

Metformin is recommended as the first-line treatment for most people with type 2 diabetes whose glucose levels remain above target despite optimal health behaviour management.[28] However, for those with or at high risk of atherosclerotic CVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven CVD benefit are preferred. SGLT2 inhibitors are also preferred for individuals with heart failure or chronic kidney disease.

If there is a pressing need to minimise weight gain or promote loss, again GLP-1 receptor agonists or SGLT2 inhibitors are recommended. Where there is a need to avoid hypoglycaemia, GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors and thiazolidinediones may be used. When dual or triple therapy is needed, other recommended drugs can be added, but beyond triple therapy, insulin is required, as further additional treatments have only a minimal effect, if any.

Monitoring glucose levels in people with diabetes

Measures of glucose levels are needed to help people with diabetes, and their HCPs make rational choices about therapy and assess long-term risk of complications.[15,28] Measurements of glucose levels can be divided into short-term measures that provide an almost instantaneous record of the current glucose concentration and long-term measures that provide an assessment of average glucose concentration over the preceding weeks or months. Traditionally, capillary blood glucose was the short-term measure of choice, but increasingly continuous glucose monitoring of interstitial glucose is being used for people with type 1 diabetes and people with insulin-treated type 2 diabetes.[15] HbA1c is the most well-validated long-term measure of an individual's average blood glucose concentration over the previous 6–8 weeks.

Cardiovascular disease in people with diabetes

Cardiovascular complications develop in people with all types of diabetes.[57–60] They tend to occur at an earlier age, progress more rapidly and are more distal and diffuse than in people without diabetes. Even after adjusting for other known CV risk factors, such as hypertension and hyperlipidaemia, there remains an excess risk for CVD in people with diabetes,[61,62] such that diabetes accounts for 75–90% of the excess coronary artery disease risk in people with diabetes. Death from stroke and MI are leading causes of mortality in people with type 1 diabetes and people with type 2 diabetes.[58,63]

Although the link between hyperglycaemia and the development of macrovascular disease is less firmly established than for microvascular complications, such as retinopathy and nephropathy, hyperglycaemia is important for the pathogenesis of macrovascular disease.[64–66] HbA1c is an independent risk factor for macrovascular disease,[67–70] which continues across the normal and diabetes range of glucose, with the risk of macrovascular disease increasing twofold between a HbA1c of 37 mmol/mol (5.5%) and 80 mmol/mol (9.5%). Hyperglycaemia has direct and indirect toxic inflammatory effects on vascular cells.

In addition to hyperglycaemia, other important factors that are responsible for the development and progression of macrovascular disease in people with diabetes include hypertension, dyslipidaemia [characterised by low high-density lipoprotein (HDL) cholesterol and high triglyceride concentrations], obesity, hyperinsulinaemia and proteinuria.[71] The renin–angiotensin–aldosterone system (RAAS) plays a pivotal role in diabetes-associated atherosclerosis, but other vasoactive hormone systems, such as the endothelin[72] and urotensin systems,[73,74] have also been implicated.

Interventions to reduce diabetes-associated macrovascular complications

Reducing the CV risk in people with diabetes requires the aggressive and systematic management of each of the predisposing factors.[75–77]

Glucose management

Most guidelines recommend a target HbA1c of < 53 mmol/mol (7%), with the caveat that a more cautious target is needed in those with underlying and pre-existing CVD.[15,28] Although the evidence for beneficial effects of optimising glucose management per se on macrovascular outcomes is uncertain, there is high-quality evidence from randomised controlled trials (RCTs) about the use of newer antidiabetes agents. These trials have shown that GLP-1 receptor agonists and SGLT-2 inhibitors reduce the risk for CV death, MI and stroke.[47,78]

Blood pressure management

Cardiovascular risk doubles for every increase of 20 mmHg in systolic and 10 mmHg in diastolic BP from BP values as low as 115/75 mmHg in the general population.[79] Antihypertensive treatment reduces the risk of adverse

CV outcomes as well as microvascular events;[80] however, the ideal systolic or diastolic BP target has not been completely determined, although a maximum systolic BP of 130–135 mmHg should be the goal for most people with diabetes.

Combination drug therapy, usually beginning with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), is often needed to achieve the target for BP.[79] Treating people with diabetes and at least one other major CV risk factor with an ACE inhibitor produces a 25–35% lowering of the risk of heart attack, stroke, overt nephropathy or CV death. ARBs are sometimes preferred initially and are also used for those intolerant to ACE inhibitors.

Lipid management

For any given level of cholesterol, a person with diabetes has a two- to threefold increased CV risk compared with a person without diabetes. Current guidelines suggest reducing low-density lipoprotein (LDL) cholesterol levels to < 2.5 mmol/l, although some more recent evidence has indicated further benefits if LDL cholesterol is lowered to below 2.0 mmol/l.[81] Targets for triglycerides and HDL cholesterol are < 1 mmol/l and > 1 mmol/l, respectively.[82]

Statins are recommended for those with diabetes over the age of 40 years or after a 10-year history of diabetes if microvascular complications are present, as CVEs are reduced by 20% for every 1 mmol/l reduction in LDL cholesterol. Other lipid-lowering agents, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors, are indicated if statins are not tolerated or do not bring the cholesterol to target.

Antiplatelet management

Diabetes is associated with pro-thrombotic changes and enhanced coagulability, which increase CV risk.[83,84] Low-dose aspirin reduces macrovascular risk but is associated with increased morbidity and mortality from bleeding. The benefits of aspirin outweigh the bleeding risk when used for secondary prevention, but in Europe, unlike the USA, it is not recommended for primary prevention.[81] Clopidogrel and other agents, such as abciximab,[85] have also been reported to be effective in people with diabetes.

Health behaviours

Behavioural strategies to reduce CVD include smoking cessation, physical activity, eating a healthy diet, maintaining a healthy weight and a regular sleep pattern.

Surgery in people with diabetes

Having diabetes more than doubles the risk of being hospitalised for any given condition. In 2019, when the prevalence of diabetes in the general population was approximately 6.5%, the UK National Diabetes Inpatient Audit showed that 18.1% of hospital inpatients had diabetes.[86,87] In the majority, diabetes was not the reason for their admission, but suboptimal management of diabetes lengthens hospital stay and increases the risk of developing complications, such as hospital-acquired infection, or dying. This applies equally to medical and surgical inpatients.

Surgical outcomes in people with diabetes

With the increasing prevalence of diabetes, more people with diabetes are undergoing elective or emergency surgery. In the UK, it is estimated that at least 330,000 surgical procedures are undertaken on people with diabetes each year, of which 100,000 are emergency procedures.[88] Suboptimal surgical outcomes associated with perioperative hyperglycaemia have been observed across multiple surgical disciplines, most markedly in individuals not previously known to have diabetes.[5,89–95] These include an increased LOS in hospital, increased time spent in intensive care units (ICUs) and increased surgical site or urinary tract infections. In the UK, the LOS for people with diabetes admitted for surgery is, on average, three days longer than those without diabetes, but in some hospitals, the excess LOS may be as much as 4.5 days.[88] An additional concern is that new-onset hyperglycaemia is also associated with increased in-hospital mortality in people *without* known diabetes, compared to those with diabetes.[96]

As part of the first phase of the OCTOPuS project to design the intervention, we undertook two rapid literature reviews. In the first, we sought to identify the modifiable factors associated with suboptimal surgical outcomes in people with diabetes. We identified eight published systematic reviews or meta-analyses[97–104] with the aspect of diabetes management or the comparison of interest differing between them.

Three of the systematic reviews reported on the impact of the patients' HbA1c level on surgical outcomes.[97–99] The systematic reviews were assessed according to A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2) criteria, and each was given an overall rating of confidence in the systematic review of 'critically low' because of critical flaws.[105] Of these three systematic reviews, we concluded that the systematic review by Zheng *et al.*[99] was more reliable and most relevant to our purpose

of informing the development of an intervention for people with diabetes who are scheduled for elective major cardiac surgery. This review examined the literature on the association between pre-operative HbA1c levels in people with diabetes undergoing coronary artery bypass graft (CABG) surgery and found by meta-analysis a statistically significant increase in both mortality and stroke after CABG surgery when the patients' glycaemic levels were suboptimal. In the studies included in the Zheng *et al.*[99] systematic review, optimal glycaemic levels were defined as a HbA1c ≤ 53 mmol/mol (7%) in six studies, with cut-off points for optimal glycaemic levels of 52 mmol/mol (6.9%) and 48 mmol/mol (6.5%) in the other two studies. Zheng *et al.*[99] also reported on MI and renal failure, and meta-analysis indicated a statistically significant increase in the risk of both outcomes after CABG surgery for those with suboptimal glycaemic levels.

Three systematic reviews reported on the impact of different intensities of glycaemic management in the perioperative or post-operative period or both.[100–102] Of these, the most reliable findings are likely to come from the Buchleitner *et al.* systematic review, which was the only one to achieve a 'high' overall AMSTAR 2 rating.[101] Buchleitner *et al.* reported on mortality outcomes and found that intensive versus conventional perioperative blood glucose management did not significantly reduce the risk of death from any cause. Buchleitner *et al.* also found that there was no statistically significant reduction in the risk of CVEs with an intensive versus conventional blood glucose management strategy and did not identify statistically significant differences by glucose management in either infectious complications or wound infections, respectively.

One systematic review compared clinical outcomes after CABG surgery among insulin-treated and non-insulin-treated patients with type 2 diabetes and had an overall rating of confidence of 'critically low' by AMSTAR 2 criteria.[103] Meta-analyses were conducted for short-term and long-term events with mixed results reported. Among the short-term events, both short-term mortality and short-term major adverse events were statistically significantly higher in the insulin-treated group than in the non-insulin-treated group. However, no statistically significant difference was observed for the short-term stroke outcome. For the long-term outcomes of mortality, stroke, and major adverse events results again indicated that insulin-treated patients experienced a higher rate of events than non-insulin-treated patients. In contrast, the long term MI and repeated revascularisation rates were similar between the insulin-treated and non-insulin-treated groups.

The final systematic review of the eight included in our overview was conducted to assess the effects of inhibitors of the RAAS on major adverse cardiac events in people undergoing cardiac surgery, and it had an overall rating of confidence of 'critically low' by AMSTAR 2 criteria.[104] The review reported on the outcome of early all-cause mortality for a subgroup of studies in which 40% or more of the participants had diabetes. The meta-analysis showed that treatment with pre-operative RAAS inhibitors was associated with a statistically significant reduction in the risk of early all-cause mortality.

Mechanisms to explain the effect of hyperglycaemia on surgical outcomes

The underlying reasons for the suboptimal outcomes in people with diabetes undergoing surgery are multifactorial. The requirement for prolonged perioperative fasting increases the risk of hypoglycaemia compared to those without diabetes. By contrast, the catabolic effect of surgery induces a counter-regulatory response to this state of physiological stress. Ordinarily, more insulin is secreted to maintain normal glucose levels. However, in people with diabetes, this does not occur sufficiently, and furthermore, the catabolic state also increases insulin resistance, which is associated with increased glycogenolysis and gluconeogenesis, as well as reduced peripheral glucose uptake and utilisation, all of which combine to result in hyperglycaemia.[106,107] Left unmanaged, persistent severe hyperglycaemia will drive an osmotic diuresis, which in turn can cause electrolyte disturbances and dehydration, with the associated increased plasma osmolality driving a pro-thrombotic state. Hyperglycaemia post-operatively can also be further aggravated if use of vasopressors or enteral or parental nutrition are indicated. In addition to the effects of hyperglycaemia, surgical patients with diabetes have multiple comorbidities, including obesity and vascular complications,[108–114] which are independently associated with suboptimal surgical outcomes.

Lack of preparation and inadequate management of diabetes during the perioperative period may further contribute to the suboptimal outcomes. Key factors include insufficient action to address perioperative hypoglycaemia or hyperglycaemia,[90,115] insulin-prescribing errors or complex polypharmacy,[116] inadequate organisational diabetes perioperative guidelines[90,117] and gaps in diabetes management knowledge among staff supporting perioperative care.[118–120]

Having insulin function at an appropriate level by addressing perioperative hyperglycaemia can support its ability to reduce oxidative stress and clear free radicals,[121] as well as improving endothelial and white cell

function,[122–124] which could contribute to the reduced risk of surgical site infections and mortality.[125,126]

It has also been observed that having a known diagnosis of diabetes *before* surgery is associated with a reduced risk of hyperglycaemia-associated harm.[89,90,127] This could reflect the fact that knowing about diabetes early can serve as a means of highlighting potentially 'at risk' individuals, resulting in more vigilance, and potential perioperative hyperglycaemia-related issues are identified and addressed earlier.[127]

Perioperative management of diabetes

Given the risk of harm associated with perioperative hyperglycaemia, the case to optimise diabetes management ahead of elective surgery is compelling. This requires a co-ordinated approach between different clinical teams supporting the person with diabetes. Current evidence suggests that the risks of post-operative morbidity and mortality increase when the HbA1c is above 64 mmol/mol (8.0%), with guidance from the UK JBDS-IP recommending a pre-operative level of less than 69 mmol/mol (8.5%).[5]

The surgical pathway usually starts with a referral from primary care to a surgical team for consideration of an operation. Evidence would suggest the quality of diabetes-related communication between primary care and surgeons could be improved.[108,115] Knowing about an individual's diabetes status can reduce the risk of a poorer outcome,[89] possibly in part due to increased diabetes care and attention in hospital. This relies on the primary care referrer informing the surgical team. This would allow referral to a diabetes team and likely reduce the risk of the operation being postponed or cancelled because of pre-operative hyperglycaemia and post-operative harm.

Interventions to improve surgical outcomes in people with diabetes

Before an elective surgical admission

Once the surgeon has made the decision to operate on a person with diabetes, they should liaise with other members of the multidisciplinary team, including anaesthetists, theatre list co-ordinators and the surgical pre-assessment team to co-ordinate care. The starvation time can be reduced by listing a person with diabetes for an operation earlier in the day, thereby reducing the later risk of metabolic problems. Pre-planning increases the chance for same-day admission while allowing any pre-operative concerns around glycaemic management to be discussed and prompt consideration to be made for a potential post-operative admission to a critical care setting when necessary.

An increasing number of hospitals have put processes in place to reduce diabetes risk associated with perioperative care.[128] Involving the relevant teams to optimise elements of diabetes management and other comorbidities should also be built into the routine processes of elective surgical planning.[129] There should be open clear communication between all associated clinical teams, with the patient having clear understanding of their admission date and time as well as what adjustments to make to their diabetes medications if indicated.

It is important to offer individuals with diabetes day-case surgery when appropriate to reduce unnecessary admissions the night before.[130] It is likely that there will be fewer staff available with appropriate diabetes management skills overnight and presumptions that admission the day prior to surgery will improve optimisation of blood glucose levels are erroneous.[118–120] Increasing the frequency of capillary glucose monitoring from the point of surgical pre-assessment in clinic through to the time of admission can help ensure diabetes- or non-diabetes-associated hyperglycaemia is identified and acted on earlier.

The second of the two rapid literature reviews we conducted as part of the first phase of the OCTOPuS project to design the intervention sought to determine what pre-admission interventions to improve surgical outcomes had been published already. We identified five publications describing four separate studies, three of which were conducted in the USA[131–134] and one in Australia.[135] Only one study included any randomisation,[135] and one other prospectively collected some data and compared this to retrospective data.[131,132] The other two studies relied entirely on retrospective data obtained from databases.[133,134] Where this information was stated, either all[135] or the majority[131,132] of participants had type 2 diabetes. All the studies describe the provision of a specialist clinic or service, within an existing pre-operative clinic or centre, for people who were listed to undergo elective surgery. Only in Mendez *et al.* was one individual responsible for delivering the service (a physician diabetologist); in the other studies, a small team delivered the service.[134] All the clinics or services included glucose monitoring, typically increasing the frequency of this monitoring, and all included a review of medication. Adjustments to existing therapy (insulin or non-insulin drugs) with commencement of insulin therapy or other drug therapies were made if clinically appropriate. Dietary information was likely included in all services; although this is not mentioned by Garg *et al.*,[133] this management

programme is based on that described by Underwood *et al.* and Garg *et al.*[131,132] The content of any dietary advice was not described in detail by any of the studies. Physical activity recommendations were not mentioned by any of the studies and therefore it seems unlikely that physical activity formed part of any of the advice provided by these clinics and services. Participants in the studies were typically seen face to face. However, in the study by Underwood *et al.* and Garg *et al.*, patients were contacted by telephone if they were not available for an in-person consultation.[131,132] In Garg *et al.*, half of the patients were managed only over the telephone.[133] The follow-up visit after an initial face-to-face visit in the Mendez *et al.* study could be in person or via the telephone.[134] Mendez *et al.* appeared to be the only study which clearly stated there was more than one visit prior to surgery; the other services appeared to include only one pre-surgical consultation.[134]

Two of the 4 studies involved small numbers of patients (fewer than 15 receiving the intervention);[134,135] 1 included 386 patients (226 in phase I and 160 in phase II of the study).[131,132] The largest study was that of Garg *et al.* which appeared to be a wider assessment of the management service reported by the earlier Underwood *et al.* and Garg *et al.* studies.[131,132] This included reporting on 1835 people with diabetes in the intervention phase and 2074 with diabetes in the control phase.[133]

Three studies reported that a pre-operative intervention led to reduced pre-operative HbA1c and/or glucose.[131–134] The large study by Garg[133] reported that the intervention significantly shortened the length of hospital stay, whereas the small study by Lee found no significant difference.[135] Although the proportion of patients receiving intravenous antibiotics after 24 hours of admission fell and re-admission was reduced in the Garg study,[133] neither of these effects could be attributed to the intervention, as both were also improved in the patients without diabetes, and the *p*-values for interaction did not reach statistical significance. No statistically significant differences were observed for the other outcomes, including discharge, death, renal failure or doubling of serum creatinine, acute MI and stroke.

During the hospital admission

Optimising blood glucose levels during a hospital admission for an operation is associated with improved outcomes.[125,136] Furthermore, persistent post-operative hyperglycaemia may delay wound healing or increase the risk of hospital-acquired infection, both of which can also delay discharge. Hence, all staff involved in the patient's care and associated staff should be clear on their care plan and ensure that relevant local perioperative diabetes guidelines and protocols are followed. The need to maintain and support optimal glycaemic management should be clear to all associated staff.

While the person with diabetes is in theatre and in recovery immediately afterwards, it is essential that regular blood glucose and electrolyte monitoring is performed, seeking to maintain a state of normoglycaemia.[137] The use of analgesia and antiemetics as indicated can also both support an early return to a normal diet and usual diabetes treatment if the latter is still deemed appropriate.

It is not uncommon for elements of diabetes mismanagement, associated with insufficient staff knowledge, to contribute to a prolonged stay in hospital after surgery.[118–120] Insulin errors can also delay discharge, and although involvement of diabetes specialist nurses supports earlier discharge, only a minority of patients are seen by them in hospital.[138] Use of electronic prescribing and involvement of specialist diabetes pharmacists have contributed to reducing errors associated with insulin use.[139–141]

Several international diabetes organisations, including JBDS-IP, have prioritised earlier discharge planning, involving collaboration between the person with diabetes and diabetes teams, as a means of reducing the LOS.[4–8]

Hospital discharge

Discharge planning for individuals with diabetes should commence at the pre-operative stage, thus identifying factors that could delay discharge early, so pre-emptive actions can be taken. Individuals should be aware that blood glucose levels may be deranged for several days after surgery, in response to the impact of dietary changes, reduced physical activity and increased stress hormone as a result of the surgery. There may be a need for increased blood glucose monitoring, as well as possible change in diabetes treatments or doses.

The role of the diabetes specialist team

Involvement of inpatient diabetes teams has reduced hypoglycaemia and 30-day re-admission rates, as well as LOS.[142] Inpatient diabetes specialist teams are usually multidisciplinary and often include a consultant in diabetes, diabetes nurses, pharmacists, diabetes dietitians and vascular teams. This diverse clinical team can then work collaboratively, offering their specialist skills as needed to support the delivery of holistic diabetes care. It is important that the diabetes teams work closely with non-specialist teams who will often be primarily responsible for this group of patients recovering from surgery. Involvement of the specialist diabetes team,

and, in particular, diabetes nurses, contributes to an improved patient experience, a reduction in insulin errors, a shorter duration of inpatient stay as well as a reduced rate of hospital re-admissions.[130,138,143–145] Even with this positive contribution from multidisciplinary diabetes teams to support diabetes care in hospital, results from the 2019 National Diabetes Inpatient Audit revealed that almost 20% of UK hospitals do not have diabetes nurses supporting inpatient care, with even fewer hospitals supporting inpatient podiatry or dietetics.[87]

Staff education Aside from offering clinical support, another key role for inpatient diabetes teams is to educate other ward-based non-specialist HCPs, as well as nursing, pharmacy, dietitian and medical students. As a requirement for broader elements of diabetes knowledge beyond blood glucose monitoring are often not deemed to be mandatory for staff, people with diabetes, who may be well informed about the disease, are often cared for by nursing and medical staff who only have a limited knowledge of diabetes.[118–120,146] Hence, it is strongly recommended that diabetes physicians take responsibility for educating junior medical staff, while specialist nurses and pharmacists educate ward-based staff. This can be opportunistically offered when patients are being reviewed. Using the multidisciplinary diabetes team helps to ensure that consistent diabetes educational messaging, particularly around supporting safe care, will help to maximise the impact of education in hospital at scale.

Getting It Right First Time initiative

The NHS England Getting It Right First Time (GIRFT) initiative is a national programme designed to improve the treatment and care of patients through in-depth review of services, benchmarking and presenting a data-driven evidence base to support better clinical practice. The programme has identified considerable variation in the LOS for people with diabetes undergoing surgery across England. This presents an opportunity to increase patient experience and outcomes through improved HCP education in this area and sharing of best practice.

The Improve the Perioperative Pathway for Patients with Diabetes (IP3D) project at Ipswich Hospital has brought about a 1.4-day reduction in LOS, with more day-case surgery, and led to patients feeling more involved in their diabetes care.[147] There were also significant improvements in episodes of hypoglycaemia and hyperglycaemia, wound complications and diabetes-related complications. Key elements of the programme were the use of a patient-empowering perioperative passport and the employment of a perioperative diabetes specialist nurse.

Under the auspices of the GIRFT initiative, the IP3D model of care is now being delivered to 10 trusts across the UK.[88] Each trust has received an initial visit from the GIRFT IP3D programme manager, and over an 18-month period, GIRFT is supporting trusts to implement the core features of the programme with the aim of establishing whether the benefits seen in Ipswich can be replicated elsewhere.

Rationale, hypothesis and objectives

Rationale

The increasing number of people with diabetes and the high prevalence of CVD in among these people have increased the demand for cardiac surgery. Currently, up to 35% of those presenting for elective cardiac revascularisation have diabetes.[87,148] Similar to other types of surgery, these individuals experience an increase in the risk of wound and chest infections, renal impairment and death.[5,149–153] They have longer lengths of hospital stay and higher re-admission rates, placing a large financial burden on the NHS.

International and national groups, such as the JBDS-IP, have provided recommendations to improve the management of adults with diabetes undergoing surgery.[4–8] As suboptimal perioperative hyperglycaemia is associated with an increased risk of all surgical complications, the guidelines recommend improving glycaemic management to optimise surgical outcomes.

There are currently two important uncertainties in the management of people with suboptimally managed diabetes undergoing intermediate and major surgery:[154]

1. how to improve glycaemic management in the weeks leading up to an elective procedure, and
2. whether that improved glycaemia is reflected in improved outcomes post surgery.[98]

Practice is varied, with current UK guidelines recommending a delay to surgery if HbA1c is above 69 mmol/mol; whereas in the USA, guidance recommends considering delaying surgery at HbA1c above 53 mmol/mol. The NICE guidelines at the time of application recognised an evidence gap,[155] as did the JBDS-IP.[5]

In the 5 years leading up to funding of this project, the diabetes team at the Royal Bournemouth and Christchurch Hospitals Foundation Trust in Dorset developed a nurse-led outpatient intervention, delivered in the 3 months before elective lower-limb orthopaedic surgery, to people with suboptimally managed diabetes. Using this intervention, they achieved a reduction in HbA1c from

a mean of 85 mmol/mol at first referral to 74 mmol/mol on admission for surgery.[154] This has been associated with a reduced LOS from a mean of 5.9 days to a mean of 3 days, while the LOS for those without diabetes remained constant at 5 days. Other work has shown the practicality of improving HbA1c over a period of weeks in primary care.[156]

The OCTOPuS project set out to adapt and manualise the Bournemouth intervention to be used in other surgical centres, and for elective major surgery beyond joint replacement. We then planned to test the adapted intervention, to assess its effectiveness in improving outcomes in people waiting for surgery compared to usual care.

We needed a defined set of procedures in order to address the uncertainties. Our main goal was to reduce the duration of hospital stay, but we also wanted to look at the incidence of surgical complications. We considered three possible surgical configurations when designing this study: (1) any major surgery, (2) major procedures in two or more surgical disciplines – for example, orthopaedic and gynaecological major procedures and (3) one exemplar discipline.

While the first two options potentially offered a more generalisable conclusion, the inherent differences in LOS and complication rates across many different surgical procedures would make it significantly harder to demonstrate an effect of the intervention and would thus significantly inflate the required sample size with resulting increase in the cost of the trial and logistical difficulties in trial management.

We, therefore, chose to investigate the effectiveness of the intervention for people with diabetes by using a specific surgical discipline as an exemplar. This allowed us to work with a limited set of surgical colleagues, using similar surgical procedures which prevented the procedure from becoming a confounder of our outcome of interest. We chose cardiothoracic surgery due to the high prevalence of CVD in people with diabetes and consequently a high proportion of people with diabetes undergoing procedures in this specialty, especially cardiac revascularisation. In 2017, the waiting time for people listed for elective cardiothoracic surgery in the UK was 12–16 weeks for their procedure, thus providing sufficient time for our intervention to be delivered effectively without having to delay care. As the major surgical insult, sternotomy, is consistent, a potential major confounder is removed. Furthermore, cardiothoracic surgery is the first specialty in the UK where all patients and procedures are centrally registered (in the Society for Cardiothoracic Surgery National Adult Cardiac Surgery Audit) and outcomes are systematically collected and collated, and summary information is openly published.[157] By using a single surgical discipline, we were also able to access the relevant surgical communities through their specialist society – in this case, the Society for Cardiothoracic Surgery in Great Britain and Ireland.

If the pre-operative intervention was successful in improving glycaemic management, this may reduce the complication rate and improve the clinical outcomes. It may also have proved cost-effective and even cost-saving.

Hypotheses

This project set out to address whether a pre-operative outpatient intervention delivered by a multidisciplinary diabetes team could improve glycaemic management and improve cardiothoracic surgical outcomes for people with diabetes.

The hypotheses were threefold:

- It is possible to develop a patient-acceptable manualised intervention, which can be delivered to people with suboptimally managed diabetes through an appropriately trained clinician (e.g. doctor, nurse, pharmacist) in the 3 months prior to an elective cardiac procedure.
- This intervention will improve the HbA1c of the person with diabetes between baseline and the time they are admitted for their elective procedure.
- People who receive the intervention will have a shorter LOS and fewer post-operative complications than those who do not.

Aims and objectives

This study aimed to investigate whether an outpatient-based intervention, delivered in the weeks running up to elective major cardiac surgery, could improve outcomes of people with suboptimally managed diabetes. To do this, we adapted an intervention, which had been used for several years for people undergoing elective orthopaedic surgery in Bournemouth, to make it suitable for a broader UK cardiothoracic population. We used the approach recommended by the Medical Research Council (MRC) complex intervention framework to do so.[158]

We set out to do the following:

1. In partnership with people with diabetes, people who have undergone cardiac surgery and clinicians,

adapt the Bournemouth intervention to be applicable to our more geographically dispersed cardiothoracic population.
2. Conduct a multicentre RCT in adults with suboptimally managed diabetes who are scheduled for elective cardiac surgery. The trial protocol included rules, which would result in stopping the trial early if we could not recruit sufficient centres or participants or if we failed to show the anticipated physiological effect of the intervention of a reduction in HbA1c
3. Ensure fidelity of the intervention when scaled up, through a robust assessment of its delivery.
4. Through qualitative and psychosocial research, assess whether the intervention when scaled up, is appropriate and acceptable to clinicians and people with suboptimally managed diabetes.
5. Undertake a health economic evaluation of the intervention.

Overview of the rest of the report

The first phase of the project was to develop the OCTOPuS intervention. This was undertaken following the MRC framework for the development of complex interventions[158] and adapted from a pre-operative nurse-delivered intervention, which had been used for several years for people undergoing elective orthopaedic surgery in Bournemouth. At the outset, the exact configuration and components of the intervention were not fixed, but we envisaged an initial consultation with a trained HCP, who would advise on diabetes management as well as the likely benefits that improved glycaemia would provide in the run-up to surgery. The patient and practitioner would agree on an action plan tailored to the individual needs and capabilities of the patient. These were 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 among the cardiothoracic community that limited exercise can be allowed prior to surgery. This needs to be individualised for each person and should not provoke symptoms. The usual format of exercise suggested is walking on the flat, for short, frequent, episodes.
- Dietary advice, possibly supplemented by a consultation with a dietitian.
- Medication review, which may lead to the introduction of insulin. Treatment choices would be guided by NICE guidelines[159] and the European Association for the Study of Diabetes (EASD) – ADA consensus reports on the management of type 1 diabetes and type 2 diabetes.[15,28]
- Specific advice about managing expectations, understanding facilitators to achieve change and overcoming barriers to improve medical and psychosocial outcomes.

After the initial consultation, there would be regular review with the OCTOPuS practitioner, probably by telephone once a fortnight. This will be an opportunity to offer encouragement and support and address any issues which have arisen for the patient. Where necessary, the OCTOPuS practitioner would liaise with local services, for example, the patient's general practitioners or a dietitian, to facilitate delivery of the action plan.

It was envisaged that the OCTOPuS practitioner would be a clinically qualified HCP with expertise in diabetes. They would most likely be a diabetes nurse specialist but might, for example, be a pharmacist, dietitian or physician. The OCTOPuS practitioner would receive additional specific training about the OCTOPuS intervention.[154]

The management of diabetes is multifaceted, and it was important to understand the modifiable factors associated with poor surgical outcomes in people with diabetes. We, therefore, undertook two rapid literature reviews to ensure that all potential elements of the intervention were considered and to determine what pre-admission interventions to improve surgical outcomes had been evaluated previously. The results of these reviews are described above.

We then consulted on these findings and the content of the Bournemouth intervention with HCPs. People with diabetes who had undergone surgery discussed the intervention as well as the Patient Involvement Advisory Group and local branch of Diabetes UK. Having agreed the content, we manualised the intervention (see *Report Supplementary Material 1*).

The next step was to pilot the intervention in a single centre to test its acceptability and feasibility for people with diabetes awaiting cardiac surgery and the HCPs delivering the intervention to allow further adaptations as necessary. This process was reported by Holt *et al.* in Pilot Feasibility Studies,[160] which forms the next section. In summary, we recruited 17 people with diabetes awaiting cardiothoracic surgery. Thirteen people recruited completed the study and underwent cardiothoracic surgery. All components of the OCTOPuS intervention were used, but not all parts were used for all participants. Minor changes were made to the intervention as a result of feedback from the participants and HCPs. Median (interquartile range)

HbA1c was 10 mmol/mol (3–13) lower prior to surgery than at baseline.

In parallel to the development of the intervention, we needed to prepare the protocol for the main trial. The aim of the main trial was to compare the clinical effectiveness and cost-effectiveness of the OCTOPuS intervention compared with usual care. To do this, it was important to carefully define the 'usual care' and so we designed a survey for cardiothoracic surgeons to explore the management of people with diabetes in UK cardiac surgery units. This survey was sent to cardiothoracic surgeons who were members of the Society of Cardiothoracic Surgery in Great Britain and Ireland. Sixty-two cardiothoracic surgeons from all 33 UK cardiac centres completed the survey. The survey indicated that there is only limited perioperative management of diabetes in people undergoing cardiac surgery in the UK and considerable variability from one centre to another and within centres. The results of the survey were published by Luthra *et al.* in Diabetic Medicine[161] which is reproduced in Current management of people with diabetes during cardiothoracic surgery.

The pilot study was almost completed by the time of the first UK lockdown for the COVID-19 pandemic in March 2020, and we decided to end the study and make plans for the main trial to commence once services returned to normal after COVID. Despite the challenges of COVID, the research team made significant progress in the preparation for the full trial. This included:

- development of the trial database
- randomisation system established
- trial documentation completed
- trial website created
- research ethics and governance approval
- recruitment of four external sites to Southampton.

The trial protocol was published by Holt *et al.* in *BMJ Open*,[154] which is reproduced in Development of protocol for main randomised controlled study. The intervention manual was published as a supplement to this paper.

The final section of the report describes the lessons learnt from the pilot study. It then goes on to discuss why the trial could not be completed as planned before giving research recommendations for alternative ways of testing the effectiveness of the intervention.

Intervention development and feasibility study

Holt RIG, Barnard-Kelly K, Dritsakis G, Thorne KI, Cohen L, Dixon E, *et al.* Developing an intervention to optimise the outcome of cardiac surgery in people with diabetes: the OCTOPuS pilot study. *Pilot Feasibility Stud* 2021;**7**:157.

Current management of people with diabetes during cardiothoracic surgery

Luthra S, Salhiyyah K, Dritsakis G, Thorne KI, Dixon E, Ohri S, Holt RIG; OCTOPuS study group. Diabetes management during cardiac surgery in the UK: a survey. *Diabet Med* 2021;**38**:e14388. https://doi.org/10.1111/dme.14388. Epub 6 October 2020.

Development of protocol for main randomised controlled study

Holt RIG, Dritsakis G, Barnard-Kelly K, Thorne K, Whitehead A, Cohen L, *et al.*; OCTOPuS Study Group. 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. *BMJ Open* 2021;**11**:e050919. https://doi.org10.1136/bmjopen-2021-050919

Discussion and conclusions

Summary of findings

The pilot study demonstrated that it was feasible to develop a manual for the pre-operative management of people with diabetes that was acceptable to both people with diabetes and HCPs. The intervention involved regular contact between a specialist diabetes team and the person with diabetes in the time between listing for surgery and the operation.

The manual[154] encompassed optimal diabetes management as recommended by NICE[159] and the EASD-ADA consensus reports and focused on areas beyond glucose management.[15,28] This was important given the many reasons beyond glucose that affect surgical outcomes in people with diabetes. We were keen to avoid contentious management plans to ensure the manual was appropriate for a broad clinical audience to help with implementation. We were aware the diabetes management has evolved rapidly in recent years, and we always expected that the manual would be a 'living document' that could be updated as clinical guidelines and diabetes management change.

The study provided useful information about how to implement the intervention. Initially, we had envisaged a first contact between the patient and diabetes team on

the day that the surgery was booked. We chose this model to reduce the number of hospital visits, but for logistical reasons, it was impossible to arrange the review on the same day. Partly, this reflected the working patterns of the diabetes teams, but we also found that many patients were exhausted after all the other pre-operative assessments and information given during the cardiothoracic outpatient appointment. We, therefore, created a dedicated once-weekly OCTOPuS clinic. Furthermore, as previously noted,[115] many referrals did not contain information about a diagnosis of diabetes. Although this could disadvantage people living at a distance from the hospital, it meant that patients were more receptive to advice about diabetes management. This clinic was designed as an in-person visit but could be delivered remotely to prevent a further visit to the hospital. At the time, this was not common practice but has been widely implemented in diabetes care following the COVID-19 pandemic.[162]

Two further changes were made to the visit schedule. Based on participant feedback, the manual was modified to reduce the frequency of contacts from at least once a fortnight to a minimum of once every 6 weeks once the diabetes management had been optimised and no further changes were possible to improve the clinical state. This reduced participant burden and freed up the HCP team. We also added a final post-operative contact in response to participant feedback to improve the continuity of diabetes care after discharge. During the qualitative study, it became apparent that the participants valued the interaction with the OCTOPuS practitioner and felt that this came to an abrupt end when the person was admitted for surgery. While the participants recognised that ongoing contact with the OCTOPuS practitioner was not possible in the long term, they expressed a desire for one post-operative contact to provide a management plan as care returned to primary care.

The minimal clinically relevant change in HbA1c is estimated to be 5 mmol/mol. The pilot study indicated that we were able to support a reduction of 10 mmol/mol between enrolment and surgery. This is similar to the 11 mmol/mol HbA1c reduction seen with the Bournemouth intervention, despite the lower mean baseline HbA1c of our participants.

We were surprised by how many people had a baseline HbA1c below the inclusion threshold of > 53 mmol/mol (7%). Previous studies, such as the E-CABG registry,[2] have reported much higher pre-operative HbA1c values, and it is unclear why our participants had better glucose management. It is possible that the JBDS-IP guidelines[5] have promoted greater awareness of the need for optimal glycaemia in people with diabetes awaiting surgery.

The OCTOPuS project was originally conceived for adults aged under 75 years because of concerns about overaggressive glucose lowering in older people and the risks of iatrogenic hypoglycaemia. As the pilot study progressed, it became apparent that this excluded a significant number of people, reducing the generalisability of the intervention. More older people with comorbidities, of which diabetes is a major contributor, are being referred for cardiothoracic surgery, and it was important to ensure that the intervention could be used for this age group.[10]

The participants in the pilot trial communicated a good understanding of the purpose of the intervention. However, while most participants said they were aware that a relationship existed between diabetes management and surgical outcomes, they expressed very limited knowledge on this topic. Some participants provided brief anecdotal commentary when asked about their understanding of the relationship, while one participant reported never having thought about the relationship before. This was important because we approached several patients with elevated HbA1c who declined to participate because they thought their glycaemic management was good enough. Although important for study recruitment, this also has implications for implementation of the intervention. Education about the importance of diabetes management should, therefore, form part of the clinical discussions about referral for cardiothoracic surgery.

Participants generally understood the logistical aspects of the trial and that it would involve regular contact with HCPs as participants prepared for their upcoming surgery. A few participants mentioned that they had contact information or knew who to call if they needed support. Two participants expressed confusion regarding the duration of the study and whether it would continue after the operation. Participants appeared motivated to make changes and improve their health. Among participants who had already received advice from HCPs in the trial, most found this advice to be helpful and felt confident that they would be able to make the advised changes.

Healthcare professionals were supportive of the holistic approach as well as the use of phone calls to provide regular support to participants. HCPs believed that the ability to receive support from a specialist was a major benefit for participants, as many had not previously had access to one. Accordingly, the HCPs felt this was an opportunity to help people with diabetes that they would not normally get to see. While HCPs felt participants generally understood the demands of the intervention, they expressed some concern about patients' limited knowledge regarding the relationship between diabetes

management and surgical outcomes. HCPs described how patients often did not recognise the link between their diabetes and other conditions. HCPs who expressed these concerns also suspected that general practitioners were not regularly conveying this type of information to their patients. Despite these concerns, HCPs were optimistic that participants would be motivated to make behavioural changes. HCPs felt participants were driven by their circumstances and the high stakes involved in major surgery. Overall, HCPs generally reported that the participants would be capable of coping with the demands of the trial and intervention. However, HCPs still felt that there would be challenges for participants. In particular, HCPs felt weight loss and behavioural changes would be the most difficult. They were generally less concerned about participants' ability to take new medications as prescribed. Furthermore, HCPs were uncertain about the long-term outcomes and whether participants would be able to maintain behavioural changes over time. HCPs described various challenges encountered during the pilot trial. There were logistical issues, such as diaries not being uploaded on time, which made it difficult to provide phone call support. Another concern was the slow pace of recruitment. HCPs also discussed potential barriers to delivering the intervention in routine practice. There were concerns about whether HCPs would be available to see patients and if they would be able to reach patients at the right time. Despite these challenges and barriers, HCPs generally remained enthusiastic about the intervention's potential and the possibility that it could be delivered in routine practice.

Recruitment rate for the pilot study

We were concerned about the low recruitment rate for the pilot study (17 of the 153 potential participants; 11.1%), and we undertook a detailed analysis of the reasons for the low uptake. We can divide these into two main groups: those that relate to the clinical relevance of the intervention, and those that relate to trial-related activities. When deciding the applicability of the study intervention to a generalised patient population, the first group of reasons are important, although the latter reasons are also important to consider when considering the main trial and its recruitment.

Clinical relevance of the intervention

Four of the 153 did not have diabetes and so should not have been considered for the trial, but this highlights the problem of inaccurate recording of diabetes in the notes.[115] Thirty required urgent surgery or were not listed for open heart surgery. In addition, three people did not attend their cardiothoracic outpatient clinic and were therefore not considered for surgery. Arguably, those not listed or considered for open-heart surgery should not have formed part of the denominator, as these people did not go forward for surgery. The reason for excluding people waiting for urgent surgery was that if an urgent operation was required, there would be insufficient time for an outpatient intervention to have an effect prior to surgery. Two people opted for private surgery at a different hospital. Post trial, people opting for private surgery could still be offered the intervention but were excluded from the trial because of the challenges involved in undertaking research observations in a private hospital without a research infrastructure.

Thirty-five (23%) potential participants had a HbA1c < 53 mmol/mol. We were surprised by this, as this was not the experience in Bournemouth in people awaiting orthopaedic surgery or in other reports.[2] In practice, however, we do not believe that an intervention that particularly targets glucose management is likely to be of benefit for those with a low baseline HbA1c. There were a further three participants who declined to take part because they thought that their diabetes was 'well controlled' and therefore would not benefit from the intervention. In real-life clinical practice, those with elevated HbA1c should be encouraged to take advantage of the diabetes review by the referring clinician.

Initially, our protocol excluded people aged over 75 years old because of the differential benefit–risk considerations for glucose management in older people. When it became apparent that there was a significant number of people with diabetes aged over 75 years old undergoing surgery, we changed the trial protocol to include these individuals and this improved our recruitment rate.

Nine people were excluded because they had had previous cardiac surgery. This exclusion criterion was made because of the different LOSs for people undergoing a second sternotomy. In reality, the difference would probably not have a major effect on the power calculation for the trial, and if the intervention was implemented in clinical practice, there would be no need to exclude these people.

Of the remaining 35 people who did not participate for personal or other reasons, some did not want to travel back to the hospital for a further diabetes appointment. This is entirely understandable given the distance that some patients lived from Southampton. We could have addressed this barrier by offering a virtual first appointment as a feasible alternative to providing the intervention face to face. Overall, we, therefore, estimate that if the intervention were proven to reduce LOS and adverse surgical outcomes, the numbers who would potentially

benefit in clinical practice would approach two-thirds of those listed for routine surgery.

Why we were unable to undertake the trial

Impact of COVID on cardiothoracic surgical services

The COVID-19 pandemic caused an unprecedented and challenging impact on delivery of medical and surgical services. Globally, health services were overwhelmed, and there was drastic scaling down of specialist services. National emergency plans were established to ring-fence respiratory services, ICU beds and ventilator capacities to care for those developing severe COVID-19 infection while HCPs were redeployed to front-line areas. This led to significant disruption of normal rotas and work shift patterns and diverted resources and personnel from cardiothoracic surgery services with severe curtailment of delivery of cardiac care.[163–169]

The number of people on waiting lists for invasive heart procedures and operations in England increased by over 40% following the pandemic.[170] By the end of February 2021, almost 204,000 people were on waiting lists for cardiac procedures and operations. There has been a 50% rise in people waiting for more than 18 weeks for a heart operation or heart procedure, with 48,390 waiting in February 2021 compared to 32,186 before the pandemic. Over 5000 people had waited more than a year for heart surgery or other procedure by the end of February 2021, compared with just 28 people in the same month the previous year.[171]

The effect of the COVID-19 pandemic has been assessed on cardiothoracic surgical services in Southampton, with the utilisation and efficiency of the operating room compared during the lockdown period and the immediate pre-pandemic.[172] Southampton provides a quaternary multispecialty teaching hospital in the South East of England and was the site of the OCTOPuS pilot study. In the 3 months preceding the 2020 UK COVID-19 lockdown, 304 operations were performed compared with only 59 during a comparable period during lockdown. There was a significant reduction in workflow, with the capacity for operations per operating theatre falling from six cases per day to three cases per day. Overall, a median of five operations were performed per day pre COVID compared with only one during the COVID lockdown. Operating theatre capacity was < 50% for 55% of the time compared with 8.5% of the time pre COVID. No operations were performed on almost half of the days (43%) during the COVID lockdown period; by contrast, operations were performed on every working day prior to the pandemic.

The change in operating theatre availability altered the characteristics of the patient group who had their operations during COVID. All elective surgery was completely stopped due to pressure on resources and manpower during various stages of the pandemic. Those who underwent surgery were younger (median 62 years vs. 69 years), were at higher risk (logistic European System for Cardiac Operative Risk Evaluation 6.6 vs. 4.7, $p < 0.01$) and required longer ICU admission (51 hours vs. 48 hours, $p = 0.05$), although the intubation times and the overall LOS did not change significantly. Induction times and sign-out times from the recovery room were significantly longer for the COVID period, although preparation times and surgical times were no different.

The experience in Southampton is not unique with a major reduction in the number of cardiac surgery operations worldwide during the pandemic.[163–169] Utilisation and efficiency in the cardiac operating room is central to resource and manpower usage, revenues and output through the overall cardiac surgery care pathway. The pandemic created an unprecedented emergency with reduced efficiencies and loss of operating room and ICU capacity. Part of the reduced flow was caused by the additional measures needed to screen patients and staff to reduce cross-infections. The challenge was to mitigate cross-infection despite constrained resources and manpower while maintaining efficient workflow in the critical parts of the cardiac surgery care pathway.[167,173–175]

Coronavirus disease continues to have an influence on cardiothoracic surgical services. Cumulatively, waiting lists have grown as trusts have prioritised emergency services with resources diverted from specialist services. The current waiting time in Southampton as of December 2023 is now almost a year, and capacity has only just returned to pre-COVID levels in the last few months. People who are currently being listed for surgery tend to be at higher risk as delays in accessing primary care have had knock-on effects to reduce referrals to cardiology and then onwards for cardiac surgery.

Impact of Coronavirus disease on diabetes services

The intervention was designed to be delivered by specialist diabetes teams. COVID also disrupted diabetes teams, who were often redeployed to acute medicine services during COVID.[176–178] Clinic visits were also postponed, and treatment for diabetes-related issues delayed. The reduced access to routine diabetes care was associated with fewer new diagnoses of diabetes, poorer self-management and

reduced availability of diabetes medications and devices, all of which led to compromised glycaemic levels.[179] In the UK, fewer people had all eight regular diabetes care assessments (i.e. weight, BP, cholesterol, smoking status, HbA1c, urinary albumin, serum creatinine and foot examinations).[180] Arguably, diabetes services have recovered quicker than cardiothoracic surgery services, but the impact of COVID limited the ability of diabetes team to participate in this research.

Impact of coronavirus disease on research capacity

Clinical research is embedded within the NHS and formed an important part of the response to the COVID-19 pandemic.[181] The UK Department of Health prioritised COVID-19 research projects, labelled Urgent Public Health studies, have commenced, and a large number of COVID-19 studies were set up and rolled out across UK hospitals. The NHS's existing research infrastructure supported and facilitated this research and has received international praise.[182–184] While instrumental in combatting the COVID-19 pandemic, the change in focus had a substantial impact on non-COVID-19 research. There was reduced availability of research staff for non-COVID studies, and regulatory bodies have been slower in supporting these studies. The pandemic increased the number of trials that were suspended, terminated or withdrawn.[182]

In May 2020, the Department for Health and Social Care and NIHR circulated a framework for restarting new and paused non-COVID-19 research.[185] Research studies were stratified into three levels of priority, but the framework did not distinguish between commercial and non-commercial research. Recommendations on which research studies were important or urgent to restart within each directorate was managed at a trust level. However, the pace of resuming non-COVID studies could not match the pace required, and uncertainty about future waves of COVID hampered efforts to restart research, leading to significant delays. Recruitment and site set-up remain disrupted. Staffing issues relating to redeployment, prioritisation of COVID-19 care or research and staff sickness has reduced capacity of research staff for non-COVID studies. This has impacted site initiation and participant recruitment.[181] There have also been reports of difficulties in recruiting and retaining research staff, in part because of the high workload and trial complexity.[186,187] Staff report feeling stressed and exhausted,[184] morale is low and there is a lack of support and opportunities for promotion.[186] The OCTOPuS project was not the only cardiothoracic study to be stopped in the wake of COVID.

Decision to terminate the project

The project team held several meetings with the HTA monitoring team to discuss the progress of the trial and the constraints placed on the project because of COVID. On 10 February 2022, the trial was suspended, pending a decision about whether to proceed to the full trial. At the time, the uncertainties of both clinical and research capacity made the trial unfeasible. However, the research question remained important, and we had hoped that we could resume the project once services had returned to a more normal level when the trial could be delivered in a more efficient way. There was minimum expenditure during the suspension which would reduce NIHR expenditure at a time when it is particularly stretched. The project was finally closed on 28 October 2022 as cardiothoracic surgery services remained significantly disrupted, and it was apparent that the trial could not be completed in a timely manner.

Patient and public involvement

The involvement of people with diabetes and CVD was integral to the OCTOPuS project trial. People with diabetes and CVD contributed to the development and progression of the project at various stages throughout the project.

Pre-funding preparation

The research team co-applicant leading on public involvement was involved with the trial from the outline bid stage. Early engagement and involvement of people with diabetes and CVD to define the research question and to determine interest in the project were facilitated by the NIHR Research Design Service South. The chief investigator presented the proposed study to the members of the NIHR Service User Research Panel to discuss the trial and obtain feedback on the potential value of the project. We discussed possible concerns with individuals who had personal experience of living with diabetes and undergoing surgery. Feedback from these service users influenced our research questions and project design.

Post-award preparatory work

Our patient and public involvement (PPI) co-applicant became too unwell to remain within the research team, and a new person with diabetes and CVD joined the trial management team once the project was funded. Our new PPI lead was involved in frequent communications (e-mail, teleconference and face-to-face meetings) to develop study protocols (including the safety protocol) and participant documentation.

Participant information sheets, consent forms and other participant-related documentation were reviewed by our PPI lead. We amended the documentation in light of their feedback.

Intervention development

During the intervention development stage of the project, the research team, supported by the PPI lead, engaged with individual people living with diabetes and CVD to help produce the prototype intervention as well as the local Diabetes UK branch. This involved discussions of the Bournemouth intervention and ways that it could be adapted to meet the needs of people undergoing cardiothoracic surgery. We conducted in-depth interviews with people who had participated in the pilot trial to modify the intervention to meet their needs.

Conduct of pilot trial

Throughout the course of the pilot trial, the progress was discussed with the PPI lead co-applicant. We discussed how we could improve recruitment for the study which led to detailed conversations about the importance of ensuring that people with diabetes undergoing cardiothoracic surgery understood the value of improved diabetes management in the months leading up to the surgery. This provided important information as we planned the main RCT.

Dissemination of the results

Our PPI lead co-applicant contributed to the analysis and preparation of the academic papers from the study.

Equality, diversity and inclusion

Equality, diversity and inclusion was considered and incorporated throughout the OCTOPuS project. The use of language followed the principles of version 1 of the NHS England Language Matters position statement.

The prevalence of type 2 diabetes is higher in people whose race is other than White and in people from lower socioeconomic backgrounds. Diabetes and surgery outcomes are also worse in these groups. The intervention was designed to reach all groups listed for cardiothoracic surgery and was delivered in a way that did not disadvantage any particular group. We were unable to determine whether our aim was achieved, as the pilot study only included 17 participants.

When planning the main trial, we aimed to recruit centres from across England to ensure that the trial was generalisable and to ensure that the intervention met the needs of all groups across the country. However, as the main trial was not performed, we were unable to determine this.

Impact and learning

The findings and learning of the OCTOPuS trial are described in the *Discussion and conclusions*. As the study was not completed as planned, it has not had the impact that was hoped at its inception. Within Southampton, we have learnt how to deliver a pre-operative outpatient intervention within the context of busy diabetes and cardiothoracic clinical services. However, without evidence of long-term impact, these services will not continue beyond the end of the project.

Implications for decision-makers

As we were unable to complete the project as planned, we are not able to make firm recommendations for decision-makers. However, the intervention is available for use by clinical teams.

Future research and recommendations

While the work package to develop the OCTOPuS intervention was successfully completed,[160] we were unable to evaluate this intervention due to issues in delivering a trial in elective cardiothoracic surgery caused by the COVID pandemic. Our pilot study has shown that the intervention, which is deliverable and acceptable to people with diabetes awaiting cardiothoracic surgery, appears to have a physiological effect. However, we do not know whether the improvement in pre-operative diabetes management translates into reduced hospital stay or post-operative complications and improves the patient journey during and after surgery. Ideally, the intervention should be tested, as originally planned, in a RCT, to establish whether it is clinically effective and cost-effective. However, there may be alternative ways to demonstrate whether this intervention is likely to improve surgical outcomes in people with diabetes.

Our choice of cardiothoracic surgery, while a reasonable choice in 2017, led to the study falling victim to the reduction in cardiothoracic surgery and substantially longer waiting lists induced by the pandemic. The effects of the pandemic have also been compounded by a gradual increase in NHS waiting times over the last decade. Cardiothoracic surgery has been slower to restore its elective services following the pandemic. This is partly

because most patients undergoing sternotomy require ventilation to be available immediately after surgery, and the availability of ventilated beds has been limited because they have been needed for people with respiratory failure due to infectious disease. Consequently, the capacity for centres to deliver elective CV procedures has reduced and is less predictable.

Given the uncertainties relating to cardiothoracic surgery for the immediate future, it would be reasonable to consider a future trial in a different, albeit common, set of exemplar procedures. The original use of the Bournemouth intervention was to optimise outcomes in people undergoing lower-limb joint replacements, and this might be a reasonable group to address. While the population would not have as high a proportion of people with diabetes as those undergoing cardiothoracic surgery, the numbers of people with diabetes undergoing hip and knee replacements are significantly larger, ensuring that it would be possible to recruit enough people for the trial. Furthermore, there would also be the opportunity to recruit more centres. While there are only 38 centres undertaking cardiothoracic surgery in the UK,[157] some of them with small volumes, there are 200 trusts delivering elective orthopaedic procedures.

The patient populations are not completely comparable. For example, people undergoing lower-limb orthopaedic surgery may be less able to undertake physical activity to improve their glucose levels. There is also less impetus to use drugs that have proven CV benefit, although many will have coexisting CVD, and SGLT2 inhibitors and GLP-1 receptor agonists are effective glucose-lowering agents in any case. Furthermore, the weight loss induced by both classes of drugs, but particularly GLP-1 receptor agonists, is likely to be of benefit in orthopaedic patients.

The average hospital stay for a hip and knee replacement is about 1–2 days and 3–5 days, respectively. Although this is shorter than for cardiothoracic surgery, there is still the potential to significantly influence LOS as well as other surgical outcomes.

Before undertaking a trial, it would be important to assess the current glycaemic levels in the target population. We were surprised how many of our potential participants in Southampton had HbA1c values within the target range. It is unclear whether this was an anomalous finding or whether it would be seen in other UK centres as a result of improved diabetes management.

The intervention and manual are published and available for use within the NHS.[154] In the absence of funding for a randomised trial, a further means to evaluate its effectiveness would be for hospital diabetes and surgical services to introduce the OCTOPuS intervention, with appropriate plans for implementation research and evaluation through case studies. Although this is less robust than a RCT and commissioners may be reluctant to fund the intervention without evidence of effectiveness, this may be a cheaper and quicker option than a full trial.

Research recommendations

1. The HTA programme should consider a further commissioned call similar to 16/25, asking for a randomised evaluation of interventions to improve outcomes for people with suboptimally managed diabetes undergoing elective major surgery. There would be no need to ask investigators to develop an intervention, as OCTOPuS has already been developed. As there may be other appropriate interventions to assess, it may be inappropriate to mandate OCTOPuS as the intervention to be evaluated.
2. In the absence of a randomised trial, NIHR might consider requesting implementation research, asking investigators to evaluate the introduction of OCTOPuS or similar interventions into practice to assess their real-world usefulness.

Conclusions

There is an urgent need to improve the surgical outcomes for people with diabetes, and one way of doing so is by optimising their clinical state prior to admission for surgery. This study has shown that it is possible to develop a clinical pathway to improve diabetes management prior to admission. Although we were unable to test the effectiveness in a multicentre RCT in cardiothoracic centres across the UK, the intervention has been made available for use and should form the basis for future research or clinical implementation.

Additional information

CRediT contribution statement

Richard IG Holt (https://orcid.org/0000-0001-8911-6744): Conceptualisation (lead), Formal analysis (lead), Funding acquisition (lead), Investigation (lead), Methodology (lead), Supervision (lead), Writing – original draft (lead), Writing – reviewing and editing (lead).

Katharine Barnard-Kelly (https://orcid.org/0000-0002-3888-3123): Conceptualisation (supporting), Formal analysis (equal), Funding acquisition (supporting), Investigation (lead), Methodology (lead), Writing – reviewing and editing (equal).

Mayank Patel (https://orcid.org/0000-0002-6609-5394): Conceptualisation (supporting), Formal analysis (supporting), Funding acquisition (supporting), Investigation (supporting), Methodology (supporting), Writing – reviewing and editing (equal).

Philip Newland-Jones (https://orcid.org/0000-0001-6056-0008): Conceptualisation (supporting), Formal analysis (supporting), Funding acquisition (supporting), Investigation (supporting), Methodology (supporting), Writing – reviewing and editing (equal).

Suvitesh Luthra (https://orcid.org/0000-0001-7911-1894): Formal analysis (equal), Investigation (supporting), Methodology (supporting), Writing – reviewing and editing (equal).

Jo Picot (https://orcid.org/0000-0001-5987-996X): Conceptualisation (supporting), Formal analysis (equal), Funding acquisition (supporting), Investigation (lead), Methodology (lead), Writing – reviewing and editing (equal).

Helen Partridge (https://orcid.org/0009-0001-0454-7148): Conceptualisation (supporting), Formal analysis (supporting), Funding acquisition (supporting), Investigation (supporting), Methodology (supporting), Writing – reviewing and editing (equal).

Andrew Cook (https://orcid.org/0000-0002-6680-439X): Conceptualisation (lead), Formal analysis (equal), Funding acquisition (lead), Investigation (equal), Methodology (equal), Supervision (equal), Writing – reviewing and editing (equal).

Acknowledgements

University Hospital Southampton (UHS) diabetes team: Paula Johnson, Rita Trodden, Mark Green.

UHS research and development nurses: Jana Rojkova, Thea Sass, Jo Stanley, Alexandra Collier.

Southampton Clinical Trials Unit: Susi Renz, Jess Boxall, Josh Northey, Louise Stanton, Amy Whitehead, Karensa Thorne.

Trial Steering Committee (TSC): Ketan Dhatariya (chair), Debbie Stanisstreet, Kamran Baig, Merryn Voysey, Donna Drinkwater, Clare Hambling.

Southampton Health Technology Assessments Centre: Joanne Lord, Jonathan Shepherd, Petra Harris.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

The study was conducted in accordance with World Medical Association Declaration of Helsinki and as revised and recognised by governing laws and European Union directives. The feasibility trial was approved by the South Central – Hampshire A Research Ethics Committee (18/SC/0508) on 12 November 2018. The main trial was approved by the South Central – Hampshire A Research Ethics Committee (20/SC/0271) on 25 August 2020. University Hospital Southampton NHS Foundation Trust sponsored the study (RHM MED1368). The trial was registered with ISRCTN (ISRCTN10170306). The study was funded by the National Institute of Health and Care Research *Health Technology Assessment* programme (16/25/12). The day-to-day management of the trial was co-ordinated through the Southampton Clinical Trials Unit, and oversight was maintained by the TSC.

Information governance statement

University Hospitals Southampton NHS Foundation Trust is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, University Hospitals Southampton NHS Foundation Trust is the Data Controller, and information about how we handle personal data, including how to exercise individual rights and the contact details for the Data Protection Officer, is found at dataprotection@uhs.nhs.uk.

Further information can be found at www.uhs.nhs.uk/Media/UHS-website-2019/Patientinformation/Visitinghospital/Your-personal-data-and-your-rights.x6fc0ae74.pdf

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/POYW3311.

Primary conflicts of interest: Richard IG Holt has received fees for lecturing from EASD, Eli Lilly, Encore, Liberum, Novo Nordisk, ROVI and funding for conference attendance from Novo Nordisk and Eli Lilly. Richard IG Holt is the chair of the European Association for the Study of Diabetes Committee for Clinical Affairs. Richard IG Holt was a member of HTA MNCH Panel, HTA Prioritisation Committee C (Mental health, women and children's health).

Katharine Barnard-Kelly has received research funding from Dexcom, Juvenile Diabetes Research Foundation and Embecta. Katharine Barnard-Kelly has received consulting from Roche Diabetes Care. Katharine Barnard-Kelly has received fees for lecturing from Sanofi and Roche Diabetes Care. Katharine Barnard-Kelly is the founder and shareholder of Spotlight Consultations Limited.

Mayank Patel has received fees for lecturing from AstraZeneca, Boehringer-Ingelheim and Eli Lilly. Mayank Patel is a member of Diabetes Research and Wellness Foundation Editorial Board. Mayank Patel is a member of Diabetes UK HCP Advisory Committee.

Philip Newland-Jones has received consulting fees from Sanofi and Menarini and fees for lecturing from Novo Nordisk, Boehringer Ingelheim, Astra-Zeneca, Eli Lilly, Bayer and Menarini. Philip Newland-Jones is an unpaid Editorial Board member of Diabetes and Primary Care and Practical Diabetes. Philip Newland-Jones is a committee member and guideline writing group for the Centre for Perioperative care CPOC (Diabetes).

Suvitesh Luthra, Jo Picot and Helen Partridge have no competing interests.

Andrew Cook has received funding from NIHR for various projects. Funding for accommodation at a meeting in Brescia, Italy, to develop guidelines on pancreatic surgery was provided by Poliambulanza Foundation Hospital. Andrew Cook is the chair of the Trial of the Committee 2024, Society for Clinical Trials (https://sctweb.org). Andrew Cook is a member of PHR Prioritisation Group, HTA Prioritisation Committee B Methods Group, EME Funding Committee Member and EME Funding Committee Sub-Group Remit and Comp Check. Member of the Research for Patient Benefit committee for the West Midlands.

Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Health Technology Assessment programme or the Department of Health and Social Care.

This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

This trial is registered as ISRCTN10170306.

Funding

This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number 16/25/12.

Award publications

This synopsis provided an overview of the research award Optimising Cardiac Surgery ouTcOmes in People with diabeteS (OCTOPuS). Other articles published as part of this thread are:

Luthra S, Salhiyyah K, Dritsakis G, Thorne KI, Dixon E, Ohri S, Holt RIG; OCTOPuS Study Group. Diabetes management during cardiac surgery in the UK: a survey. *Diabet Med* 2021;**38**:e14388. https://doi.org/10.1111/dme.14388

Holt RIG, Barnard-Kelly K, Dritsakis G, Thorne KI, Cohen L, Dixon E, *et al*. Developing an intervention to optimise the outcome of cardiac surgery in people with diabetes: the OCTOPuS pilot study. *Pilot Feasibility Stud* 2021;**7**:157. https://doi.org/10.1186/s40814-021-00887-z

Holt RIG, Dritsakis G, Barnard-Kelly K, *et al*. 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. *BMJ Open* 2021;**11**:e050919. https://doi.org/10.1136/bmjopen-2021-050919

For more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/16/25/12).

Additional outputs

Online lecture to the 14th International Jordan Cardiac Society conference entitled 'Developing an intervention to optimise cardiac surgery outcomes in people with diabetes: the OCTOPuS pilot study'. Delivered by Richard Holt. 25 February 2022.

About this synopsis

The contractual start date for this research was in January 2018. This synopsis began editorial review in January 2024 and was accepted for publication in April 2025. The authors have been wholly responsible for all data collection, analysis

and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' synopsis and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this synopsis.

OCTOPuS Study Group

Lauren Cohen, Elizabeth Dixon, Giorgos Dritsakis, John Niven, Sunil Ohri, Kareem Salhiyyah, Kerensa I Thorne, Theodore Velissaris.

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List of supplementary material

Report Supplementary Material 1
OCTOPuS intervention manual

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/POYW3311).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ACE	angiotensin-converting enzyme
ADA	American Diabetes Association
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
ARB	angiotensin receptor blocker
BP	blood pressure
CABG	coronary artery bypass graft
CV	cardiovascular
CVD	cardiovascular disease
CVE	cardiovascular event
DPP-4	dipeptidyl peptidase 4
EASD	European Association for the Study of Diabetes
GIRFT	Getting It Right First Time
GLP-1	glucagon-like peptide 1
HbA1c	glycated haemoglobin
HCP	healthcare professional
HDL	high-density lipoprotein
HTA	Health Technology Assessment
ICU	intensive care unit
IDF	International Diabetes Federation
JBDS-IP	Joint British Diabetes Societies for Inpatient Care
LDL	low-density lipoprotein
LOS	length of stay
MI	myocardial infarction
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OCTOPUS	Optimising Cardiac Surgery ouTcOmes in People with diabetes
PPI	patient and public involvement
QOL	quality of life
RCT	randomised controlled trial
RAAS	renin–angiotensin–aldosterone system
RCTs	randomised controlled trials
SGLT2	sodium-glucose transporter 2 inhibitors

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