Full Title	Cluster randomised trial on optimising shared decision-making for high-risk major surgery
Short Title	OSIRIS trial
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Participating sites	For a list of participating sites please refer to the IRAS application

PROTOCOL CONTRIBUTORS

The Sponsor and funders have not played, nor will play a role in the study design, conduct, data analysis and interpretation, manuscript writing, and/or dissemination of results.

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1. Contents

2. Glossary of terms and abbreviations

APR	Annual Progress Report
CRF	Case Report Form
DRS	Decision Regret Score
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
MCS	Mental Component Summary
MHRA	Medicines and Healthcare products Regulatory Agency
Participant	An individual who takes part in a clinical trial
PCS	Physical component survey
PCTU	Pragmatic Clinical Trials Unit
PIS	Participant Information Sheet
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SF-12	Short form-12
SOP	Standard Operating Procedure
QALY	Quality Adjusted Life Year

3. Signature page

Chief Investigator Agreement

The study as detailed within this clinical investigation plan will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medical Device Regulations 2002 and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **Professor Rupert Pearse**

Signature:

Date:

Statistician's Agreement

The statistical aspects of the clinical study as detailed in this clinical investigation plan are in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medical Device Regulations 2002 and all subsequent amendments.

I take responsibility for ensuring the statistical work in this clinical investigation plan is accurate, and for the statistical analysis and oversight of this study.

Statistician's name: **Dr Thomas Hamborg**

Signature:

Date:

Principal Investigator Agreement Page

The clinical study as detailed within this clinical investigation plan, or any subsequent amendments, involves the use of an investigational medical device and will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), Principles of ISO14155 GCP, and the current regulatory requirements, as detailed in the Medical Device Regulations 2002 and any subsequent amendments of the regulations.

Principal Investigator Name:

Principal Investigator Site:

Signature and Date:

4. Synopsis

Full title	Cluster randomised trial on optimising shared decision-making for high-risk major surgery
Short title and / or acronym	OSIRIS Trial
Sponsor	Queen Mary University of London
Device Classification	Class I
Medical condition or disease under investigation	Surgical patients
Study design and methodology	National multi-centre cluster randomised trial
Planned number of clusters (hospitals)	40 (approx. 20 hospitals in the usual care arm and 20 hospitals in the intervention arm)
Planned number of participants	600 in total
Objectives	To evaluate the clinical effectiveness of a decision support intervention in a cluster randomised trial to improve shared decision making for high-risk surgical patients and their doctors
Inclusion and exclusion criteria for hospitals	Hospitals providing services for high-risk patients in one or more of the following surgical procedures: • Elective colorectal bowel resection for cancer, • Hip-replacement or • Abdominal aortic aneurysm surgery
Inclusion and exclusion criteria for participants	Inclusion criteria • Patients contemplating elective colorectal bowel resection for cancer, hip-replacement or abdominal aortic aneurysm surgery • Age 60 years and over • Age-adjusted Charlson co-morbidity index ≥3 Exclusion criteria • Inability or refusal to provide informed consent • Patients expected to die within 12 months of treatment
Investigational device	Decision aid
Treatment duration	Length of the surgical consultation (approximately 15-20 minutes)
Follow-up duration	180 days from patient visit at which surgery decision is made (index decision making episode)
Total duration for participants	180 days
Planned enrolment period	12 months
Planned duration of investigation	24 months
End of trial definition	The end of the study is defined as the point when the last patient has completed the 180-day follow-up

5. Introduction

Far from being replaced by new drug therapies, surgical treatments are offered to more patients than ever before. This is a particular concern for the 250,000 NHS patients at high risk of post-operative complications who undergo major surgery each year [1]. These patients are older, and usually have chronic disease. Even when surgery and anaesthesia are straightforward, one in three high-risk patients still develops medical complications in the days following surgery [2]. These complications delay recovery, with prolonged hospital stays and poor functional independence once patients return home. Critically, many high-risk surgical patients never recover from these adverse effects, suffering significant reductions in long-term quality of life and survival [2, 3]. For many, surgery is not the successful treatment they hoped for. Feelings of guilt or regret over the decision to undergo surgery are commonplace [4]. Doctors recognise the urgent need to improve decision making for this patient group but clearly feel ill-equipped to tackle this [5]. This problem is becoming more frequent as surgical treatments are offered to more patients living with chronic disease.

Understandably, surgeons and anaesthetists are focused on safe and effective care during surgery and the days that follow. High-risk patients are most likely to experience life-threatening complications during this period and receive good information about these short-term risks. Meanwhile, information on long-term outcomes is mostly focused on the index disease that surgery is treating e.g. osteoarthritis, bowel cancer or vascular disease. The benefits of surgical treatment may, however, be self-limiting for high-risk patients who experience deterioration in other aspects of their health. Few doctors have the breadth of expertise, or the detailed knowledge needed to forecast every likely long-term outcome for complex surgical patients with multiple co-morbid diseases, whilst patients often have unrealistic expectations of what surgery can achieve. High-risk patients frequently consent to surgery unaware that poor long-term outcomes may completely negate the potential benefits.

We know patient opinions about high-burden treatments vary widely, and that quality of life is valued above quantity of life in some situations [6-9]. Patients in their last year of life are more likely to accept treatments with a high risk of death but refuse those with a high risk of functional impairment [10]. Shared decision making is clearly a very different challenge for the high-risk surgical patient but there is little evidence to inform this process. It is likely that doctors and patients use different values to inform their decisions, leading to differences in forecasting and mismatch in expectations. The

information patients seek before surgery may not be the information they need to make an informed decision they do not regret. Most NHS hospitals now offer a consultant delivered pre-operative risk assessment service with access to various predictive tests. Currently these clinics only focus on short term (<30 days) risks of surgery [11], but they are also ideally suited to offer counselling and advice to complex patients about the long-term risks of major surgery and how these may be mitigated.

As the standard of decision making for the high-risk surgical patient falls further behind that of surgery in general, there is a growing urgency to address this problem. UK General Medical Council guidelines specify shared decision making as the standard of care for consent for surgery, but most doctors do not feel prepared to meet this standard for complex high-risk surgical patients for whom the risks and benefits of surgery may be uncertain [5]. There is a need for a user-friendly decision support intervention, which highlights the key information high-risk patients, and their doctors require as they contemplate major surgery, delivering this information in an accurate and easily understood way to ensure patients make an informed decision they do not regret. However, this technology might have adverse effects such as causing greater confusion or stress amongst patients contemplating surgery. It is imperative that the effectiveness of any decision support tool is assessed thoroughly before wider dissemination. The OSIRIS team has developed decision support intervention software to provide an individualised forecast of key long-term outcomes for each high-risk surgical patient, to help doctors and patients understand the long-term implications of decisions about surgery for each patient. We now need to evaluate the clinical effectiveness of this intervention.

6. Trial objectives

The primary trial objective is to determine the clinical and cost-effectiveness of a decision support intervention relative to best standard of care for shared decision making in reducing decision regret after surgery whilst not adversely affecting mental health-related quality of life at 180 days after the index decision making episode at which the decision to proceed or not proceed with surgery is made.

6.1 Primary outcome measure

The co-primary outcome measures are as follows:

- Patients' decision regret at 180 days after the index decision making episode using the Decision Regret Scale (DRS) [12]. The DRS is an easily administered 5-item Likert-type measure written to assess regret or remorse following a medical decision. To help others interpret the score more readily with other scales ranging from 0 to 100, scores are converted to a 0-100 scale by subtracting 1 from each item then multiply by 25. To obtain a final score, the items are summed and averaged. A score of 0 means no regret; a score of 100 means high regret. It has been validated as a useful indicator of health care decision regret at a given point in time [12]. DRS manual: https://decisionaid.ohri.ca/docs/develop/User_manuals/UM_Regret_Scale.pdf
- Patients' mental-health related quality of life at 180 days after the index decision making episode using the Mental Component Summary (MCS) score of the Short Form-12 (SF-12) Health Survey with UK derived weightings [13, 14]. The SF-12 Health Survey is a generic health-related quality-of-life instrument. It was originally developed in 1994 as a shorter alternative (12 items) to the widely used Short-Form 36 Health Survey, for studies in which a 36-item form was too long. The items of the SF-12 were selected to reproduce the two summary measures, Physical Component Summary (PCS) and Mental Component Summary (MCS), of the SF-36. The SF-12 mental component summary (MCS-12) scoring method proposed by Ware et al will be used, [15] this assumes that each item contributes to both physical component summary and that these two measures are uncorrelated. Validation studies have shown the SF-12 yielded acceptable results for detecting both active and recent depressive disorders in general population samples. MCS-12 use norm-based scoring, where the mental summary measures have a mean of 50 and an SD of 10 in the general population and scores greater than 50 reflect better mental health status than the general population and scores lower than 50 worse mental health.

6.2 Secondary outcome measures

- The SF-12 PCS Score at 180 days after the index decision making episode.
- Patient satisfaction with decision making using the Shared Decision-Making Questionnaire within 48 hours of decision making [16].
- Generic health-related quality of life utility, derived from participants' EQ-5D-5L questionnaire responses at 180 days after the index decision making episode.

6.3 Estimand framework

Inference on the primary outcomes is complicated by the potential occurrence of inter-current events. The estimand framework is used to describe how these events are dealt with. Details of the analytical strategy for each intercurrent event type are presented in Appendix 1. The estimand of primary interest for both primary outcomes is the participant–average (rather than cluster-average) treatment effect.

6.3.1 Primary estimand for Decision Regret Scale

In patients aged ≥60 years with age-adjusted Charlson co-morbidity index ≥3 who contemplate elective surgery for colorectal resection for cancer, total hip replacement or abdominal aortic aneurysm, what is the difference in mean decision regret score (as measured with the DRS and death defined as a score of 50) between the decision support intervention followed by any subsequent medication or procedure (as needed) compared with Best Standard of Care for shared decision making followed by any subsequent medication or procedure (as needed), at 180 days from the index decision making episode, regardless of whether surgery (if chosen) has been delayed or taken place and any deaths that may have occurred. The objective is to demonstrate statistical superiority of the decision support intervention compared with Best Standard Care for this estimand.

6.3.2 Primary estimand for Mental Component Summary

In patients aged ≥60 years with age-adjusted Charlson co-morbidity index ≥3 who contemplate elective surgery for colorectal resection for cancer, total hip replacement or abdominal aortic aneurysm, what is the difference in mean mental-health related quality of life score (as measured with the MCS of the Short Form-12 Health Survey and death defined as a score of 50) between the decision support intervention followed by any subsequent medication or procedure (as needed) compared with best standard of care for shared decision making followed by any subsequent medication or procedure (as needed), at 180 days from the index decision making episode, regardless of whether surgery (if chosen) has been delayed or taken place and any deaths that may have occurred. The objective is to demonstrate non-inferiority of the decision support intervention compared with best standard care for this estimand.

7. Trial methodology

7.1 Study design

Multi-centre, open, cluster randomised controlled trial.

7.2 Study setting

The study will take place in the UK across 40 NHS hospitals (approximately 20 hospitals in the intervention arm and 20 hospitals in the usual care arm) and there may be multiple hospitals from single Trust included in the study. Hospitals are the units of randomisation (clusters).

7.3 Assessment and management of risk

Risks: There is a small risk that patients may find it distressing to be provided with information, which may indicate poor expected outcomes in the following months and years. Additionally, it is expected that the use of the decision aid will lengthen the consultation itself (this will be measured as part of the study).

Benefits: There is a potential benefit of increased patient involvement in decision making resulting in reduced decision regret after surgery, and improved satisfaction with the decision making process. Enhanced patient participation in decision-making could also potentially improve mental quality of life outcomes. This device is categorised as a Class I.

8. Patient recruitment

8.1 Target accrual

600 patients across 40 hospitals.

8.2 Participant identification and screening

Potential participants will be screened by the direct care team at the site having been identified from pre-admission clinic lists, operating theatre lists and by communication with the relevant nursing and medical staff. In this trial, the member of the research team conducting the screening activity can be considered part of the direct care team in accordance with local hospital policy.

All study related correspondence should be documented in the medical record as per GCP and local hospital guidelines. If participants are approached by a research nurse, eligibility will need to be confirmed by the surgeon or delegated clinician prior to enrolment. All patients that undergo screening and meet the inclusion criteria will be recorded on the paper screening log stored in the investigator site file. Only anonymised screening data will be collected by the central trial coordinating team for publication purposes. Once the patient has been enrolled, they will also be recorded on the study enrolment log together with their trial ID.

9. Informed consent procedures

At each site it is the responsibility of the Principal Investigator or appropriately trained delegate, i.e. research nurse, to obtain consent from each subject prior to participation in this trial. All staff taking consent will be trained in taking consent and this will be evidenced on the on the delegation log. They will also have appropriate Good Clinical Practice (GCP) training.

The consent process will take place face to face or via a locally approved remote method (phone, video conferencing etc.). All potential participants will be provided with a copy of the latest versions of the patient information sheet and informed consent form together with an explanation of the aims, methods, anticipated benefits and potential hazards of the trial. This will be done either in person (preferred), via email or by post. The patients will be given the opportunity to ask questions about the study to a medically qualified member of the research team (i.e., doctor). All patients will be given a minimum of 24 hours between the time they are approached about the study and the time when consent is given. Prior to consent a member of the research team will confirm how consent will be provided by the patient (face to face, email or post) and this will be documented on the informed consent form itself. For those patients who have not been contacted face-to-face, the signed consent form will be returned via email or by post and counter-signed a member of the research team.

For patients who are consented to participate in the trial a copy of the patient information sheet and signed informed consent form will be filed in the medical notes. Patients who are consented but not entered into this study should be recorded

(including reason not entered) on the screening log in the Investigator Site File. Original signed consent forms will be kept by the investigators and a copy will be given to the participant. The discussion and the consenting process will be documented in the patients' medical records. If any further safety information arises, which may result in significant changes in the risk/benefit analysis, the patient information sheet and informed consent form must be reviewed and if applicable updated accordingly.

The Principal Investigator has overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki. If delegation of consent occurs, then details will be provided in the site delegation log.

The right of a participant to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing their further treatment and will be provided with a contact point where they may obtain further information about the study. Where a participant is required to re-consent (for example if new Research Safety Information becomes available during the study, or following an amendment that affects the participant, or new information needs to be provided to a participant) it is the responsibility of the Principal Investigator to ensure this is done in a timely manner and prior to the next use of the investigational device (where applicable).

10. Writing, reading and translation considerations

If verbal translation is needed, this will be done via a hospital interpreter as per usual practice.

11. Eligibility criteria

11.1 Hospital inclusion criteria

- Provide services for high-risk patients in one or more of the following surgical procedures: elective colorectal bowel resection for cancer, hip-replacement, or abdominal aortic aneurysm surgery

11.2 Patient inclusion criteria

- Patients contemplating elective colorectal bowel resection for cancer, hip-replacement, or abdominal aortic aneurysm surgery
- Age 60 years and over
- Age-adjusted Charlson co-morbidity index ≥3

11.3 Patient exclusion criteria

- Inability or refusal to provide informed consent
- Patients expected to die within 12 months of treatment*

** Determined by the treating clinician which may include consultant surgeons and anaesthetists leading the patient care.*

12. Study procedures

12.1 Schedule of measurements for each visit

Visit	Pre-surgical /surgical clinic	Index decision making episode	Post-surgical clinic visit	Surgery	Hospital discharge	30-day follow-up after surgery ± 3 days	180-day follow-up after index decision ± 3 days
Data sources	In person and/or medical records	In person	In person or via telephone	Medical records	Medical records	Medical records and telephone interview	Medical records and telephone interview
Eligibility	X						
Informed consent	X	X[1]					
Demographics	X						
NHS number, gender, date of birth, postcode	X						
Co-morbidities	X						
EQ-5D-5L	X		X			X	X
SF-12	X						X
Decision aid		X					
Details of planned and actual treatment		X		X			
SDM-Q9			X[2]				
Health services resource use questionnaire			X				X
Complications						X[5]	
Patient vital status					X	X[5]	X
Patient discharge location					X	X[5]	
Decision Regret Score							X
Follow-up interview		X[4]	X[4]			X[5]	X

[1] If obtained before the surgical clinic, consent should be confirmed before the intervention takes place
[2] Patient identifiable data collected for NHS Digital
[3] Within 48h of decision making
[4] Where possible and appropriate
[5] The interview can be completed either immediately after the consultation or subsequently over the phone
[6] Data collected from 30 days after surgery (only applicable if a patient has had surgery)

12.2 Randomisation method

Clusters (hospitals) will be randomised to either intervention or control with a 1:1 allocation ratio. Random permuted blocks randomisation with block sizes of m=4 and 2 will be used. This is a restricted randomisation scheme without stratification. A manual randomisation system (see 12.3) will be used and no adaptive element is envisaged.

12.3 Randomisation procedure

The code creating the randomisation list will be prepared by the trial statistician. The live allocation list will be generated by an independent statistician from within the Pragmatic Clinical Trials Unit (PCTU). Manual randomisation will be carried out remotely by the PCTU. A member of the research team who is un-blinded will be authorised to request randomisation of a cluster via email to the named independent statistician who will return the allocation also via email within one working day. PCTU will designate a stand-by who can provide allocations should the independent statistician be unavailable.
Further details will be explained the Data Management plan which will be agreed and signed off between the trial study team and PCTU.

12.4 Study assessments

Screening

- Checklist to ensure the patient meets the eligibility criteria

Demographic information

- Date of informed consent
- Initials
- Age
- Sex
- Full Name and Date of Birth for registry linkage
- Residential postcode for registry linkage
- NHS number for registry linkage
- Ethnic background
- Trial ID (generated automatically at the point of registration)

Baseline data

- BMI category

- Laboratory data (preoperative haemoglobin, estimated glomerular filtration rate)
- Co-morbid disease including mental illness
- Quality of life according to EQ-5D-5L
- 12-Item Short Form Survey

Index decision making episode

- Use of the decision aid intervention
- Details of planned and actual treatment

Post-clinic follow up

- SDM-Q-9
- Healthcare use questionnaire
- Predicted post-operative quality of life according to EQ-5D-5L

Surgical admission

- Date of surgery (Patients who do not undergo surgery will be coded as 'not applicable').
- Date of discharge
- Patient vital status (dead/alive, cause of death)
- Discharge destination

Follow-up data

30-day after date of surgery follow-up

- Patient vital status (dead/alive)
- Complications measured according to Clavien-Dindo scale (Patients who don't undergo surgery will be coded as 'not applicable'.)
- Patients discharge location
- Quality of life according to EQ-5D-5L

180-days after index decision making episode follow-up

- Patient vital status (dead/alive)
- Hospital admissions
- Quality of life according to EQ-5D-5L

- 12-Item Short Form Survey
- Healthcare use questionnaire
- Decision regret score

Supplementary forms

- Withdrawal
- Protocol deviation
- Safety report

12.5 Training and preparation

The training packages for the intervention have been developed and tested in previous projects within the OSIRIS programme. The materials will provide easily understood information about the intervention and its use for both doctors and patients. Local clinical teams at the participating hospitals will receive additional training to support use of the intervention. We anticipate delivering interactive training for doctors that focuses on practical issues, combining didactic sessions, workshops and role-play followed by structured debriefing to establish clear plans for intervention use in patient encounters. We will deliver investigator training sessions and local small group training, either in person or online to standardise the delivery of the intervention.

12.6 Intervention

This is a complex intervention, combining training to promote effective shared decision making for high-risk surgical patients (see above) together with a software-based decision support intervention. This software utilises a series of computational models developed by the OSIRIS team, which incorporates modelling of patient outcomes using NHS registry data, and patient-level information on quality of life outcomes after major surgery. Patients and doctors will use the intervention during all decision making encounters with the surgeons and other healthcare staff (e.g. anaesthetists, specialist nurses). By combining data sources from previous studies within this programme of work with NHS registry data the intervention will generate a forecast of important long-term outcomes for the patient. This forecast is presented using a clear and simple user interface with icon arrays and other patient friendly display methods to ensure it is correctly understood. Patients will be able to select and focus on outcomes of most relevance to them, whilst the intervention could highlight important outcomes which the patient might not have considered.

12.7 Control

In control group hospitals, shared decision making for high-risk patients will follow current local practices. There will be no additional training or changes to care processes for these sites.

12.8 Mixed method process evaluation of the OSIRIS cluster trial

The process evaluation will examine how the intervention works in practice during the trial, focusing on the national-level context for introducing shared decision making (macro-level), the organisational challenges of implementing a new service model based on the intervention (meso-level), and the fine-grained detail of how the intervention shapes shared decision making (micro-level).

Setting and data collection

At macro-level, we will conduct up to **ten interviews** with a maximum variation sample of national stakeholders (ensuring representation from Royal Colleges, policymakers and patient groups), combined with analysis of up to ten documents (identified e.g. via Kings Fund library) to understand how national initiatives/guidance supports or inhibits shared decision making.

At the meso-level, we will conduct **12 episodes of observation** in **six clinics in intervention sites** to understand how the intervention is adapted and delivered. The focus will be on observing the work involved in delivering the intervention, involving physically visiting selected clinics and observing the clinical/administrative work that takes place as staff seek to integrate the intervention with the existing routines of the clinic. Naturalistic interviews with clinicians and (where relevant) administrators during observation visits will enable ‘on the job’ discussion about what they are doing and why they are doing it (since people often find it easier to talk about the detail of their work while they are actually doing it), of how well they felt the training and implementation package prepared and supported them, and how challenges in using the intervention are identified, negotiated and (where relevant) resolved. Data will be recorded in field notes and supplemented with contextual data for each site (e.g. hospital size, surgical procedure volume).

At micro level, in the same six clinics, we plan evaluation of selected consultations (to examine intervention use in vivo) and matched patient/clinician interviews (to explore how they understand and respond to the intervention, how local/organisational context shapes intervention use and any unintended consequences). We will audio-record (with consent) up to **24 decision making consultations** with a purposive sample of **between 12 and 18 doctors**, (ensuring a mix of clinical experience and hospital type/location). We will conduct interviews (face-to-face or telephone) with the same doctors and patient **24 patients** (ensuring a mix of clinical condition, age, gender, ethnicity and social circumstances) about their perceptions of the intervention. Doctor and patient interviews will be audio-recorded with consent.

Process evaluation data analysis and synthesis

Data at the macro level will be analysed thematically and data analysis at the meso and micro levels will combine thematic and comparative analysis. Synthesis across macro, meso and micro levels will focus on generating in-depth narrative accounts of how the introduction of the intervention has affected the process of shared decision making. We will use the OSIRIS programme theory as the organising device for data synthesis, guiding us to identify the key linkages and mechanisms, ex-post, for implementation of a decision aid for major surgery.

12.9 Follow-up procedures

Investigators will review a participant's medical record and contact participants by telephone to conduct brief interviews at 30 days from surgery for those participants who have undergone surgery and at 180 days after index decision making episode for all patients. To collect data on secondary outcomes and facilitate the health economic analysis, we will request hospital episode statistics and mortality data from NHS Digital (formerly HSCIC) for participants in England or equivalent national database. Prospective consent for ONS/HES (or equivalent national database) data linkage will be sought before enrolment into the trial.

12.10 Minimising bias

It is not possible to conceal treatment allocation from all staff in trials of this type. Patients and staff delivering the intervention will be unblinded. However, by randomising

at the level of hospitals, we will eliminate the possibility of between group/surgeon contamination. All doctors in both groups will experience similar levels of additional observation. It is understood that the standard of shared decision making may improve for all patients regardless of study group allocation due to the raised awareness and scrutiny of trial participation. The trial management group and the trial steering committee will not see results broken down by treatment arm during the trial. Final analysis will occur once all follow up data is collected, the final statistical analysis plan has been signed off and data cleaning has occurred.

12.11 Participant, study and site discontinuation

The right of a participant to refuse participation without giving reasons will be respected. All trial participants are free to withdraw from the trial at any time without giving reasons and without prejudicing their further treatment. They will be provided with a contact point where they may obtain further information about the study. Those participants with a recorded outcome will be included in the final analysis on an intention to treat basis. The withdrawal will be documented in the case report form and medical records. Participants are not obliged to give the reason for withdrawing their consent, but we will attempt to ascertain trends if possible, relating to trial procedures in case this necessitates a protocol amendment.

12.12 End of trial definition

The end of trial is defined as the time point when the last patient last visit has been completed (last 180-day follow-up). The Chief Investigator is delegated the responsibility of submitting the end of trial notification to REC and MHRA once reviewed by the sponsor. The end of trial notification must be received by the REC and MHRA within 90 days of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the Sponsor, REC, and MHRA within 15 days, including the reasons for the premature termination

13. Investigational device

13.1 Name and description of Investigational Device

OSIRIS decision aid software is a web-based application hosted on a dedicated secure server. This software has physical components and there will be no physical contact

with humans or bodily fluids. The software has been specifically generated for this study and is described in OSIRIS study Investigator Brochure.

14. Legal status of Investigational Device

The OSIRIS Study Software (vx.x, xx.xx.xxx) is not currently authorised for clinical use in the UK and does not have a CE or UKCA mark. There will be one version of the software accessible as a single device by all sites within the study as a secure weblink. The decision aid is a piece of software being used as a standard medical device for use as a decision support tool in shared decision making about surgical treatment. The patient population is high risk patients contemplating elective colorectal bowel resection for cancer, hip replacement or abdominal aortic aneurysm surgery.

The device provides and illustrates medical complications and outcomes of surgery for patient groups with specific comorbidity profiles, based on modelling of historic surgical data from the United Kingdom. The models used have been developed and cross-validated prior to the study and will be fixed during the study with no active learning elements. The device will enable clinicians to illustrate surgical outcomes seen in similar patients rather than using generic population risks when discussion surgical treatment with higher risk patients.

The device will be used in a cluster randomised study (comparator standard surgical consultation). This study is intended to evaluate the acceptability and utility of a personalized decision aid within shared decision making around surgery. The device outcomes forecast is presented as outcomes of similar patients from historic data and this study is not intended nor powered to evaluate these historic risk estimates against actual patient outcomes.

The device is intended and labelled only for use during the OSIRIS trial, and we do not intend to commercial this version of the device beyond this study.

14.1 Device manufacturer and supply arrangements

This device has been manufactured in house with Queen Mary University of London it is not intended for commercialisation. Only one 'device' will be maintained and used for the proposed study. QMUL will take on all responsibilities of a manufacturer for the purposes of the proposed trial only. As a centralised piece of software there are no shipping, distribution or recall arrangements.

14.2 Investigational device software

This device is one central piece of software. There will be no local installation or configuration. The software will be accessed through a secure weblink and will be used only on the following browsers: Google Chrome, Apple Safari, Mozilla Firefox, Microsoft Edge, iOS Safari on iPhone/ iPad and Android Google Chrome.

14.3 Packaging and labelling of investigational device

As a stand-alone software there is no packaging required. The device is labeled as an investigational medical device exclusively for use within the OSIRIS trial following *ISO14155 GCP.* Users will be required to acknowledge this label text prior to use.

14.4 Accountability and traceability

One version of the device will be maintained on a central server by the software development team. Access to the software will be via personalized password for each local team member.

14.5 Assessment of compliance

The device will be used only by trained investigators during the clinical study, Use of the device will be recorded within the study documentation, non-use of the device for consented patients in intervention sites will be recorded as a protocol deviation.

14.6 Device training and experience requirements

A training package for the use of the device within a shared decision-making encounter has been developed and is documented in the Investigator Brochure (vx.x, xx.xx.xxx). Training will be provided by the central study team and recorded in the site delegation log. Training will be required for issuing of a password to access the device online.

14.7 Administration of investigational device

The device will be used by surgeons, anaesthetists and nurses participating in the clinical trial and recorded in the site delegation log. It will be used during clinical consultation with patients regarding proposed surgery.

14.8 Destruction, return and recall devices

One device will be maintained centrally during the study and will be taken offline upon completion of the study.

14.9 Usage modifications and delays

Use of the device will only be by a clinician who routinely assesses and counsels patients around the risks of surgery and participates in shared decision making. All device outputs will be reviewed considering this experience. Should the device by unavailable or fail due to internet disruption local network failure or other reasons the clinician will revert to existing standard of care practice in providing information regarding surgical risk and shared decision making.

14.10 Management of device specific adverse events

In the event of device failure clinician will revert to standard of care provision of information and shared decision making according to their usual practice outside of the clinical trial and documented as a protocol deviation. All device outputs will be reviewed by experienced clinicians for consistency with the patient's background and characteristics.

14.11 Management of incorrect usage

All users will be experienced clinicians who have undergone study specific training. A risk analysis is provided within the study software documentation.

The following controls will be used:

a. software replaces no existing essential function

b. all outputs from the decision aid will be reviewed by experienced clinician for consistency prior to use. The device will not be used directly by patients.

c. Labelling of device will limit use to the study only. Label text will need to be acknowledged by used. Access to device only by password to trained users in study team.

d. Skilled clinician will elicit patient worries and preferences prior to using software and will be able to recognise any distress and contextualise risk.

15. Safety reporting

15.1 General definitions

Term	Definition
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.
Adverse Device Event (ADE)	Adverse event related to the use of an investigational medical device.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: a) death b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: a. a life-threatening illness or injury, or b. a permanent impairment of a body structure or a body function including chronic disease, or c. in-patient or prolonged hospitalisation d. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function c) foetal distress, foetal death, a congenital abnormality, or a birth defect including physical or mental impairment.
Serious Adverse Device Effect	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated serious adverse device effect (USADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

15.2 Adverse events

An AE is any untoward medical occurrence in a subject to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporarily associated with study activities. These events will be monitored at intervals by the trial steering committee and will not be recorded separately as an AE on the CRF.

15.3 Site investigator assessment

The Principal Investigator is responsible for the care of the participant, or in their absence an authorised medic within the research team is responsible for assessment of any event for:

- **Seriousness:** Assessing whether the event is serious according to the definitions given in sections 15.1, 15.2 and 15.3.
- **Causality:** Assessing the causality of all serious adverse events in relation to the study treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship with the investigational device, then it is defined as an ADE.
- **Expectedness:** Assessing the expectedness of all ADEs according to the definition given. If the ADE is unexpected (as per the risk analysis or other RSI document), then it is a USADE.
- **Severity:** Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on participant/event endpoint criteria.
    - **Mild**: Some discomfort noted but without disruption of daily life
    - **Moderate**: Discomfort enough to affect/reduce normal activity
    - **Severe**: Complete inability to perform daily activities and lead a normal life

It is expected that patients undergoing major abdominal surgery will suffer medical complications, with consequences up to and including death. **Only complications considered by the Chief Investigator to be related to the use of study procedures and not a typical complication of surgery should be reported as SAEs.**

15.4 Notification and recording of adverse events (AEs), Adverse Device Events (ADEs)

All AEs and ADEs are to be documented in the participants' medical notes or other source data documents and the CRF. Once assessed, if the AE is not defined as SERIOUS, the AE is recorded in the investigator study file and the participant is followed up by the research team.

15.5 Notification and reporting of Serious Adverse Events(SAEs), and Unexpected Serious Adverse Device Events (USADEs)

All Serious Adverse Event (SAEs) and Unexpected Serious Adverse Device Events (USADEs) will be recorded in the participants' notes, the CRF, the sponsor SAE form and reported to the sponsor (administered by the Joint Research Management Office or agreed representative) and the investigational device manufacturer within 24 hours of the site becoming aware of the event (except those specified in this protocol as not requiring reporting). Nominated co-investigators (as listed) will be authorised to sign the SAE forms in the absence of the PI at the participating sites. SAEs and reportable device deficiencies must be reported from consent until the participant's last follow-up visit.

15.6 Device deficiencies

All device deficiencies will be recorded on the Clinical investigation device deficiency log and where appropriate in the participant's medical records. Device deficiencies which could have caused a Serious Adverse Device Event must be reported to the sponsor within 24 hours of becoming aware of the event by submitting a Device Reporting Form to research.safety@qmul.ac.uk. Device deficiencies must be recorded and reported throughout the Clinical Investigation.

15.7 Sponsor medical assessment

Sponsor has delegated the responsibility for oversight of investigational device safety profile and medical assessment of safety events to the Chief Investigator as medical assessor. The CI must review all SAEs and reportable device deficiencies within 72 hours of receipt. This review should encompass seriousness, relatedness, and expectedness. Day 0 for all USADEs is when the USADE is received by the Chief Investigator and / or coordinating team and / or sponsor (whichever is first). It is noted that the Chief Investigator cannot downgrade the PI assessment of an event's causality. If there is disagreement between Chief Investigator and Principal Investigator assessment, no pressure should be placed on the Principal Investigator to alter their assessment, but the Chief Investigator can liaise with the site Principal Investigator before the CI's final decision. The Chief Investigator and Principal Investigator assessment can differ. The Chief Investigator must also maintain oversite of non-serious AEs reported on the case report forms and review them periodically to confirm agreement.

16. Annual reporting

16.1 Annual progress report

The APR will be written by the Chief Investigator (using the HRA's template) and submitted to the Sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the "favourable opinion" letter from the REC.

17. Statistical and data analysis considerations

17.1 Sample size calculation

The sample size calculation is considering both primary endpoints individually. The unit of randomisation is hospitals and an intra-cluster correlation of 0.01 within hospitals is assumed for each outcome. Furthermore 20% loss to follow-up at the individual participant level is assumed at the primary outcome time point of 180 days. No clusters are anticipated to drop out. For the non-inferiority comparison of the MCS a non-inferiority margin of 3.5 points is chosen. A standard deviation (sd) of 11 is assumed for MCS [75] which means that the margin corresponds to approximately 30% of the sd. Accounting for clustering, 460 participants would be needed to demonstrate non-inferiority with 90% power and a one-sided 2.5% significance level if there truly is no difference in MCS between groups. This equates to a recruitment target of 40 hospitals recruiting 15 participants each after accounting for loss to follow-up, i.e. 600 in total. The minimum clinically relevant difference on the DRS is a 7.5 point between-group difference in mean scores. The literature suggests a standard deviation of 16 for DRS [67] which means that the 7.5 point difference corresponds to a small to medium effect size. With the sample size required for the non-inferiority comparison and again accounting for clustering this difference can be detected with 99.8% power at the 5% significance level for a two-sided superiority test. The overall power to reject the null hypotheses for both primary outcomes is at least 89.8%.

17.2 Statistical analysis

The statistical analysis plan (SAP) is the principal document guiding the statistical analysis and describing it in full. All signed off versions of the SAP will be made available in a publicly accessible location. The trial statistician will not receive the treatment allocation code until after the SAP is finalised and the trial database is locked and ready for analysis. Reporting of statistical analysis results will be compliant with the CONSORT extension for Cluster Randomised trials and a CONSORT Flow diagram will

be produced. The statistical analysis will be carried out using Stata v17.0 or later and the following general analysis principle will apply:

- For each analysis the number of patients included in the analysis, a summary measure of the outcome in each treatment group, treatment effect, 95% confidence interval and a two-sided p-value will be presented
- A significance level of α=0.05 is used throughout
- No adjustment for multiple testing of (secondary) outcomes is made
- No interim analyses are prospectively planned
- Secondary outcomes will be analysed with the same analysis model and co-variates as the primary outcomes (see 18.6).

17.3 Analysis of participant populations

The participants population whose data will be subjected to the study analysis is dictated by the treatment of intercurrent events. The primary estimand specifies an intention to treat analysis, that is, the outcome data of all recruited and consented participants (no individual participant randomisation) will be included in the main analysis according to their assigned treatment group regardless of their protocol adherence. All clusters will be included in the analysis in the group they were randomised to regardless of their implementation of the intervention. Certain participants may be excluded in sensitivity analyses but no analysis excluding whole clusters is envisaged.

17.4 Primary endpoint analysis

MCS and DRS are co-primary outcomes, that is, the intervention is declared clinically effective only if both primary endpoints are statistically significant. The estimand for both outcomes will be estimated using a linear mixed-effects model with a random intercept for hospital. Restricted maximum likelihood estimation with Kenward-Roger correction will be used. Models will be adjusted for the following individual level baseline covariates (without treatment by covariate interaction) to increase power: age [continuous], surgical procedure [categorical] and Charlson co-morbidity score [ordinal]. MCS will additionally be adjusted for the MCS score at baseline. Missing covariate data will be accounted for using mean imputation [17] for continuous variables and the missing indicator approach [18] for categorical variables. The strategy for accounting for intercurrent events in the analysis models is described in section 6.3 and Appendix 1. If the patient status at 180 days follow-up is ‘dead’ the outcome values are defined (imputed) as a neutral position on decision regret and a population median for Mental Health Component (DRS=50,

MCS=50). Multiple imputation under missing at random assumption will be used to impute missing outcomes where the participant has not died. Values will be imputed using predictive mean matching with 10 donors and 50 imputations. The complete set of variables included in the imputation model with be specified in the SAP.

The non-inferiority comparison for the MCS will be based on a two-sided 95% confidence interval (equivalent to a one-sided 2.5% alpha level). If the lower bound of the confidence interval is greater than the non-inferiority margin of 3.5, then non-inferiority will be declared. For both co-primary outcomes, we will present a participant-average treatment effect estimate (difference in means between the two treatment groups) along with a confidence interval. The primary outcome Decision regret will be assessed using a superiority test at the conventional 5% alpha level.

17.5 Subgroup analysis

Subgroup analyses will be conducted by fitting an interaction term between the study group indicator variable and the variable defining the subgroup in the primary outcome analysis model. The following subgroup analyses are currently planned:

- Surgical procedure (colorectal bowel resection for cancer, hip-replacement, abdominal aortic aneurysm surgery)
- Patient gender
- Ethnicity

Other subgroup analyses may be added in the future and be pre-specified in the SAP prior to the final statistical analysis commencing.

17.6 Planned sensitivity analysis

There are two planned sensitivity analyses that target the primary estimands.

1. Unadjusted analysis accounting for clustering by hospital but no individual participant characteristics including planned surgery
2. Model assuming clustering by doctor involved in index decision making episode within hospital

Four sensitivity (secondary) analyses which target different estimands involving the primary outcomes are planned. The estimands for these analyses will be fully specified in the SAP

1. An analysis as described in 17.4 using all available data without imputation of outcomes (imputation of co-variates only)

2. An analysis as described in 17.4 but excluding all participants whose surgery has been cancelled or delayed by more than 180 days. A principle stratum approach is used for these intercurrent events in which the treatment effect is estimated in the subpopulation of patients in which the event didn't occur. This estimate is unbiased under plausible assumptions [19].
3. An analysis as described in 2 but additionally excluding participants who did not initiate their assigned intervention as planned. This is akin to a per-protocol analysis.
4. An analysis as described in 17.4 assuming a range of more negative values of DRS and MCS for participants who died within the 180 days follow-up.

17.7 Procedures to account for missing or spurious data

The handling of missing data and the multiple imputation methods used has been described in section 17.4 for the primary estimand and in section 17.6 for certain sensitivity analyses of the primary outcomes analysis. Categories for reasons for missing follow-up data will be defined in the data management plan and added as a variable in the trial database.

17.8 Economic evaluation

Cost-effectiveness of the intervention within the 180 day follow-up will be estimated from the perspective of health and social care services. The intervention costs will include any costs associated with training, supervision and equipment and additional consultation time to deliver the intervention. Additionally, with patient consent, we will request linked data describing secondary care attendances from 180 days prior to entry into the study until the end of follow-up in the trial (i.e. Hospital Episodes Statistics datasets for inpatient admissions, outpatient, critical care and A&E attendances). We will collect further resource use data (e.g. primary care consultations, community and residential care, out-of-pocket expenses and work-time loss due to ill health) using tailored self-report questions administered at entry into the study and at final follow-up 180 days later, requesting information about the previous 180 days. All healthcare use in the OSIRIS study will be costed using NHS and national reference costs [20, 21]. For the purpose of the economic analyses, health outcomes will be measured in quality-adjusted life years (QALYs). Health-related quality of life will be estimated using data from the EQ-5D-5L questionnaire collected at baseline, post-surgical clinic visit, 30 day follow-up after day of surgery and 180 day follow-up after index decision making episode in the OSIRIS study. EQ-5D-5L utilities will be derived using the NICE Decision

Support Unit (DSU) tariff [22] recommended in the latest NICE guidelines for health technology assessments [23]. Mean costs and QALYs between the trial arms will be compared using separate linear mixed-effects models with a random-intercept for hospital. The following baseline covariates will be adjusted for: age, surgical procedure, Charlson co-morbidity score and hospital care costs in the 180 days prior to entry into OSIRIS or EQ-5D-5L utility at entry, respectively. Missing baseline covariate data will be accounted for using mean imputation. The two-stage bootstrap approach will be used to assess the uncertainty in cost-effectiveness.

Cost-effectiveness of the intervention over life-time horizon will combine i) data from the trial describing resources use and cost of the intervention, and ii) long-term projections of quality of life adjusted survival and healthcare costs associated with particular treatments from the decision-analytic models to project long-term effectiveness and cost-effectiveness of the OSIRIS decision support intervention: a) across the participants in the cluster trial, and b) in cohorts of high-risk patients in routine hospital care data (e.g. by level of risk, age). We will report incremental costs per QALY gained with the OSIRIS intervention, along with cost-effectives acceptability curves across values of cost-effectiveness threshold (£0 to £50,000). All future costs and health outcomes will be discounted as recommended [23]. The wider implications of the OSIRIS intervention on patients' families and society (e.g. employment, informal care needs) will be considered. A health economics analysis plan, specifying in detail the health economics analyses of the OSIRIS intervention, will be finalised and signed off prior to un-blinding the team analysing the study.

18. Data handling and record keeping

18.1 Source data and source documents

Source data is defined as all information in original patient records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the clinical investigation. Source data are contained in source documents (original records or certified copies). Only members of the direct care team are entitled to have access to patients' medical records. Direct access will be granted to authorised representatives from the sponsor, host institution, and the regulatory authorities to permit study-related monitoring, audits, and inspections.

18.2 Case report forms

A summary of the data collection points and times can be found in section 12.1 Research staff at each hospital will be responsible for the completion of the electronic case report form for the duration of the study. The electronic case report form will be custom designed by Queen Mary University of London and will be hosted on a secure server. A requirement specifications document will be created detailing these aspects of the database. Sites will be provided with a paper data collection tool that matches the electronic case report form however, it is not compulsory to complete this. The electronic patient questionnaire will act as source data for patient reported outcomes collecting during the 30 day and 180 day follow-up. Patient's medical notes will act as source for the rest of the data. It is expected that the exact source data list will vary by site. A site agreement will be in place at each site.

18.3 Transferring and transporting data

All data must be handled in accordance with the Data Protection Act (2018) and General Data Protection Regulations. Identifiable information must not be stored or transported on any portable device (e.g., laptops, memory sticks, CD / DVDs) unless it is encrypted. Similarly, data must not be sent electronically if it is not subject to end-to-end encryption. In the event that Patient Identifiable Data needs to be transferred between authorized users, this will occur by email from @nhs.net to @nhs.net accounts.

For registry linkage QMUL will apply to NHS digital for HES and Civil Registrations (Deaths) data. Following approvals for the proposed linkage, QMUL will send the Study ID, NHS Number, Forename, Surname, Sex, Date of Birth and Postcode to NHS Digital to link the cohort to HES and Civil Registrations data. NHS digital will send the relevant data for QMUL to be perform the linkage data to the trial data based on the Study ID.

18.4 Data management

A full data management plan will be developed to describe in detail the methods of data management. All participant data collected will be entered onto a secure electronic data entry system. The site Principal Investigators will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated (as per the Delegation Log) by the site Principal Investigators to qualified members of the research team. Data entered onto the secure electronic data entry system will undergo validation

checks for completeness, accuracy and consistency of data. The electronic storage will be located on a restricted area of the file server. Submitted data will be stored securely against unauthorised manipulation and accidental loss. Queries on incomplete, inaccurate or inconsistent data will be sent to the local research team at participating sites for resolution. Security of the electronic data entry system is maintained through user names and individual permissions approved centrally by the OSRIS trial mangers. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act (2018) and General Data Protection Regulations. Representatives of the trial management team will require access to patient notes for quality assurance purposes and source data verification, but patients' confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected.

18.5 Confidentiality

The Chief Investigator will be the data custodian for all data generated during the study. The Chief Investigator and the study team will ensure that all participants' identities are protected at every stage of the study. The patient's NHS Number, gender, date of birth and postcode will be collected at randomisation through the trial database and sent to NHS Digital to allow tracing through national records. The personal data recorded on all documents will be regarded as confidential.

The Principal Investigator is responsible for protecting the identity of participants at their site. Participants will be referred to only by their unique study identifier whenever data is transferred outside of the site, and in all correspondence between the site and the coordinating centre, co-investigators, Sponsor, or anyone associated with the study. No participants will be individually identifiable from any publications resulting from the study.

Information regarding study participants will be kept confidential and managed in accordance with the Data Protection Act (2018), the UK Policy Framework for Health and Social Care and Research Ethics Committee approval. All study data will be stored in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Data Protection Act. Study data will be archived in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments, and as defined in the Sponsor SOP for archiving.

19. Participants

A screening log will be maintained throughout the study. Usually this includes the potential participant's initials to allow their identification by relevant site staff. Once the participant has completed screening procedures and enrolled onto the study, they must be allocated a unique study identifier generated by the OSRIS trial database.

The participant's full name, date of birth, hospital number and NHS number (UK) will be entered on to the secure data entry web portal to allow tracing through national records. The personal data recorded on all documents will be regarded as confidential. All participant related trial documents are confidential and must be stored securely at each hospital (e.g. participant consent forms). The Principal Investigator must ensure the patient's confidentiality is maintained at all times. The Sponsor will ensure that all participating partner organisations will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Data will be stored and handled in accordance with the Data Protection Act 2018 (UK). In the event that patient identifiable data needs to be transferred between authorised users, this will occur by email from @nhs.net to @nhs.net accounts in the UK

20. Monitoring, audit and inspection

20.1 Monitoring

A Trial Monitoring Plan will be developed and agreed by the Sponsor and Chief Investigator based on the sponsor's risk assessment, which will include on site monitoring. Monitoring procedures are detailed in the Trial Monitoring Plan.

20.2 Auditing

The Sponsor retains the right to audit any aspect of the study, study sites, or central facilities. In addition, any part of the study may be inspected by the regulatory bodies, and funders where applicable. All sites and vendors are asked to inform the sponsor if notified of any audit or inspection affecting this study

21. Compliance

The Chief Investigator will ensure that the protocol and study is conducted in compliance with the principles outlined in the Medical Device Regulations 2002 and subsequent amendments, current UK Policy Framework for Social and health care research (2017), ISO14155 GCP guidelines, the World Medical Association Declaration of Helsinki, the Sponsor's and study specific SOPs, and other regulatory requirements. The study will not commence until approval from the relevant competent authorities, ethics committees and sponsor permission to activate sites is received. Any additional terms set by the competent authorities and ethics committees shall be followed. Sites will be individually activated by the Chief Investigator and team; this will not occur until site approval is granted.

The trial team will take day-to-day responsibility for ensuring compliance with the requirements of Good Clinical Practice (GCP) in terms of quality control and quality assurance of the data collected as well as safety reporting. The OSIRIS Trial Management Group will communicate closely with individual sites and the Sponsor's representatives to ensure these processes are effective. The Sponsor will conduct a study risk assessment in collaboration with the Chief Investigator. Based on the risk assessment, an appropriate study monitoring, and auditing plan will be produced according to Sponsor Standard Operating Procedures. Any changes to the monitoring plan must be agreed by the Sponsor and Chief Investigator. The Chief Investigator will ensure that the protocol and study is conducted in compliance with the principles outlined in the ISO14155 GCP guidelines and subsequent amendments, current UK Policy Framework for Social and health care research (2017), the World Medical Association Declaration of Helsinki, the Sponsor's and trial specific Standard Operating Procedures, and other regulatory requirements. The study will not commence until Sponsor permission to activate sites is received. Sites will be individually activated by the Chief Investigator and team; this will not occur until site approval is granted.

21.1 Non-compliance

With the exception of urgent safety measures, prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used (i.e. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the study protocol). Systematic failure of both the Chief Investigator and the study staff adhering to SOPs, protocol, ICH GCP or UK regulations, which leads to prolonged collection of deviations, may constitute breaches or suspected fraud and may result in the removal of the Investigator or study team member from the clinical investigation.

Non-compliances may be captured from a variety of different sources including monitoring visits, Case Report Forms, communications and updates. The Sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated. The Chief Investigator and the trial management team should assess the non-compliances and action a timeframe in which they need to be dealt with. This assessment should include the need to escalate to the Sponsor. Any event with the potential to affect participant safety or data integrity should be reported to the Sponsor within 24 hours of the trial coordinating team becoming aware. Where applicable corrective and preventative actions (CAPA) should be assigned. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the Sponsor will agree an appropriate action, including an on-site audit. Deviations from the protocol which are found to frequently recur are not acceptable. This will require immediate action and could potentially be classified as a serious breach. Protocol deviations must be documented on the supplementary form in the Case Report Form and on the deviation log.

21.2 Notification of serious breaches to GCP and/ or the protocol

A ‘serious breach’ is a breach which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants of the study; or
- The scientific value of the study.

The site Principal Investigator is responsible for reporting any potential serious breaches to the sponsor (research.safety@qmul.ac.uk) within **24 hours** of becoming aware of the event.

The Chief Investigator is responsible for reporting any potential serious breaches to the Sponsor **within 24 hours** of becoming aware of the event. The Sponsor is responsible for determining whether a potential serious breach constitutes a serious breach and will work with the Chief Investigator to investigate and notify and report to the MHRA and REC (as applicable) within seven working days of becoming aware of the serious breach.

21.3 Amendments to the Clinical Investigation

Should the Chief Investigator or Sponsor deem it necessary to make an amendment to the protocol or to the documents submitted with the Clinical Investigation application these will be implements as amendments.

21.4 Suspension or early termination of the Clinical Investigation

If the clinical investigation is temporarily suspended, this will be notified to the ethics committee and competent authority via a substantial amendment. A further substantial amendment will be implemented to resume the clinical investigation. If a decision is made to terminate the clinical investigation early the ethics committee and competent authority will be notified within 15 days through the submission of an End of Study notification form.

22. Declaration of interests

The Chief Investigator, Principal Investigators at each hospital, and all committee members for the overall study management will provide the below details as required by the Sponsor:

- All competing interests.
- Ownership interests that may be related to products, services, or interventions considered for use in the study or that may be significantly affected by the study.
- Commercial ties (e.g., pharmaceutical, behaviour modification, and/or technology companies).
- Non-commercial potential conflicts (e.g., professional collaborations that may impact on academic promotion).

These will be held within the Trial master file. Please address enquiries to admin@osiris-programme.org.

23. Peer review

This piece of research detailed in the protocol is part of a larger NIHR programme grant, which was peer reviewed by internal and external experts during the funding process. Since securing the award, the protocol has since been further reviewed during the trial design process.

24. Public and Patient Involvement (PPI)

Patients have been involved from the outset of the OSIRIS programme, advising on the ethics of research involving patients making life changing decisions, patients' likely values and expectations of surgical treatments, our wider strategy for involving patients as both investigators and research participants, and our implementation plan. In addition to our patient co-applicants, proposals related to OSIRIS activity have been constantly reviewed in detail by the Royal College of Anaesthetists Patient & Public Involvement group. We have fully incorporated several of their suggestions into this programme including strategies to improve patient participants' experience of this research, and the development of a 'shadow' patient steering committee who review and provide feedback on patient facing documents.

25. Insurance

The insurance that Queen Mary University of London has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

26. Study committees

The Chief Investigator will take overall responsibility for the delivery of the OSIRIS trial and oversee progress against timelines/milestones.

26.1 Trial Management Group

Trial Management Group consisting of the Chief Investigator, Trial Managers, Trial Statistician and members of the Pragmatic Clinical Trials Unit. Meetings will be held monthly to ensure the progress of the study against milestones and to ensure effective communication across the team. The day-to-day trial team will meet regularly to discuss and monitor progress.

26.2 Trial Steering Committee

The OSIRIS programme steering committee will act in the role of Trial Steering Committee to oversee the trial and will consist of several independent clinicians and trialists, lay representation, co-investigators, and an independent Chair. Meetings will be held at regular intervals determined by need but not less than once a year. The TSC will take responsibility for:

- approving the final trial protocol
- major decisions such as a need to change the protocol for any reason
- monitoring and supervising the progress of the trial
- reviewing relevant information from other sources
- informing and advising on all aspects of the trial
- advising on issues of patient safety during the trial (a Data Monitoring and Ethics Committee will not be appointed given the trial design)

27. Publication and dissemination policy

27.1 Publication

Responsibility for ensuring accuracy of any publication from this study is delegated to the Chief Investigator. All publications should acknowledge the Sponsor. Data arising from this research will be made available to the scientific community in a timely and responsible manner. A detailed scientific report will be submitted to a widely accessible scientific journal on behalf of the OSIRIS Trial Group. The programme steering committee will agree the membership of a writing committee, which will take primary responsibility for final data analysis and writing of the scientific report. All members of the writing committee will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission. Please see OSIRIS trial publication charter for further details.

All publications will be sent to the Sponsor prior to publication. The clinical investigation will be registered on a publically accessible database. The full study report will be accessible via the public website within one year of the End of Trial Notification. The full study report will also be submitted to the NIHR.

27.2 Dissemination policy

Data arising from this research will be made available to the scientific community in a timely and responsible manner. A detailed scientific report will be submitted to a widely accessible scientific journal on behalf of the OSIRIS Trial Group. The PSC will agree the

membership of a writing committee, which will take primary responsibility for approval of the final data analysis and writing of the scientific report. All members of the writing committee will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission. Please see the OSIRIS trial publication charter for further details.

27.3 Access to the final study dataset

Access to the final dataset will be granted only to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

28. Archiving

During the course of the research, all records are the responsibility of the Chief Investigator and will be kept in secure conditions. When the research study is complete, it is a requirement of the Barts Health Policy that the records are kept for a further 25 years. Site files from other sites must be archived for 25 years at the external site and will not be stored at the Barts Health Modern Records Centre or within Queen Mary. Destruction of essential documents will require authorisation from the Sponsor. The sites are responsible for maintaining and archiving all local records including the investigator site file and paper CRFs. These records should be archived together once authorisation has been given by the Sponsor. It is the responsibility of the PI to ensure a full set of records is collated and documented. In addition, source documentation should be retained, as per local policy, for the duration of the archiving period. Destruction of essential documents will require authorisation from the Sponsor.

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