Full Title	A national perioperative platform trial to improve outcomes for surgical patients
Short Title	PROTECT
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Committees	The Chief Investigator will appoint a Platform Management Group (PMG). Tom Abbott (Chair) Clinical Senior Lecturer, Queen Mary University of London The Chief Investigator will appoint a Platform Steering Committee (PSC). Rupert Pearse (Chair) Professor & Consultant in Intensive Care Medicine, Queen Mary University of London
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.

The provenance of the PROTECT platform, including contributors to the protocol, are described in the Contributor and authorship SOP.

1. Contents

2. Glossary of terms and abbreviations

AE	Adverse Event
AR	Adverse Reaction
CAPA	Corrective and preventative actions
CI	Chief Investigator
CRF	Case Report Form
CSC	Comparison Steering Committee
CTIMP	Clinical Trials of an Investigations Medicinal Product
DAH	Days Alive and at Home
DMEC	Data Monitoring & Ethics Committee
DSUR	Development Safety Update Report
EAS	Episode-based Activity Statistics
eConsent	Electronic Consent
eCRF	Electronic Case Report Form
eDRIS	Electronic Data Research and Innovation Service
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HRA	Health Research Authority
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ITT	Intention To Treat
JRMO	Joint Research Management Office
MHRA	Medicines and Healthcare products Regulatory Agency
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Non-Investigational Medicinal Product
ONS	Office for National Statistics
PCTU	Pragmatic Clinical Trials Unit
PEDW	Patient Episode Database for Wales
PI	Principal Investigator
PIS	Patient Information Sheet
PMG	Platform Management Group
PSC	Platform Steering Committee
QMUL	Queen Mary University of London
QALY	Quality Life Adjusted Years
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAIL	Secure Anonymised Information Linkage Databank

SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SMS	Short Messaging Service
SOP	Standard Operating Procedure
Sub-PI	Sub Principal Investigator
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UKSeRP	UK Secure Research Platform

3. Signature page

CI Agreement

The study as detailed within this research protocol 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 Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

CI name: Dr Tom Abbott

Signature: **Date:** Tom Abbott Digitally signed by Tom Abbott Date: 2025.01.31 16:10:31 Z

Co-CI name: Professor Rupert Pearse

Signature: **Date:** Rupert Pearse Digitally signed by Rupert Pearse Date: 2025.01.31 16:14:31 Z

Statistician's Agreement

The study as detailed within this research protocol 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 Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments, and ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

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

Statistician's name: Jo Haviland

Signature: **Date:** Jo Haviland Digitally signed by Jo Haviland Date: 2025.01.31 15:28:34 Z

PI Agreement Page

The clinical study as detailed within this research protocol **(version xx.xx, dated xx.xx.xxxx)**, or any subsequent amendments, involves the use of an investigational medicinal product 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 ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

PI Name:

PI Site:

Signature and Date:

4. Synopsis

Full title	A national perioperative platform trial to improve outcomes for surgical patients
Short title	PROTECT (each trial question will be given this as a prefix)
Sponsor	Queen Mary University of London
MHRA risk level of CTIMP comparison appendices	Type A
Phase of the trial of CTIMP comparison appendices	Trial phases II to IV depending on the specific research question in each comparison appendix.
Medical condition or disease under investigation	Patients aged 18 years and over being treated in an NHS surgical care pathway.
Study design and methodology	Platform trial for the delivery of multi-centre randomised and non-randomised research questions (CTIMPs and non-CTIMPs) for adult patients undergoing surgery.
Study setting	NHS Surgical care services
Planned number of participants	See specific comparison appendix.
Outcome measures	PROTECT will include a range of standard patient outcomes common to all trial questions provided they are applicable. The key patient outcomes will include: • Complications within 30 days after surgery. • Days alive and at home at 30 and 90 days after surgery. • Mortality at 30 and 90 days, and one year after surgery. • Health-related quality of Life (EQ-5D-5L) at 30 and 90 days after surgery. • Duration of primary hospital admission up to 90 days after surgery. • Re-admission to hospital within 90 days of surgery.
Inclusion and exclusion criteria	Inclusion criteria: • Adult patients (≥18 years) being treated within a surgical care pathway at the recruitment sites. Exclusion criteria: • Inability or refusal to provide informed consent. Each comparison appendix will define comparison-specific eligibility criteria within this study population.

Investigational Medicinal Product(s)	See specific appendix.
Treatment duration	See specific appendix.
Follow-up duration	90 days for patient collected data. One-year for linked health services data (if applicable).
End of trial definition	See specific appendix.
Study duration	PROTECT has been designed to run for at least 10 years and to accommodate multiple specific research questions, described in individual appendices, which will be added to the master protocol during the course of study. Separate start and end definitions will be described in each comparison appendix.

5. Introduction

5.1 Background

Surgery is a highly effective treatment for many diseases. In the UK, 5 million NHS patients undergo surgery each year, at a cost of £11 billion (1). The surgical population is expected to grow by 1% every year to 6.5 million patients by 2030 (2). However, this growth is skewed toward older patients, so the average age of surgical patients is increasing at a faster rate than the general population (2). Increasing proportions of patients are presenting for surgery with multiple co-morbidities and impaired functional status, resulting in an increased risk of postoperative complications (3-7). Postoperative complications (like respiratory failure, myocardial infarction, or wound infection) affect one in five patients, and are strongly associated with subsequent mortality (7-12). Research is needed to identify the optimal ways to prevent and treat postoperative complications.

The gold standard method for testing new treatments is the randomised clinical trial. However, traditional parallel group trials are time-consuming and resource intensive (13). A typical clinical trial takes five years to conduct and two years to publish, and in many cases, several clinical trials are required to change clinical practice (14). Important delays can occur during trial set-up, regulatory approvals, opening of hospital sites, patient recruitment, and finalising data collection (15). Most trials compare outcomes in one participant group receiving an intervention and one group receiving usual care (control). Therefore, across multiple trials many patients will receive no new treatment. This is inefficient and not well optimised for either patient participants, or for researchers.

Platform clinical trials take a different methodological approach, which was used to great effect during the pandemic (16-17). Platform trials allow simultaneous comparison of multiple treatments in a single population, reducing the total number of participants required. Platform trials can continue in perpetuity, with new treatments added as they become available, which greatly reduces the administrative burden in setting up a new trial and opening hospital sites to contribute participant recruitment (17-19). There is widespread recognition that platform trials could accelerate generation of new clinical evidence at reduced cost.

PROTECT is a UK-wide perioperative platform trial, led from Queen Mary University of London (QMUL). The trial will simultaneously test multiple interventions and is planned to run for a minimum of ten years, adding new treatments as they are developed. This clinical trial will drive a transformation in the care of five million NHS surgical patients each year.

5.2 Rationale for study design

To establish a research and governance infrastructure for the efficient delivery of a suite of surgical and/or perioperative care comparisons to improve outcomes for patients undergoing surgery.

5.3 Assessment and management of risk

Each comparison (research question) will be conducted in accordance with the current approved PROTECT master protocol and comparison appendix, Good Clinical Practice (GCP), relevant regulations and standard operating procedures. A risk assessment will be carried out both for the PROTECT Platform and for each comparison (CTIMPs and non-CTIMPs). Ongoing risk assessments will be conducted and/or reviewed over the course of the Platform to reflect significant changes to the master protocol and appendices, or outcomes of monitoring activities.

6. Trial objectives

6.1 Primary objective(s)

To provide a research platform for the simultaneous testing of multiple treatment approaches with the overarching aim of improving the care of patients treated on a surgical care pathway.

6.2 Primary outcomes

A common outcome dataset (Table 1) will be collected for all patients at 30 days and 90 days after surgery. In addition, longer-term outcomes may be collected using routinely collected data (for example Hospital Episode Statistics (HES) and Civil Registration data) up until the last follow up time-point for the participant according to the nature of the groups in which they are enrolled in. Where applicable, primary and secondary outcomes will be described in full in the relevant appendix. Additionally, for CTIMPs, depending on the risk and status of the investigations, part of the objectives will be to collect safety endpoints.

Outcomes	Outcome Measures
Clinical outcomes	Complications within 30 days after surgery.
	Days Alive and at Home (DAH) at 30 and 90 days after surgery.
	Mortality at 30 and 90 days after surgery.
Quality of life measures	Health-related quality of life (EQ-5D-5L) at 30 and 90 days after surgery.
Process measures	Duration of primary hospital admission within 90 days after surgery.
	Re-admission to hospital within 90 days of surgery.
Health services data	Mortality at one year after surgery.

Table 1: Common outcome dataset

6.7 Study design

This is a multi-centre multi-factorial platform trial designed to test multiple comparisons (research questions) for patients undergoing surgery, or within a surgical care pathway. Patient eligibility will be evaluated for the platform (master protocol) and for each comparison (protocol appendix). Patients enrolled in the PROTECT platform will be offered the opportunity to take part in any and/or all of the comparisons for which they are eligible. Patients can be enrolled in the platform (master protocol) only or the platform (master protocol) plus one or more comparison(s). Comparisons may be contemporaneous or distributed throughout the surgical care pathway. As new comparisons are added to the platform, they will be assigned a comparison-specific acronym suffix (e.g. PROTECT-AEGIS, etc.), and the comparison-specific trial methodology and delivery will be described in separate appendices to this master protocol document. Each comparison will be added as an individual submission to the relevant regulatory authorities. Amendments made to the master protocol will apply to all appendices. Amendments to an appendix describing an individual comparison(s) will only be relevant to that appendix.

The PROTECT master protocol is the over-arching protocol which describes the common trial design, delivery and data sets, as well as trial governance procedures common to all comparisons within the platform. Where additional procedures are required, specific to a comparison, for example the collection of additional safety data, these will be described in the appendix for that comparison. The individual appendices are not co-dependent and each will have a separate start and end date. Appendices to the PROTECT master protocol will be added and/or removed throughout the course of the programme. Analyses will be conducted on locked comparison specific datasets and published without compromising the integrity of ongoing platform comparisons. Each individual comparison will have a lead investigator listed in the comparison appendix. Participants enrolled into PROTECT will fall into one or more of the below study categories depending on the eligibility criteria and the journey of their care pathway:

- PROTECT platform
- Non-interventional (non-randomised) studies
- Interventional studies that do not involve Investigational Medicinal Products (IMPs)
- Interventional studies that involve an IMP

6.8 Study setting

Surgical services of NHS hospitals and other NHS institutions involved in delivering the surgical care pathway. Interventions may be simple, complex or multi-modal, e.g., IMPs,

surgical interventions or care pathways; delivered at any stage along the diagnostic, treatment and rehabilitation pathway.

7. Patient recruitment sites

7.1 Selection of sites

Each trial recruitment site will have a named medical doctor (Principal Investigator (PI)), appropriately trained research staff, appropriate capacity for data collection and be willing to screen all eligible patients. Sites will not be obliged to participate in all comparisons. Instead, site participation will be based upon the ability to deliver the requirements of each comparison, and will be assessed as each comparison is added to the platform.

7.2 Recruitment site training

Sites will be required to have a PI, one research nurse or research associate and any relevant additional staff (e.g. pharmacist if appropriate for the intervention) to participate in training prior to opening to patient recruitment. This may be face-to-face or online training as appropriate to each comparison. The PI has overall responsibility for the training of site personnel. Once training has been completed, the members of staff who have completed the training should be added to the training and delegation logs and signed off by the local PI. Each comparison being conducted at the recruitment site will require a named sub-PI who may be the overall site PI or a different investigator. Multiple comparisons can be led by the same PI provided they have completed the training for each comparison they lead and they have adequate time and resources. Staff carrying out randomisation and/or data entry within each site must attend data management training to be given access to the trial database.

8. Patient recruitment

8.1 Target accrual

Please refer to the individual comparison appendices for specific patient recruitment targets.

8.2 Participant identification and recruitment

Potentially eligible participants will be pre-screened by the direct care team for entry into PROTECT and associated comparisons. Pre-screening may take the form of reviewing medial records, associated imaging, test results and operating theatre, clinic and/or scheduling lists. Research delivery staff at each recruiting site should be regarded as part of the direct care team. Research is a routine part of effective healthcare and will be subject to the same information governance requirements in this respect. Research delivery staff will therefore be able to pre-screen operating theatre lists, electronic patient records, etc. for

eligible patients. All study related correspondence should be documented in the medical record as per GCP and local hospital guidelines.

If the investigator who approaches the potential participant is not permitted to assess their eligibility, this will need to be confirmed prior to enrolment by a clinician who has been authorised to complete this task, as listed on the site delegation log. Specific guidance on eligibility criteria will be detailed in each comparison appendix. All patients who undergo screening will be recorded on the screening log for each comparison and reasons given for any exclusion. Only anonymised screening data will be collected to allow assessment and reporting of selection bias. Once the participant has been enrolled, they will also be recorded on the study enrolment log together with their study ID. Both the screening and enrolment logs will be stored in the investigator site file.

Patients may be enrolled into multiple comparisons, and they will make the final decision into which comparison(s) they will be enrolled to. Eligibility for comparisons may be contingent on the patient's specific care pathway and in some cases, upon enrolment to other comparisons. In these circumstances, additional eligibility assessments will be made. Once the participant has been enrolled, they will also be recorded on the enrolment log.

9. Informed consent procedures

Informed consent will be obtained after pre-screening and prior to the participant undergoing procedures that are specifically for the purposes of the study and are outside routine care at participating sites. This includes collection of identifiable participant data.

The PI 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 GCP and Declaration of Helsinki. If delegation of consent occurs, then details will be provided in the site delegation log. The PI or appropriately trained delegate e.g. research nurse, will obtain consent from each patient prior to participation in this trial. All staff taking consent will be trained in taking consent and this will be evidenced on the local delegation log(s). They will also have appropriate GCP training. Some comparisons may simply involve an observational study of routine patient data and may not require individual patient consent, provided the relevant information governance regulations have been followed and the relevant regulatory approvals are in place. In these cases, consent waivers will be specified justified in the relevant comparison appendix.

For CTIMP comparisons, if consent is not taken by a medically qualified person, the PI or delegated doctor will confirm eligibility prior to approach and the informed consent form will be verified in a timely manner. For CTIMP comparisons, where taking informed consent is the role of someone who is not a medically qualified doctor, it is expected that a medically qualified doctor who is part of the trial team is available during or following the consent process if the participant requests further discussion relating to the medical care that is to be provided as part of the trial. For non-CTIMP comparisons, the informed consent form does not require verification by the PI.

The consent process may use either electronic (eConsent) or paper-based consent, with eConsent the preferred method where possible. The consent process can take place either face-to-face or using a locally approved remote method (phone, video call, etc.). All potential participants will be provided with a copy of the latest versions of the Patient Information Sheet (PIS) and Informed Consent Form (ICF) together with an explanation of the aims, methods, anticipated benefits and potential hazards of participation. This will be done either in person, using electronic methods, or by post. The patients will be given the opportunity to ask questions about the study by a qualified healthcare professional who is a member of the research team. Where possible all patients will be given a minimum of 24 hours between the time they are approached about the trial and the time when consent is given. For those patients who have not been contacted face-to-face, the signed consent form will be returned via electronic methods or by post and counter-signed by a member of the research team.

For patients who have chosen eConsent, the form may be completed on a computer, smartphone or tablet/electronic device. Informed consent will be recorded by means of a dated participant electronic signature before they may enter the trial. The signature will be generated either by a finger tracing across a tablet device, or using an electronic stylus on a tablet device or using a mouse dragging the cursor across the screen – all methods are to be used as if signing with a traditional pen. The member of the research team taking consent will then add their own dated electronic signature to the consent form. One copy of the consent form will be sent to the participant using electronic methods (e.g. email), and the hospital site will be able to download a copy of the consent form from the PROTECT online e-Consent system and/or trial database.

Following consent, a copy of the PIS and signed ICF will be filed in the medical notes. If an electronic health record is used, the documents will be uploaded to the electronic health record. Original signed consent forms will be retained and stored by the site investigators

and a copy given to the participant. The discussion and the consenting process will be documented in the patients' medical records.

The right of a patient to refuse participation without giving a reason 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. They 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 (RSI) becomes available during the study, or new information needs to be provided to a participant) it is the responsibility of the PI to ensure this is done in a timely manner and prior to the next use of any investigational treatment. The study will not involve the participation of vulnerable subjects or subjects lacking capacity.

Any variation to this consent model for specific comparisons will be detailed in the relevant appendix.

9.1 Writing, reading, and translation considerations

If a participant is unable to read or sign the informed consent form but has capacity to give consent, this can be provided on the participant's behalf by a witness. A statement will be included in the consent form explaining that the participant understood the information and informed consent was given freely.

If translation of consent materials is required this will be done via the recruiting site's interpreting service, which may be an in-person interpreter, or a video/telephone interpreter service (e.g. Language Line). The details of the interpreter should be in the participant's medical record, in addition to the standard record of the consent process. The use of friends or family members for translation of consent materials is prohibited. We will develop non-English ICF and PIS as we learn more about those most in demand for the PROTECT eligible patient population.

9.2 Initiation of platform procedures

All procedures including randomisation, safety reporting, data collection, including linkage to routine NHS datasets, will commence as soon as informed consent has been obtained. For those participants who are unable to self-report, questionnaires may be proxy-reported by an appropriate individual.

10. Participant eligibility criteria

Inclusion criteria

- All adult patients (≥18 years) being treated within a surgical care pathway at the recruitment sites will be eligible for the trial.

Exclusion criteria

- Inability or refusal to provide informed consent.

Each comparison appendix will define comparison-specific eligibility criteria within this study population.

11. Study Schedule

11.1 Schedule of treatment for each visit

Please refer to the individual comparison-specific appendices for the specific treatment schedules.

11.2 Randomisation method

For each comparison, participants may be allocated to receive an intervention as specified in the relevant comparison appendix, which will also describe the allocation sequence(s) for each comparison. All sites will have access to a secure randomisation system. When a participant is allocated to an arm within a comparison, sufficient identifiable details (e.g. participant name, date of birth) will be logged on a secure, encrypted, web-based system. Each participant will receive a unique study ID.

11.3 Randomisation procedure

The code creating the randomisation sequence will be approved by the lead statistician for each comparison. Further details will be explained in the data management plan which will be agreed and signed off by the comparison team and CTU. Blinding and/or unblinding procedures, if applicable, will be described in the individual comparison appendices.

11.4 Study assessments

The patient's medical record including historical data will be reviewed. Please refer to comparison-specific appendices for the specific study assessments.

11.4.1 Baseline data

After a participant is enrolled, we will collect baseline data which includes: randomisation data (if applicable), demographic and diversity information (e.g. age, sex at birth, ethnicity etc), baseline data (e.g. co-morbidities, current health status, etc.), surgical procedure details (e.g. details of the anaesthetic, surgical approach, procedure performed, duration etc.) and level of care on the first night after surgery. Each comparison appendix will detail additional comparison-specific data.

11.4.2 Common outcome data

A common outcome dataset will be collected for every participant enrolled in PROTECT (table 1). Complications within 30 days after surgery will be graded according to the Clavien-Dindo scale (where applicable), and will include (but not limited to): Infections (e.g. surgical site, body cavity, pneumonia, urinary tract, bloodstream etc.), cardiovascular (e.g. myocardial infarction, arrhythmia, pulmonary oedema, pulmonary embolism, stroke, cardiac arrest etc.), other (e.g. postoperative bleed, acute respiratory distress syndrome, delirium/psychosis, perforation of viscus, anastomotic leak etc.) and treatment for postoperative complications (e.g. drug therapy, blood transfusion, total parenteral nutrition, surgical/radiological procedure, critical care admission etc.). Definitions of individual complications will be provided in a Trial Specific Standard Operating Procedure.

Common outcome data will be assessed by reviewing the medical record and/or contacting patient or the GP, or through linkage to national health systems data. Days Alive and at Home (DAH), mortality at 30 and 90 days after surgery, and hospital length of stay and readmission within 90 days after surgery will be collected by reviewing the medical record, and/or contacting the patient or GP, or through linkage to national health systems data. NHS health systems data will be collected through linkage to NHS data warehouses (see section on “Data linkage for routinely collected patient-level data”), which includes administrative/registry data (e.g. vital status, index of multiple deprivation etc). Health-related quality of life at 30 and 90 days after surgery will be assessed using the EQ-5D-5L questionnaire, by contacting the patient or by using an electronic questionnaire. The procedure for follow-up is listed in section 11.5. Any additional outcome measurements relevant to individual comparisons will be described in the relevant appendix.

11.4.3 Health-related quality of life

Where applicable, health economic analysis will compare the incremental cost per quality adjusted life year (QALY) of study comparisons to usual practice. Cost per patient in the intervention and usual care arms will be assessed from the perspective of the NHS. Costs and outcomes will be evaluated over the 90-day horizon of the trial and no discounting will

be applied due to the short length of follow-up. The analysis will include the cost of the intervention in addition to the cost of healthcare resources consumed by patients over the 90-day period.

11.5 Follow-up procedures

For all follow-up time points, contacts with the participant will be completed by a member of the local research team either in person, using a remote method (e.g. telephone), or through electronic means (e.g. email, Short Messaging Service (SMS)). The local research team will attempt to contact the participant up to three times over a four-week period. If they do not receive a response, the research team will attempt to contact them using an alternative method that hasn't been used previously. If a response is still not received within the following six weeks, the research team will attempt to complete the follow-up by contacting the GP and/or reviewing available medical records. If the participant is uncontactable, then any patient reported outcome data will be treated as missing. The local research team will review available medical records to collect follow-up data, which include additional re-admissions, outpatient and emergency contacts, and procedures and tests. Follow-up data will also be collected using routinely collected NHS health systems data, HES or the equivalent in each devolved nation and Office for National Statistics registry data. Further information on health systems data linkage is detailed below.

11.6 Participant, study and site discontinuation

Participants may decline to continue to take part in the platform, either from individual comparisons if they are recruited to multiple, or from the whole platform if they want to withdraw entirely, at any time without prejudice. A decision to decline or withdraw consent will not affect the standard of care the participant receives. Participants can withdraw their consent by contacting the research team, with the contact details provided on the PIS. Participants who decline further contact can withdraw entirely from the platform. In this case, a withdrawal form will be completed and no further data will be collected from that participant. Participants will be given the option to continue their participation in the platform, allowing the research team to use any routinely collected data through the data linkages described in the master protocol and any relevant appendices but to decline further individual (in person) data collection by the recruiting site or central research teams. If participants are enrolled in multiple comparisons, they may wish to withdraw from a particular comparison but continue in another. In this case, the same procedures will be followed as above but only for the comparison that they wish to withdraw from. Upon withdrawal of the participant, any source data recorded up to the time of withdrawal will be collected and retained by the research team and included in the final analysis. Once

withdrawn, the local clinical team will be notified to ensure participant continue to receive the care they need. Those participants with a recorded outcome will be included in any analyses (on an intention to treat (ITT) basis for interventional comparisons).

11.7 End of trial definition

The end of each comparison is defined as the time point when the last participant visit has been completed for that comparison. The individual comparisons can end independently of the platform and other comparisons. An 'end of trial notification' will be submitted when each individual comparison has been completed. Please refer to the individual appendices for the specific end of comparison definitions. The CI or delegated person is responsible for 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 comparison. If the comparison has ended prematurely, the CI will notify the Sponsor, REC, and MHRA within 15 days, including the reasons for the premature termination.

An end of trial notification will not lead to closure of the overall PROTECT platform trial unless the CI specifically states this in the end of trial notification document.

12. Laboratories and samples

For comparisons requiring sample collection and analysis, the additional details will be described in the relevant appendix.

13. Study medication

For comparisons involving the administration of an IMP detailed guidance about name, legal status, supply arrangements and drug management will be described in the relevant protocol appendix and the supporting documentation for that comparison.

14. Equipment and devices

All comparisons using equipment and/or devices would require a UKCA/CE mark prior to evaluation on the platform. Information about any equipment or devices used will be described in the relevant protocol appendix.

15. Pharmacovigilance

The overall safety reporting concept is stated here.

15.1 General definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom an investigational medicinal product (or other intervention(s) depending on the comparison) has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product (or other intervention(s) depending on the comparison) which is related to any dose administered to that participant. The phrase "*response to an investigational medicinal product*" means a causal relationship between a study medication (or other intervention), and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A SAE is any untoward medical occurrence meeting the definition of AE that also: • Results in death • Is life-threatening • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An AE that is both serious and, in the opinion of the reporting investigator or medical assessor, believed with reasonable probability to

	be due to one of the study treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the RSI: • In the case of a product with a marketing authorisation, please refer to the SmPC for that product. In the case of any other IMP, please refer to the investigator's brochure (IB) relating to the study in question.

15.2 Site investigator assessment

The PI or delegated doctor, is responsible for the care of the participant and assessment of any event for:

- Seriousness: Assessing whether the event is serious according to the definitions given in section 0.
- Causality/ Relatedness: Assessing the causality of all serious adverse events/reactions in relation to the study treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.
- Expectedness: Assessing the expectedness of all SARs according to the definition given. If the SAR is unexpected (as per the RSI), then it is a SUSAR.
- 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

Each safety event (i.e. AEs, ARs, SAEs, SARs and SUSARs) must be identified and reported separately. Screening and identification of safety events will be based on clinical events (from daily charts and/or reviews) and review of laboratory and other investigations undertaken as part of routine care. There will be no testing or investigation additional to routine care undertaken for the purpose of detection of any safety events unless specified in the relevant protocol appendix.

The guiding principle is that where a safety event is considered relevant and/or has caused an untoward medical occurrence, it is the responsibility of the PI or delegated doctor to

review all relevant medical records and report this as a safety event. Please refer to each appendix for safety events that require immediate reporting.

15.3 Reference Safety Information (RSI)

RSI is the information used for assessing whether an adverse reaction to an IMP is expected. Updates to the RSI will be reviewed annually by the CI or deputy delegated medical assessor. Changes in RSI will be submitted as a study amendment and sites will be notified accordingly. Details of the RSI will be described in each comparison appendix as applicable.

15.4 Notification and recording of Adverse Events (AEs) or Reactions (ARs)

All AEs and ARs will be documented in the participant's medical notes or other source data documents and the eCRF by the PI or delegated doctor including assessment of the event. Once assessed, if the AE is not defined as SERIOUS, the AE is recorded in the eCRF and the participant is followed up by the research team.

15.5 AEs and SAEs exempt from reporting

The purpose of pharmacovigilance is to protect trial participants when new treatment safety findings come to light during the course of the trial. However, surgery is a treatment which itself generates adverse events independent of any investigational treatments. Most PROTECT trial comparisons will address pragmatic clinical effectiveness questions where the potential treatment harms are well known (and may even be part of the patient outcomes of the trial comparison). For comparisons where common treatment harms form part of the trial comparison, these may be collected as pre-defined patient outcomes and may not need duplicate reporting as SAEs. Thus, whether medical occurrences require immediate reporting as safety events will vary with each trial comparison. Local investigators will be expected to carefully follow the safety and/or pharmacovigilance reporting process described in each protocol appendix for all comparisons the patient is enrolled in.

Enrolment in the platform (master protocol) alone without enrolment in a protocol appendix, and enrolment in protocol appendices for observational research questions without a specified intervention or treatment will be exempt from safety reporting. For protocol appendices that include a specific intervention or treatment, SAEs which are both related and unexpected will be reported.

Any safety event deemed to be exempt from reporting as an SAE will be listed in each comparison appendix with a justification as to why it is not reportable as an SAE, based on a

risk proportionate approach, and to a level of safety profile already documented for that intervention.

15.6 Notification and reporting of Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SAEs, SARs and SUSARs will be recorded in the participants' notes, the eCRF, the Sponsor SAE form and reported to the Sponsor (administered by the QMUL Joint Research Management Office or agreed representative) and the IMP provider (if applicable) within 24 hours of the site becoming aware of the event (except those specified in this protocol as not requiring reporting), unless specifically exempted from immediate reporting (see 15.5 "AEs and SAEs exempt from reporting" and comparison appendices relevant Protocol section). Delegated personnel (must be medically qualified) will be authorised to sign the safety forms in the absence of the PI at the participating sites.

For SAEs, SARs and SUSARs, causality will be assessed against all intervention comparisons the patient is enrolled in. Each comparison appendix will specify the safety events that require immediate reporting.

15.6.1 Procedure for immediate reporting of SAEs, SARs and SUSARs

- For CTIMP comparisons, the recruiting site research team will complete the following steps to report SAEs, SARs and SUSARs:
  i. The local PI or delegate (must be medically qualified) will complete the Sponsor's SAE form that will include the below information:
     a. the intervention group (where blinding is involved this may need to be reported by the central trial team)
     b. dose administered (if applicable)
     c. the type of event (using the MEDRA term if known)
     d. onset time and date (and relationship with administration)
     e. an assessment of seriousness, causality, expectedness and severity
     f. date of resolution together with any treatment or investigations required (once known)
     g. final outcome (once known)
  ii. The completed form will be signed and emailed to the PROTECT central coordinating team admin account (admin@protectresearch.org or alternative nhs.net email account if required) within 24 hours of becoming aware of the event.

iii. Following review and confirmation by the central trial team, the Sponsor's SAE form will be submitted to Sponsor and the local site team will record the event on the trial database.

iv. The team should not wait until all information about the event is available before sending the SAE notification. Information not available at the time of the initial report must be documented and submitted as it becomes available as part of the follow-up form.

- For non-CTIMP comparisons, the recruiting site research team will only report SAEs if they meet the following criteria:
  I. Related to the comparison intervention or procedures and
  II. Unexpected (i.e. not listed in the protocol as an expected occurrence)

SAEs for non-CTIMP comparisons are to be reported to the sponsor and the sponsor's representatives within 72 hours of learning of the event by submitting the SAE form and emailing the PROTECT admin account (admin@protectresearch.org). For non-CTIMP comparisons, it is the CI's responsibility to report SAEs which are unexpected and related to the comparison intervention or procedure to the REC.

The above procedures apply unless an SAE is specifically exempted from immediate reporting (see 15.5 "AEs and SAEs exempt from reporting" and comparison appendix relevant section).

15.6.2 Central review of the safety events and Sponsor medical assessment

The CI or deputy delegated medical assessor(s) for the platform will review all incoming safety events without delay and will raise any queries with the local PI until resolved. As there is no legal requirement to perform dual assessment of causality, the deputy delegated medical assessor will only query the PI assessment if there is any concern regarding the judgement. In the event that consensus is not reached between the PI and deputy delegated medical assessor about assessment of causality, both assessments will be taken into consideration. It is noted that the CI or deputy delegated medical assessor(s) cannot downgrade the PI assessment of an event's causality. No pressure should be placed on the PI to alter their assessment, The CI and PI assessment can differ. For all comparisons, assessment of expectedness will only be performed centrally by the CI or deputy delegated medical assessor.

For comparisons involving CTIMPs, the Sponsor has delegated the responsibility for oversight of IMP safety profile and medical assessment of safety events (AEs, ARs, SAEs and SUSARs) to the CI as medical assessor. The CI, or deputy delegated medical assessor(s), must review all SAEs within 72 hours of receipt. This review should encompass seriousness, causality, relatedness, and expectedness. Day 0 for all SAEs/SUSARs is defined as when the SAE/SUSAR is received by the CI and/or coordinating team and/or Sponsor (whichever is first).

Expectedness of SARs in CTIMP comparisons will be determined according to the relevant RSI in use at the time the reaction occurred. For the non-CTIMP comparisons, expectedness of events related to interventions will be assessed against the list of expected events in the relevant appendix. The CI will be responsible for assessing expectedness.

15.8 Procedures for reporting blinded SUSARs

The CI, as Sponsor's medical assessor, will assess the event blinded for all possible IMPs, placebos, and combinations. All SUSARs will be reported by the central research team (Sponsor delegate) to the relevant Competent Authority and to the REC and other parties as applicable and per instructions in the relevant Sponsor SOPs. For fatal and life-threatening SUSARs, this will be done no later than seven calendar days after the central research team is first aware of the reaction. Any additional relevant information will be reported within eight calendar days of the initial report. All other SUSARs will be reported within 15 calendar days. Treatment codes will be un-blinded for specific participants if applicable. PIs will be informed of all SUSARs for the relevant IMP or other intervention for all studies with the same Sponsor, whether or not the event occurred in the platform.

15.9 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical study participants from any immediate hazard to their health and safety, in accordance with Regulation 30 of the Medicines for Human Use (Clinical Trials) regulations. The measures should be taken immediately. In this instance, the approval of the Competent Authority prior to implementing these safety measures is not required. The CI has an obligation to inform both the MHRA and REC in writing **within three days** of implementing the Urgent Safety Measure. They must also submit a substantial amendment documenting the changes with 14 days of implementing the urgent safety measure. The JRMO must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

15.10 Pregnancy

If a participant becomes pregnant whilst involved in a CTIMP, it is not considered to be an SAE or an AE. However, it is an event that requires reporting, monitoring and follow-up. If a participant or participant's partner becomes pregnant whilst or after taking an IMP, the sponsor should be notified immediately (within 24 hours of site becoming aware of the pregnancy) using the sponsor pregnancy form. The pregnancy reporting procedure will be the same as the SAE reporting route.

The CI (in conjunction with the site PI) should determine if the foetus has been exposed to an IMP. The PI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. The initial report should be sent within 24 hours of the PI or co-investigator becoming aware of the event and follow up information submitted when it becomes available up to an agreed follow up time after birth.

The Sponsor will arrange for a review of the pregnancy report by an appropriate expert medic (usually a consultant obstetrician). The study team must follow all instructions provided by the sponsor's expert. Further details on the whether the participant can continue on the study and their follow-up will be detailed in the individual appendices.

Reporting of pregnancy is not required for non-CTIMP comparisons unless specifically stated in relevant comparison appendix.

16. Annual reporting

16.1 Development Safety Update Report (DSUR)

For CTIMPs comparisons the DSUR will be written by the CI or delegated person (following Sponsor procedures) and submitted to the Sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annual from the date on the "*Notice of acceptance letter*" from the MHRA throughout the comparison recruitment period. The Sponsor's delegated Medical assessor (CI) will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the study. REC will be sent a copy of the DSUR. Please note there will be no DSUR submitted for the master protocol as there are no IMPs associated with the main platform trial.

As this platform will involve multiple comparison appendices with their own start and end dates, some of which will have IMP comparisons and others not, the trial management team will prepare a separate DSUR for each applicable comparison appendix. The first DSUR will

start on the anniversary of the Clinical Trial Authorisation for the first comparison appendix. As more comparison appendices are added to the platform, each (if relevant) will have their own DSUR using the date of authorisation for that appendix.

17. Statistical design and data analysis

17.1 Statistical design

Details on the statistical design for the individual comparisons can be found in the relevant appendix including sample size calculations.

17.2 Statistical analysis

The principal document guiding statistical analysis is a statistical analysis plan (SAP). A detailed SAP will be prepared for each comparison. All signed off versions of SAPs will be made publicly available and finalised before statistical analysis is undertaken. Any subsequent changes to the SAP or post-hoc analyses will be justified and documented in the final report. A short summary of the planned analyses will be summarised in the relevant comparison appendix to the master protocol, but this will be superseded by the SAP.

A summary of over-arching statistical principles for analyses of intervention comparisons within PROTECT is provided here. Primary analyses will use the ITT principle (i.e. participants with available data will be analysed according to treatment group allocation regardless of treatment received). Supplementary analyses e.g. per protocol or as-treated analyses may be undertaken as outlined in the relevant comparison appendix. All analyses will be in line with the International Council for Harmonisation (ICH) E9 Statistical Principles for Clinical Trials which presents the estimand framework. Baseline data will be summarised, but not formally compared between randomised arms. Standard statistical summaries and graphical plots will be used to present findings for the primary outcome measure and secondary outcome measures. The primary analysis may be supplemented with sensitivity analyses. The platform may accommodate frequentist and Bayesian approaches to design and analysis, as outlined in the relevant comparison appendix.

17.3 Interim analysis

Some comparisons will include an interim analysis. If applicable, details will be included in the individual comparison-specific appendix, including decision criteria.

17.4 Economic evaluation

Health economic analysis may be undertaken, which will be specified in the protocol appendix for a specified comparison. If a health economic analysis is planned, a fully detailed health economic analysis plan (HEAP) will be prepared and finalised to any final analysis. Any subsequent changes to the HEAP will be justified in the final report.

18. Data linkage for routinely collected patient-level data

18.1 Concept

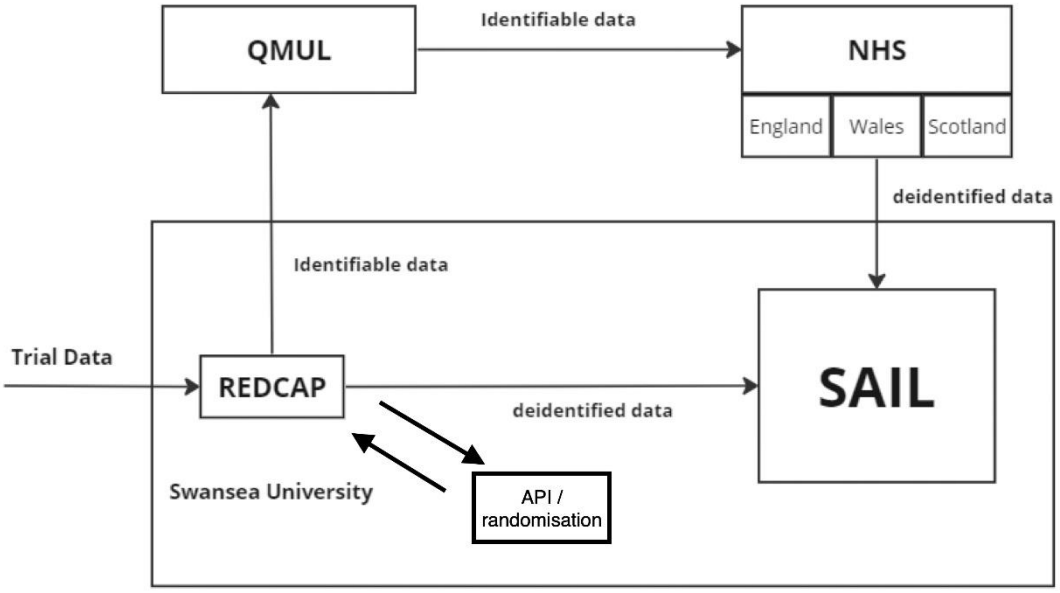
Individual participant consent will be obtained to access patient-level routinely collected health services data captured by the various UK data warehouses that hold information, including diagnostic and procedural codes relevant to hospitalisations and/or out-patient attendances for patients receiving NHS care in order to provide a measure of long-term outcomes and NHS resource use. Periodically, at convenient intervals for the ongoing analyses planned for each comparison, we will request these records and mortality records for all consenting participants.

For participants in England, linkages will be sought with the admitted patient care, out-patient care and critical care datasets within the Hospital Episode Statistics (HES) database; in Northern Ireland the Acute Episode-based Activity Statistics (EAS); in Wales, the Patient Episode Database for Wales (PEDW) derived from the Admitted Patient Care dataset; in Scotland, The Scottish Morbidity Register – General/Acute Inpatient and Day Case (SMR01). In addition, linkages will also be sought with the relevant registers of deaths and the causes of deaths in each jurisdiction. Civil Registration (deaths) provides a complete register of date and cause of death in England and Wales and is administered by NHS Digital; the General Register Office for Northern Ireland records deaths in this jurisdiction; the Statutory Registers of Births, Deaths and Marriages in Scotland is administered by the National Records of Scotland.

For the purposes of the data analyses the research team will only process de-identified data. In order that the dataset can be created, identifiable data will be provided to each data controller for the purpose of the linkage. A bespoke cohort will be generated from the platform database and sent to each data controller containing participant identifiers specified by each data warehouse, this is usually (but not limited to) health service number, date of birth, sex at birth and postcode as well as a unique identifier for linkage. The trusted third parties will link the cohort to the relevant civil register of deaths and administrative databases in their jurisdiction and return the relevant variables.

18.2 Data flows

The data controller for the PROTECT database will be QMUL and data processor will be Swansea University, Swansea, UK (encompassing the UK Secure Research Platform (UKSeRP) and the Secure Anonymised Information Linkage (SAIL) Databank). The database will be hosted and de-identified data will be processed at Swansea University. The legal basis for QMUL to collect and transfer personal data to the trusted third parties is participant consent as set out in section 261.2(c) of the Health and Social Care Act 2012 and section 251 of the NHS Act 2006 and the Health Service (Control of Patient Information) Regulations 2002. Identifiable data from the bespoke cohort will be provided to NHS England, electronic Data Research and Innovation Service (eDRIS) in Scotland, Department of Health (Northern Ireland) and NHS Wales Informatics Service for data linkage. QMUL will send participant identifiers, usually (but not limited to), the health service number, date of birth, sex at birth and postcode as well as a unique participant identifier for linkage. The data provider (NHS England [England] / Department of Health [Northern Ireland] / NHS Wales Informatics Services [Wales] / Electronic Data Research and Innovation Service [Scotland]) will link Civil Registration (deaths) data and cause of death, and health services data (e.g. HES or equivalent) data with the unique identifier. QMUL will receive from the data provider(s) patient-level de-identified data only, i.e. the linked data and cause of death as well as health services data with the unique participant identifier. The legal basis for QMUL to receive and process data from the data providers is Articles 6 and 9 of the General Data Protection Regulations (GDPR). De-identified linked data will be processed by Swansea University and aggregated with the bespoke cohort using the unique patient identifier to create a research dataset for the processing purposes described within the statistical analyses contained within the master protocol, comparison appendices and the associated statistical analysis plans.



18.3 Description of analysis methods

Linked health services data will be received at episode level (period of time a patient is under the care of a consultant), from which spells of continuous care will be built and combined with mortality data from the national registries. Events will be identified through International Classification of Diseases (ICD; diagnostic), Office of Population Censuses and Surveys (OPCS) procedure codes, Health Resource Group (HRG) codes and deaths. The specific events of interest will be described in each of the comparison appendices. Where applicable, patient-level profiles of resource use associated with linked hospital episodes encompassing in-patient admissions, out-patient visits and emergency department attendances will be costed using NHS Reference Costs.

19. 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). A source data location document will be in place for each site that will detail, for each data point to be collected what will comprise the source data and what will comprise the source documents. Only members of the direct care team within each NHS site 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.

19.1 Case Report Forms (CRFs)

A summary of the data collection points can be found in section 11.4 and the relevant comparison-specific appendix. A full list of specific data collection points will be detailed in the CRF. Research staff at each hospital site will be responsible for the completion of the electronic CRF (eCRF) for the duration of the study. The eCRF hosted on a secure server. A requirement specifications document will describe database functions. Sites will be provided with a paper data collection tool that matches the eCRF however it is not compulsory to complete this. The electronic patient questionnaire will act as source data for patient reported outcomes. Participants' medical notes will act as source data for other data. It is expected that the exact source data list will vary by site, and by patient preference (e.g. patients may choose to complete electronic follow-up). A site agreement will be in place for each recruiting site.

19.2 Data capture

The data collected from participants will be entered on to the PROTECT database. The database will be set up by a member of central research team and all specifications agreed between the CI, statistician, data manager and other relevant members of the research team. The PROTECT database is a secure, GCP compliant, web-based data collection system designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry, including forms for participants to complete directly; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. This will be used for data collection in the platform. Wherever possible, data will be entered directly into the database by recruitment site staff or trial participants themselves. The database will be hosted within a Trusted Research Environment at Swansea University, accessible only to members of the research team based on their role within PROTECT, or employees of Swansea University according to a contractual agreement with the Sponsor. Data security management systems are compliant with the requirements of ISO/IEC 27001:2013. Due to the patient population in the platform, direct electronic capture of data will not always be possible; any data recorded on paper CRFs will be transcribed into the database by the local research team. Procedures for data entry will be documented in the data management plan.

19.3 Transferring and transporting data

All data must be handled in accordance with the Data Protection Act (2018) and General Data Protection Regulations. Participant identifiable information must not be stored or

transported on any portable device (e.g., laptops, memory sticks). 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, or using authorised secure file transfer systems.

19.4 Data management

A full data management plan will be developed to describe in detail the methods of data management. PIs will oversee and be responsible for local data collection, quality and recording. Collection of data can be delegated (as per the Delegation Log) by the PI 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. 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 central study management team. 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 participant notes for quality assurance purposes and source data verification, but participants' 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.

20. Confidentiality

The CI will be the data custodian for all data generated during the study. The CI and the study team will ensure that all participants' identities are protected at every stage of the study. Identifiable data, including full name, Health Service Number, sex at birth, date of birth and postcode will be collected at enrolment to allow tracing through national records. The personal data recorded on all documents will be regarded as confidential. The PI is responsible for protecting the identity of participants at their site and must maintain in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written consent forms). The PI must ensure patients' confidentiality is maintained at all times. No participants will be individually identifiable from any publications resulting from the study. Participants will be referred to only by their unique study ID in all correspondence between the site and the coordinating centre, co-investigators, sponsor, or anyone associated with the study.

The CI 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 SAE, if applicable. 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 REC. 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.

20.1 De-identification of participants

A screening log will be maintained throughout the trial. Usually this includes potential participants' initials to allow their identification by relevant site staff. Once the participant has completed screening procedures and enrolled onto the study, they will be allocated a unique study identifier generated by the PROTECT database. The participant's full name, sex at birth, date of birth, Health Service number (UK) and postcode 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 PI must ensure that patient 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, if applicable.

21. Monitoring, Audit, and Inspection

21.1 Monitoring

A platform monitoring plan will be developed and agreed by the Sponsor and CI based on the Sponsor's risk assessment, which will include central, on site and remote monitoring in line with Sponsor SOPs. Where applicable, monitoring procedures will be detailed in the relevant study monitoring plan for the individual comparison-specific appendices.

Participating sites and PIs must agree to allow trial-related on-site and/or remote monitoring by providing direct or virtual access to source data and/or documents as required. Participating sites will be requested to conduct quality control checks of documentation held within the ISF and Pharmacy Site File (if applicable) at the frequency determined for the

comparison. Checklists detailing the current version/date of version-controlled documents will be provided by the PROTECT trial team for this purpose.

The PROTECT trial team will review trial data for errors and missing items and raise queries as appropriate. They will look at the trial data to look for anomalies and follow-up with sites when any are found.

21.2 Auditing

Sponsor retains the right to audit any trial, study sites or central facilities. In addition, any part of the trial 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.

22. Compliance

The CI will ensure that the protocol and study is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, current UK Policy Framework for Social and health care research (2017), 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 Sponsor permission to activate sites is received. Sites will be individually activated by the CI (or delegated deputy as per the delegation log) and team; this will not occur until site approval is granted.

22.1 Non-compliance

Non-compliances may be captured from a variety of different sources including monitoring visits, eCRFs, communications and updates. The PROTECT coordinating team will maintain a log of the non-compliances and will be periodically shared with the Sponsor in order for them to ascertain if there are any trends developing which need to be escalated.

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). The CI and the trial coordinating 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 eCRF.

22.1 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 PI 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 CI is responsible for reporting any potential serious breaches to the JRMO **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 CI to investigate and notify and report to the MHRA and REC (as applicable) within seven working days of becoming aware of the serious breach.

23. Declaration of interests

The Sponsor requires all study committee members to complete competing interest declarations. The CI, PIs at each hospital, and all committee members for the overall study management (PSC, CSCs, DMECs, Intervention Selection Committee and Patient Advisory Group) will provide the following information:

- 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@protectresearch.org.

24. Peer review

The PROTECT platform programme is funded by competitively awarded external grants, which were peer reviewed by internal and external experts during the funding process. Individual comparisons will undergo peer review before adoption to the PROTECT platform, and the details of this peer review will be detailed in each comparison-specific appendix.

25. Public and Patient Involvement (PPI)

Patients have been involved through the design of the PROTECT platform, 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, the PROTECT programme has been reviewed 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 patient advisory group, who will provide on-going PPI input and representation on platform committees. The patient advisory group will meet at least twice per year.

26. Indemnity/ Insurance

The insurance that QMUL 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.

27. Study committees

The CI will take overall responsibility for the delivery of the platform and oversee progress against timelines/milestones.

27.1 Platform Management Group (PMG)

Platform Management Group will consist of the CI, Trial Manager(s), Statistician and members of the Pragmatic Clinical Trials Unit (PCTU) as required. Meetings will be held regularly at an appropriate frequency to ensure the progress of the platform against milestones and to ensure effective communication across the team. The day-to-day platform team will meet regularly to discuss and monitor progress.

27.2 Platform Steering Committee (PSC)

The role of Platform Steering Committee is to oversee the platform and will consist of several independent clinicians and trialists, lay representation and co-investigators. Meetings will be held at regular intervals determined by need but not less than once a year. The PSC will take responsibility for:

- approving the final protocol
- major decisions such as a need to change the protocol for any reason and/or the addition of appendices to the protocol
- monitoring and supervising the progress of the platform
- reviewing relevant information from other sources
- informing and advising on all aspects of the platform
- advising on issues of patient safety during the platform

27.3 Comparison Management Group (CMG)

The Comparison Management Group will consist of the Lead Investigator, Trial Managers, Trial Statistician and members of the Clinical Trials Unit as required. Regular meetings will 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.

27.4 Comparison Steering Committee(s) (CSCs)

Each comparison will have a CSC, which will act as a sub-committee of the PSC. The role of the CSC will be to oversee the conduct of that intervention comparison, and to make recommendations to the PSC. Membership of each CSC will be detailed in the comparison-specific appendix and will comply with any funding requirements for make-up of a trial steering committee, if applicable. Subject to PSC approval, the CSC will take responsibility for:

- approving the final comparison-specific appendix to the master protocol
- major changes to the comparison appendix to the master protocol
- monitoring and supervising the progress of the intervention comparison
- reviewing relevant new information from other sources
- informing and advising on all aspects of the platform
- advising on issues of patient safety during the platform
- reporting to the PSC and the CI before implementing any decisions

27.5 Independent data monitoring committees (IDMC)

The IDMC is independent of the platform coordinating team and comprises a minimum of two clinicians with relevant clinical expertise and experience in undertaking clinical studies, and a trial statistician. The IDMC functions primarily to periodically review overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. The committee will also review relevant new external evidence and monitor the overall conduct of the platform. The committee will agree conduct and remit, which will include the early termination process for individual comparisons. Comparisons will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. Decision criteria will be specified in the comparison-specific appendices where applicable. Generally, the CI or comparison lead investigator identifies any relevant external evidence and passes this to the IDMC for review. The IDMC will make recommendations about stopping, modifying or continuing comparisons within the platform to the CSC and PSC. The IDMC may also make recommendations regarding selection, recruitment, or retention of participants, their management, protocol adherence and retention of participants, and procedures for data management and quality control. The CSC, and where relevant the PSC, will be responsible for promptly reviewing DMEC recommendations to decide whether to continue or terminate comparisons within the platform, and to determine whether amendments to the protocol or changes in study conduct are required. With multiple intervention comparisons it may be necessary to convene more than one IDMC to provide relevant expertise and to ensure the independence of IDMC members. The details of the IDMC associated with each intervention comparison will be detailed in comparison-specific appendix.

28. Publication and dissemination policy

28.1 Publication and dissemination policy

Responsibility for ensuring accuracy of any publication from this programme is delegated to the CI. All publications will be sent to the JRMO as Sponsor prior to publication. All publications should acknowledge the sponsor and be consistent with sponsor policy and/or MHRA/HRA/REC requirements for dissemination and publication. Data arising from this research will be made available to the scientific community in a timely and responsible manner. Detailed scientific reports will be submitted to a widely accessible scientific journal on behalf of the PROTECT Group. The PSC will agree the membership of a writing committee, which will take primary responsibility for final data analysis and writing of the scientific report(s). All members of the writing committee will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission. Final reports of PROTECT studies will be made available on a publicly accessible database,

consistent with the requirements of the Funder(s) and/or Sponsor (within one year of the End of the Trial Notification for each comparison appendix) and/or MHRA/HRA/REC and within the required timeframe(s). Please see PROTECT publication charter for further details.

28.2 Access to the final study dataset

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

29. Archiving

During the course of the research, all records are the responsibility of the CI (or deputy delegated person) and will be kept in secure conditions. When the research study is complete, it is a requirement of the QMUL policy that the records are kept for a further 25 years for research falling under remit of the MHRA and interventional studies (defined as research where the participants' care or treatment is being changed). For research studies (any clinical research study where there is no change to the participants' care or treatment, and any nonclinical research study) length of records retention is 5 years or as defined by the data sharing agreement(s) for linked datasets. If a participant is co-enrolled into multiple comparisons, the archiving process for their data will not begin until the end of the comparison with the longest duration.

Consent forms will be downloaded by local recruitment centre teams before the end of the relevant comparisons for long term storage as part of the Investigator Site File. They will be removed from the platform database once relevant central monitoring activities of the forms has been completed and participants have completed their participation in all of the comparisons that they were enrolled onto. Site files from other sites must be archived for 25 years (or 5 years as applicable) at the external site and will not be stored at QMUL. 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 any 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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