**APPENDIX 1 to the PROTECT Platform Master Protocol**

*This appendix must be read with the accompanying PROTECT Platform master protocol IRAS 353122. This appendix describes only the additional details relevant to the conduct of this randomised comparison within the context of the overarching master protocol.*

| | |
|---|---|
| **Full Title** | Analgesia with ibuprofen for patients undergoing elective major Gastro-Intestinal Surgery |
| **Short Title** | PROTECT-AEGIS |
| **Sponsor** | Queen Mary University of London<br><br>Contact person:<br>Dr Mays Jawad<br>Governance Operations Manager<br>Joint Research Management Office<br>Dept W, 69-89 Mile End Road<br>London E1 4UJ<br>Phone: +44 (0) 20 7882 7275/6574<br>Email: research.governance@qmul.ac.uk |
| **PROTECT-AEGIS IRAS Number** | 1011239 |
| **PROTECT IRAS Number** | 353122 |
| **REC Reference** | 24/LO/0885 |
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| | |
|---|---|
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| Participating sites | For a list of participating sites please refer to the IRAS application. |

## Comparison 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 comparison specific terms and abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| ASA | American Society of Anaesthesiologists Physical Status Classification System |
| CMG | Comparison Management Group |
| CSC | Comparison Steering Committee |
| eGFR | Estimated Glomerular Filtration Rate |
| GCP | Good Clinical Practice |
| IDMC | Independent Data Monitoring Committee |
| NRS | Numeric Rating Scale |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| OBAS | Overall benefit of analgesic score |
| PI | Principal Investigator |
| PPI | Patient and Public Involvement |
| RfPB | Research for Patient Benefit Programme |
| RSI | Reference Safety Information |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SmPC | Summary of Product Characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TDS | Three times a day |

## 3. Signature page

**Chief Investigator 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).

**PROTECT Platform Chief Investigator: Dr Tom Abbott**

**Signature:**

**Date:** Tom Abbott Digitally signed by Tom Abbott Date: 2025.08.13 09:52:54 +01'00'

**PROTECT-AEGIS Lead Investigator: Dr Caroline Thomas**

**Signature:**

**Date:** Caroline Thomas Digitally signed by Caroline Thomas Date: 2025.08.12 17:01:31 +01'00'

**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 name: Tom Hamborg**

**Signature:**

**Date:** Thomas Hamborg Digitally signed by Thomas Hamborg Date: 2025.08.12 17:37:36 +01'00'

**Principal Investigator Agreement**

The clinical study as detailed within this research protocol, 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.

**Principal Investigator:**

**NHS site:**

**Signature:**

**Date:**

## 4. Synopsis

| | |
|---|---|
| **Full title** | Analgesia with ibuprofen for patients undergoing elective major Gastro-Intestinal Surgery |
| **Short title** | PROTECT-AEGIS |
| **Sponsor** | Queen Mary University of London |
| **MHRA risk level** | Type A: Risk no higher than that of standard medical care<br><br>Ibuprofen will be used within its license and only patients known to be at low risk of potential side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) will be enrolled |
| **Phase of the trial** | IV |
| **Medical condition or disease under investigation** | Adult patients undergoing elective major gastrointestinal surgery. |
| **Study design and methodology** | Multi-centre individual patient randomised clinical trial |
| **Planned number of participants** | 200 |
| **Objectives** | • To demonstrate the willingness of patients to participate in the trial.<br>• To demonstrate whether relevant healthcare staff within participating hospitals were willing to randomise patients into the trial.<br>• To provide pilot data on the clinical effects of oral ibuprofen, in reducing pain after major elective gut surgery, compared to usual analgesia without a Non-Steroidal Anti-Inflammatory Drug.<br>• To provide safety data on the use of ibuprofen as an analgesic in patients undergoing major elective gut surgery. |
| **Inclusion and exclusion criteria** | *Inclusion criteria*<br>• Patients aged 18 years and over undergoing major elective gut surgery with bowel anastomosis.<br><br>*Exclusion criteria:*<br>• Inability or refusal to provide informed consent.<br>• Previous enrolment in the PROTECT-AEGIS trial.<br>• Concomitant administration of any of the below:<br>- Another Non-Steroidal Anti-Inflammatory drug<br>- Mifepristone within two weeks before surgery<br>• History of specific risk factors:<br>- Severe organ dysfunction defined as American Society of Anaesthesiologists (ASA) Physical Status Classification System 4 and/or eGFR <45<br>- Known hypersensitivity or allergic reactions to ibuprofen (or its excipients), or other Non-Steroidal Anti-Inflammatory Drugs*<br>- Peptic ulcer disease: two or more episodes of proven ulceration or bleeding, or upper gastrointestinal perforation<br>- Third trimester of pregnancy<br>- Solid organ or bone marrow transplant |

| | |
|---|---|
| **Investigational Medicinal Product** | Oral ibuprofen |
| **Treatment duration** | First five days after surgery |
| **Follow-up duration** | 30 days after surgery |
| **End of study definition** | 30-day follow-up completed for all patients |

## 5. Introduction

### 5.1 Background

One in three of the 50,000 patients who undergo major gut surgery in the NHS each year experience severe pain, which may last several days after surgery [1, 2]. Acute postoperative pain is not only a cause of patient discomfort but slows patient recovery, prolongs hospitals stays, and is an important factor in morbidity such as pneumonia [3] and myocardial infarction [4] after surgery. Many patients leave hospital with opioid pain relief, and there are growing concerns about long-term dependence to these drugs leading to a reluctance to prescribe them [5]. There is a clear need to make best possible use of non-opioid analgesia for this important patient group.

There is good evidence that ibuprofen, a Non-Steroidal Anti- Inflammatory Drug (NSAID), may prevent severe pain after major gut surgery. However, only around one in five patients receive ibuprofen because of the widespread belief that it causes gastric bleeding, anastomotic leak and acute kidney injury in this patient group. These complications are not unusual after surgery even when NSAIDs are not prescribed. For NHS patients undergoing major elective gut surgery, of whom around 20% patients receive NSAIDs, 30-day complication rates are 2% for gastric bleeding [6], 8% for anastomotic leak [7,8], and 10-15% [9] for acute kidney injury. The evidence that ibuprofen increases complication rates is contradictory.

Severe pain after surgery is not merely a temporary symptom but associated with serious postoperative harm. Patients tell us that healthcare staff repeatedly under-estimate the importance of pain relief after surgery. Of all the NSAIDs, ibuprofen is most commonly used, and has the best safety profile. Ibuprofen is cheap, easy to store, and available in all NHS hospitals. This simple drug might provide cost-effective analgesia for a patient group at significant risk of severe pain and poor postoperative outcomes [10-12]. Effective analgesia prevents the distress caused by severe pain after surgery, and also speeds patient recovery.

We need a large randomised trial to confirm whether ibuprofen provides safe and effective analgesia for low-risk patients undergoing major gut surgery. However, research experts are concerned that poor clinician equipoise would make a definitive trial undeliverable. A feasibility trial is needed to confirm patients and doctors would participate, and with high levels of intervention compliance. This would inform the design of a definitive trial, and clearly demonstrate willingness to participate and randomise patients across a representative sample of NHS hospitals.

### 5.2 Rationale for study design

Our preliminary work suggests patients and doctors support this trial, but research experts describe concern about clinical equipoise and trial feasibility because a definitive trial may require ≥3500 patients across ≥40 NHS hospitals. We need a randomised feasibility trial to confirm patients and doctors would participate with high levels of intervention compliance. This trial will also capture other data to inform the design of a definitive trial.

### 5.3 Assessment and management of risk

The trial is categorised as Type A, no higher than the risk of standard medical care (studies testing authorised medicinal products in accordance with the Marketing Authorisation in an EU member state).

In the PROTECT-AEGIS trial, participants will be allocated to receive either standard care or standard care plus oral ibuprofen (400mg three times a day (TDS)) as part of their pain management. Oral ibuprofen will be used within its license and only patients known to be at low risk of potential side effects of NSAIDs will be enrolled. Any generic, commercially available hospital stock of oral ibuprofen can be used. Intravenous ibuprofen will only be used in Trusts where this is policy or standard of care. The intervention will start from postoperative day one and continue until day five.

## 6. Trial objectives

Is it feasible to deliver a randomised controlled trial of oral ibuprofen added to standard analgesic care in patients undergoing elective major gut surgery, compared to standard analgesia without a Non-Steroidal Anti-Inflammatory Drug? The findings in this feasibility trial will not be used in managing the patient's care.

There are four main patient and hospital level objectives with the over-arching aim to provide a comprehensive portfolio of evidence to evaluate support for a definitive randomised trial:

a) To demonstrate willingness of patients to participate in the trial.
b) To demonstrate whether relevant healthcare staff within participating hospitals are willing to randomise patients into the trial.
c) To provide pilot data on the clinical effects of oral ibuprofen, in reducing pain after major elective gut surgery, compared to usual analgesia alone without a Non-Steroidal Anti-Inflammatory Drug.
d) To provide safety data on the use of oral ibuprofen as an analgesic in patients undergoing major elective gut surgery.

### 6.1 Outcome measures

**a. Patient outcome measures**

- Number of doses of ibuprofen or other NSAID administered to each patient within five days after surgery.
- Overall Benefit of Analgesia Scores (OBAS) recorded daily for five days after surgery [13].
- Total opioid dose (Oral Morphine Equivalents) within five days after surgery.
- Numeric Rating Scale (NRS) pain scale on postoperative days one to five.
- All complications within 30 days of surgery.
- Mortality within 30 days of surgery.
- Duration of hospital stay within 30 days of surgery.
- Anastomotic leak graded within 30 days of surgery.
- Acute kidney injury (KDIGO creatinine definition only) within 30 days of surgery [14].
- Gastro-intestinal bleed within 30 days of surgery.

**b. Hospital level feasibility outcome measures**

- Number of eligible patients per year in each hospital.
- Number of eligible patients randomised per year in each hospital.
- Participating hospitals randomising at least one patient within the 12-month recruitment period.
- Number of consultant surgeons and anaesthetists in each hospital who support recruitment of the patients in their care in principle and the total number delivering care for elective colorectal surgery.

### 6.2 Study design

Multi-centre, open-label, randomised feasibility trial.

### 6.3 Study setting

Surgical services of NHS hospitals.

## 7. Patient evaluability and replacement

### 7.1 Target Accrual

200 patients.

### 7.2 Participant identification and recruitment

Potentially eligible participants will be pre-screened by the direct care team before entry into the study in accordance with the PROTECT master protocol section “Participant identification and recruitment”. Informed consent will be obtained after pre-screening and prior to conducting any trial-related procedures. The pre-screening period is defined as up to 365 days before surgery. The screening period is defined as up to 28 days before surgery, where day 0 is the day of surgery. Eligibility must be confirmed within 28 days before surgery and documented in the medical records by the PI or a medical delegate prior to enrolment into the study. If surgery is delayed or rescheduled, eligibility may need to be re-confirmed and documented to meet this requirement.

## 8. Informed consent procedures

Please follow the procedures documented in the PROTECT master protocol section on “Informed consent 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.

### 8.1 Vulnerable participant considerations and participants lacking capacity

The trial will not involve the participation of vulnerable participants or subjects lacking capacity.

## 9. Participant allocation

Patients identified via screening by the research team will be confirmed for eligibility by the PI or delegated doctors, who will document this in the medical records prior to approach. Following written informed consent, the patient will be allocated to receive either standard

analgesic care or standard care plus oral ibuprofen (400mg TDS). All randomised patients will be recorded on the study enrolment log with their trial ID.

## 10. Participant eligibility criteria

### 10.1 Inclusion criteria

- Patients aged 18 years and over undergoing major elective gut surgery with bowel anastomosis.

### 10.2 Exclusion criteria

- Inability or refusal to provide informed consent.
- Previous enrolment in the PROTECT-AEGIS trial
- Concomitant administration of any of the following:
    - Another Non-Steroidal Anti-Inflammatory Drug
    - Mifepristone within two weeks before surgery
- History of specific risk factors:
    - Severe organ dysfunction defined as American Society of Anaesthesiologists (ASA) Physical Status Classification System 4 and/or eGFR <45
    - Known hypersensitivity or allergic reaction to ibuprofen (or its excipients), or other Non-Steroidal Anti-Inflammatory Drugs*
    - Peptic ulcer disease: two or more episodes of proven ulceration or bleeding, or upper gastrointestinal perforation
    - Third trimester of pregnancy
    - Solid organ or bone marrow transplant

**Hypersensitivity reactions may present as:*

*i. non-specific allergic reactions or anaphylaxis*

*ii. respiratory tract reactivity, including asthma, bronchospasm or dyspnoea, skin reactions, including pruritus, urticaria, purpura, angioedema, exfoliative and bullous dermatoses, including toxic epidermal necrolysis, Stevens-Johnson Syndrome or erythema multiforme*

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## 11. Study schedule

### 11.1 Schedule for each visit

| Visit | Pre-screening (up to 365 days before surgery) | Screening (28 days prior to surgery day 0) | Before surgery (up to Day 0) | Day of surgery (Day 0) | Postoperative pain relief | | | | | Hospital discharge (days + 7 days) | 30-day follow-up + 7 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Day 1# | Day 2# | Day 3# | Day 4# | Day 5# | | |
| Eligibility | x[1] | x | x | | | | | | | | |
| Informed consent | | x | | | | | | | | | |
| Concomitant medication review | x | x | x | x | x | x | x | x | x | | |
| Demographics | | | x | | | | | | | | |
| Review of medical notes | | | x | x | x | x | x | x | x | x | x |
| Case Report Form completion | | | x | x | x | x | x | x | x | x | x |
| Randomisation | | | | x | | | | | | | |
| Administration of standard care or standard care plus oral ibuprofen | | | | | x | x | x | x | x | | |
| OBAS score | | | | | x | x | x | x | x | | |
| NRS pain scale | | | | | x | x | x | x | x | | |
| Pharmacovigilance* | | | x | x | x | x | x | x | x | x | x |
| Post-operative follow-up | | | | | | | | | | | x |

# Or closest next working day

* For the purposes of this trial, pharmacovigilance includes the review and reporting for both adverse event (AE)/serious adverse event (SAE) safety reporting and the pre-defined safety outcomes

[1] If a participant is deemed eligible more than 28 days before surgery, their eligibility must be reconfirmed within 28 days before surgery and prior to enrolment (see section 7.2).

### 11.2 Randomisation method

Randomisation will occur after the participant has provided informed consent and after the induction of anaesthesia. Participants will be randomised 1:1 to standard care plus ibuprofen or standard care using permuted block randomisation (block size 4-6) stratified by:

i. epidural or rectus sheath catheter use,
ii. planned laparoscopic or robotic surgical approach
iii. hospital site.

### 11.3 Randomisation procedure

The code creating the randomisation list will be approved and validated by the lead trial statistician for the PROTECT-AEGIS comparison

### 11.4 Study assessments

The data points listed below will be collected in addition to those in the common dataset listed in the master protocol.

***Screening***

- Checklist to ensure the patient meets the eligibility criteria

***Baseline data***

- Diagnosis of current pain

***Day of surgery***

- Surgical procedure performed
- Immediate post-operative pain management

***Postoperative follow-up***

- Number of doses of ibuprofen or other NSAID administered
- OBAS recorded daily for five days after surgery
- NRS recorded daily for five days after surgery
- Total opioid dose (Oral Morphine Equivalents) within five days after surgery
- Acute kidney injury (using KDIGO criteria for creatinine only) within 30 days after surgery
- Anastomotic leak within 30 days after surgery

### 11.5 Trial procedures

#### 11.5.1 Intervention

The trial intervention period will commence on postoperative day one (i.e. the first day after the day of surgery) and continue for five days. Participants will receive either standard care or standard care plus oral ibuprofen (400mg TDS) as part of their pain management care.

**Standard care**

Standard care will consist of local protocolised analgesic measures without NSAIDs. All NHS hospitals have local pain management policies for this patient group. Pain relief options from postoperative day one onwards includes patient controlled intravenous opioid analgesia together with rectus sheath catheters for local anaesthetic infusion into the abdominal wound. This is supplemented with regular paracetamol, but NSAID drugs are not usually provided. In some patients, an epidural is provided instead of rectus sheath catheters, but this provides analgesia of similar clinical effectiveness. Most patients then transition to oral opioid analgesia between day four and day seven after surgery, continuing paracetamol but not usually NSAIDs. Most patients return home between day five and day eight with oral analgesia. Patients in the standard care arm will not receive NSAIDs.

**Standard care plus oral ibuprofen**

Oral ibuprofen (400mg TDS) will be commenced on postoperative day one, alongside standard analgesic measures described above and continue until postoperative day five. The timing of ibuprofen administration is left to the discretion of the direct care team. Intervention arm patients will not be prescribed any NSAID drug except ibuprofen. Any generic, commercially available hospital stock of oral ibuprofen can be used. An intravenous preparation of ibuprofen has recently become available. We do not anticipate its widespread use, however, if administered, this will not be considered a deviation and will be documented in the case report form.

**Supplemental drugs for gastric protection in the ibuprofen treatment group**

Local hospital policies on the prescription of proton pump inhibitor drugs should be followed. Patients allocated to the ibuprofen arm, will be prescribed lansoprazole at a dose of at least 15mg, or omeprazole at a dose of at least 10mg once per day taken orally (or an equipotent dose of an equivalent proton pump inhibitor). Most patients will be able to take oral tablets even if ‘nil by mouth’ following surgery (this should be clarified with the clinical team) but intravenous preparations are also acceptable. This will be clearly documented in the patient’s medical records. Some patients may already be taking a proton pump inhibitor at a

higher dose or be prescribed one at a higher dose during the perioperative period, for a different indication.

### 11.6 Follow-up procedures

Investigators will review a participant's medical record and contact participants to conduct brief interviews to collect OBAS and NRS scores post-surgery. To minimise bias, where possible follow-up data will be collected by an investigator who is unaware of the study group allocation.

## 12. Participant, study and site discontinuation

It is always within the remit of the responsible physician to withdraw the participant from the study for appropriate medical reasons. This can be (but is not limited to) individual adverse events (AEs) or toxicities, new information gained about a treatment, or if it is felt to be in the participant's best interest. Please follow the procedures documented in the PROTECT master protocol section "Participant, study and site discontinuation".

## 13. Study medication

### 13.1 Study drug

Participants will receive either standard care or standard care plus oral ibuprofen (400mg TDS) as part of their pain management, depending on the treatment allocation they are randomised to. Intervention patients will receive proton pump inhibitors (e.g. omeprazole or lansoprazole. The intervention will start from postoperative day one and continue until day five.

### 13.2 Name and description of Investigational Medicinal Product(s) (IMP)

Ibuprofen (IMP) is licensed in the UK and its use in the trial relates to the licensed range of indications, dosage and form.

### 13.3 Name and description of Non-Investigational Medicinal Product (NIMP)

Patients in the ibuprofen arm, will be prescribed lansoprazole at a dose of at least 15mg, or omeprazole 10mg once per day taken orally (or an equipotent dose of an equivalent proton pump inhibitor). Other commonly used proton pump inhibitors include esomeprazole, pantoprazole and rabeprazole. It is also possible that another proton pump inhibitor might be used dependent on the local Trust policies. The NIMPs detailed in the trial are licensed in the UK and will be used within their licensed range of indications, dosage and form.

### 13.4 Reference Safety Information (RSI)

RSI is the information used for assessing whether an adverse reaction is expected. Expectedness will be evaluated against the trial RSI in use at the time the reaction occurred. For the purposes for this trial, the RSI for oral ibuprofen will be the Summary of Product Characteristics (SmPC) provided by Flamingo Pharma (UK) Ltd and for intravenous ibuprofen will be the SmPC provided by B Braun. However, participating hospitals can use any generic hospital stock for the study. Updates to the RSI will be reviewed annually on Electronic Medicines Compendium by the PROTECT Platform Chief Investigator or Deputy delegated medical assessor. Changes in RSI will be submitted as a study amendment and sites will be notified accordingly.

### 13.5 Drug manufacturer and supply arrangements

Participating hospital pharmacies will be responsible for the supply of IMP and NIMP as per routine clinical practice. The drugs will be sourced from hospital stock as per local policy.

### 13.6 Drug accountability

Local hospital policies will be followed for drug accountability.

### 13.6 Assessment of compliance

Compliance will be assessed using the patient's drug chart, medical notes and the trial database. Non-compliances will be recorded as one of the feasibility outcomes in the study.

### 13.7 Drug storage

Hospital pharmacy will be responsible for storing the drugs in line with local procedures.

### 13.8 Prescription and dispensing of drug

The drugs will be dispensed to the participant in accordance with the prescription given by the PI or a medical delegate.

### 13.9 Administration of drug

The drugs will be administered to the patient by a healthcare practitioner who is a member of the direct care team as per local hospital policies and procedures for administration and recording. The task of administering the trial drug(s) will NOT be listed on the delegation log and staff undertaking these tasks do not need to be listed on the delegation log unless they are undertaking other trial duties.

### 13.10 Dosage schedules

Oral ibuprofen 400mg TDS for five days commencing on postoperative day one, alongside usual analgesic measures described above, plus proton pump inhibitor (e.g. omeprazole or lansoprazole). Intervention arm patients will not be prescribed any NSAID drugs except ibuprofen.

### 13.11 Destruction, return, and recall of drug

Procedures for drug destruction and/or returns will be undertaken according to local hospital policies and will fall outside of the trial procedures. If there are any drug recalls this will be done via the standard local NHS dispensing pharmacy recall process.

### 13.12 Management of ibuprofen specific adverse events

As a well-established and widely used product, the safety of ibuprofen is well documented. Any adverse events should be managed according to clinical need.

### 13.13 Arrangements for post-study access to study drug and care

In the unlikely event that the patient is discharged before the fifth postoperative day, the remaining doses will be provided to the patient to self-administer at home. These will be provided through the usual hospital pharmacy ('To Take Away') service.

### 13.14 Known drug reactions and interventions with other therapies

Please refer to the SmPC for known drug reactions and intervention with other therapies.

### 13.15 Recommended concurrent treatment

No concurrent treatment is necessary.

### 13.16 Prohibited medication

Ibuprofen should not be used in combination with aspirin and other NSAIDs including cyclooxygenase-2 selective inhibitors. Please refer to section 4.5 of the SmPC for further information.

### 13.17 Concomitant medication

The patient's medication will be reviewed at screening and if enrolled, a daily review will be conducted for concomitant medication during the trial intervention period only. This will be documented in the patient's medical notes.

### 13.18 Study restrictions

There are no study restrictions.

## 14. Pharmacovigilance

Please refer to the PROTECT master protocol section “Pharmacovigilance” for the overall safety reporting concept and general definitions.

Pharmacovigilance reporting will start from the completion of informed consent until post-operative day 30. This will require either (1) review of the participant’s medical notes if in hospital and (2) a telephone call with the participant if the patient is discharged. In the event the research team are unable to speak with the participant, their GP will be contacted.

### 14.1 Adverse events (AEs) and Serious Adverse Events (SAEs) exempt from reporting

Medical complications occur commonly after surgery and are an expected part of routine perioperative care. Consequently, the following do not constitute safety events and are exempt from routine safety reporting as AEs and/ or SAEs unless the PI and/or medical delegate believes the IMP caused the event:

- Infection (surgical site infection, respiratory infection, urinary system infection, neurological infection, laboratory confirmed blood stream infection, neurological infection, clostridium difficile infection, endometritis, pathogenic organism in tissue or fluid)
- Acute cardiac events (hypotension, arrhythmia, atrial fibrillation, myocardial infarction, myocardial injury, cardiac arrest, cardiogenic pulmonary oedema, coronary revascularisation, cardiac death, pulmonary embolism, deep vein thrombosis, stroke)
- Respiratory events (Atelectasis, pulmonary aspiration, Acute Respiratory Distress Syndrome (ARDS), pleural effusion, pneumothorax, bronchospasm).
- Renal replacement therapy
- Postoperative haemorrhage
- Acute psychosis or delirium
- Anaphylaxis
- Bowel infarction
- Multi-organ dysfunction syndrome
- Paralytic ileus
- Perforated viscus

- Anaemia

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

The following safety events will require reporting for PROTECT-AEGIS:

- Pre-defined safety data: anastomotic leak, gastrointestinal bleed and acute kidney injury.
- Events possibly or definitely related to the IMP.
- All SAEs, except those listed in section “Adverse events (AEs) and Serious Adverse Events (SAEs) exempt from reporting” unless the PI believes that the IMP caused the event.

Please refer to the PROTECT master protocol section “Procedure for immediate reporting of SAEs, SARs and SUSARs” for further details on the reporting procedure. The completed form will be signed and submitted to the PROTECT admin account (admin@protectresearch.org) within 24 hours of becoming aware of the event.

### 14.2 Pregnancy

Please refer to the PROTECT master protocol section “Pregnancy” for further details.

## 15. Statistical and data analysis

### 15.1 Statistical design

We have selected a feasibility sample size of 200 patients in 10 NHS hospitals over a 12-month recruitment period providing robust estimates of patient and clinician willingness to participate. This will also provide robust data on rates of possible treatment harms which are a key driver of the sample size for the main trial. The 95% confidence interval width for feasibility objective rate estimates is at most are +/- 7.1% with a sample size of 200.

### 15.2 Statistical analysis

As this is a feasibility study, the analysis will be descriptive. Feasibility outcomes will be summarised as frequencies and percentages with 95% confidence intervals, using the method of Clopper and Pearson. Patient and safety outcomes will also be summarised by treatment group using measures of central tendencies and variability for continuous data, and frequencies and proportions for categorical data.

### 15.3 Statistical analysis plan

A full statistical analysis plan will be developed and signed off prior to unblinding and final analysis of this comparison.

### 15.4 End of trial definition

The end of trial is defined as the time point when the last 30 day participant visit has been completed.

## 16. Annual reporting

Please refer to the PROTECT master protocol section “Annual reporting” for further details.

## 17. Data handling and record keeping

Please refer to the PROTECT master protocol section “Data management” for further details.

## 18. Confidentiality

Please refer to the PROTECT master protocol section “Confidentiality” for further details.

## 19. Monitoring, audit and inspection

Please refer to the PROTECT master protocol “Monitoring, audit and inspection section” for further details.

## 20. Compliance

Please refer to the PROTECT master protocol “Compliance” section for further details.

## 21. Declaration of interests

Please refer to the PROTECT master protocol “Declaration of interests” section for further details.

## 22. Peer review

This research was funded in open competition by NIHR RfPB (Ref: NIHR205324). The proposal 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 study design process.

## 23. Public and Patient Involvement (PPI)

Patients have been involved from the outset of the design of this intervention comparison. Our patient researchers and members of our patient focus groups have highlighted the ongoing problem of postoperative pain management and have advised us on the importance they place on research to investigate the best management of acute pain after major gut surgery. During project development, we have been supported by Sam Rose, PPI manager at the charity Bowel Research UK, and members of the charity's Patient Involvement team. In addition to our patient co-applicants, proposals related to trial activity have also been reviewed in detail by the Royal College of Anaesthetists Patient & Public Involvement group. We have fully incorporated several of their suggestions into AEGIS, including strategies to improve recruitment, and the development of a patient advisory group to review and provide feedback on patient facing documents.

## 24. Indemnity/ Insurance

Please refer to the PROTECT master protocol "Indemnity/ insurance" section for further details.

## 25. Study committees

### 25.1 Comparison Management Group (CMG)

Please refer to the PROTECT master protocol "Study committees" section for further details.

### 25.2 Comparison Steering Committee(s) (CSCs)

Please refer to the PROTECT master protocol "Study committees" section for further details.

### 25.3 Independent Data Monitoring Committees (IDMC)

Please refer to the PROTECT master protocol "Study committees" section for further details.

## 26. Publication and dissemination policy

Please refer to the PROTECT master protocol "Publication and dissemination policy" section for further details.

## 27. Archiving

Please refer to the PROTECT master protocol "Archiving" section for further details.

## 28. References


1. Small C, Laycock H. Br J Surg 2020;107:e70-e80.10.1002/bjs.11477

2. Gerbershagen H, Aduckathil S, Van Wijck A et al. Anesthesiology. 2013;118:934-44 10.1097/ALN.0b013e31828866b3

3. Miskovic A, Lumb A. Br J Anaesth. 2017;118(3):317-34.10.1093/bja/aex002

4. Verbree-Willemsen L, Grobben R, Van Waes J et al. Eur J Prev Cardiol. 2019;26(1):59 - 67

5. Opioids: risk of dependence and addiction - GOV.UK (www.gov.uk) [Accessed 19th March 2023]

6. Wichmann D, Orlova O, Königsrainer A, Quante M. J Clin Med. 2023 Feb 9;12(4):1374. doi: 10.3390/jcm12041374. PMID: 36835910; PMCID: PMC9965273.

7. European Society of Coloproctology Collaborating Group. Dis Colon Rectum. 2020;63(5): 606-618. doi:10.1097/DCR.0000000000001590. PMID: 32032201.

8. European Society of Coloproctology (ESCP) collaborating group. Colorectal Dis. 2018; 20(6):15-32. doi: 10.1111/codi.14362. PMID: 30255646.

9. Garg AX, Kurz A, Sessler DI et a.l BMJ Open 2014;4: e004886. doi: 10.1136/bmjopen-2014-004886

10. Schlachta, C.M., Burpee, S.E., Fernandez, C. et al. Optimizing recovery after laparoscopic colon surgery (ORAL-CS). Surg Endosc 21, 2212–2219 (2007). https://doi.org/10.1007/s00464-007-9335-4

11. Chen J, Ko T, Wen Y et al. Clin J Pain. 2009; 25(6):485-489 doi:10.1097/AJP.0b013e31819a506b

12. Bhangu A, Singh P, Fitzgerald J et al. World J Surg. 2014;38(9):2247- 57.doi: 10.1007/s00268-014-2531-1

13. Lehmann N, Joshi G, Dirkmann D et al. Br J Anaesth. 2010;105:511-18. doi: 10.1093/bja/aeq186

14. Acute Kidney Injury (AKI) – KDIGO (accessed 22nd September 2023)