Academic and Clinical Central Office for Research and Development

Study Protocol

NIHR project No 15/130/95 - A placebo controlled randomised trial of intravenous lidocaine in accelerating gastrointestinal recovery after colorectal surgery

The ALLEGRO trial:

A placebo controlled r**A**ndomised trial of intravenous **L**idocaine in acce**LE**rating **G**astrointestinal **R**ecovery after c**O**lorectal surgery

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PROTOCOL APPROVAL SIGNATURE PAGE

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EudraCT 2017-003835-12

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Hugh Paterson **Chief Investigator**		**Signature**	**Date**
Graeme MacLennan **Trial Statistician**		**Signature**	**Date**
Fiach O'Mahony **Lead Co-Sponsor Representative**		**Signature**	**Date**

For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

Principal Investigator		**Signature**	**Site**	**Date**

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Nurse
CRO	Contract Research Organisation
CRP	C-reactive Protein
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EQ-5D	European Quality of Life- 5 Dimensions
ERAS	Enhanced Recovery After Surgery
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GI-2/3	Gastrointestinal Recovery
GMP	Good Manufacturing Practice
GP	General Practitioner
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use

IDMC	Investigational Medicinal Product Dossier
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
IV	Intravenous
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NG	Nasogastric
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
OBAS	Overall Benefit of Analgesia Score
PCA	Patient-Controlled Analgesia
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
POI	Postoperative Ileus
PONV	Postoperative Nausea and Vomiting
PPOI	Prolonged Postoperative Ileus
p-POSSUM	Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity.
PROM	Patient Reported Outcome Measurement
QA	Quality Assurance
QC	Quality Control
QoR	Quality of Results
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee

SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Product Characteristic
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

TRIAL SUMMARY

Trial Title	The ALLEGRO trial: A placebo controlled r**A**ndomised trial of intravenous **L**idocaine in acce**LE**rating **G**astrointestinal **R**ecovery after c**O**lorectal surgery
Study Acronym	ALLEGRO
Clinical Phase	Phase III
Trial Design	Multi-centre double blind placebo-controlled RCT
Trial Participants	Patients listed for elective minimally invasive (laparoscopic or robotic) colorectal resection for cancer, benign polyps, benign stricture or diverticular disease
Planned Number of Participants	The study is primarily powered for laparoscopic cases and will require 562 patients.
Planned Number of Sites	30
Countries Anticipated to be Involved in Trial	UK
Treatment Duration	Minimum 6 hours up to maximum 12 hours depending on participating unit existing perioperative practice and facilities for postoperative cardiac monitoring
Follow up Duration	90 days
Total Planned Trial Duration	5 years (not including planned record linkage)
Primary Objective	Postoperative return of gut function
Secondary Objectives	Analgesia, length of stay, quality of recovery, vomiting, complications, quality of life, safety
Primary Endpoint	Proportion of participants meeting GI-3 return of gut function definition (tolerating diet PLUS passage of flatus or stool) at 72 hours postoperatively.
Secondary Endpoints	Time to return of gut function, OBAS pain score, QoR score (both PROMs), nausea and vomiting, EQ5D, mortality
IMP(s)	Lidocaine hydrochloride 2%
IMP Route of Administration	intravenous IV bolus at induction of anaesthesia (1.5mg/kg ideal body weight) followed by infusion of 1.5mg/kg/hr (ideal body weight) with maximum rate of 120mg/hour. In patients whose weight is less than ideal body weight, actual weight will be used to calculate dose. Duration of infusion: 6 or 12 hours, depending on local facilities for postoperative cardiac monitoring.

NIMP(s)	Placebo: 0.9% Sodium Chloride.
Lay Summary of Trial	Return of gut function is fundamental to recovery after abdominal surgery. Up to 40% of patients suffer delayed return of gut function after colorectal surgery, manifesting as nausea, vomiting, constipation and abdominal distension. It is the most common reason for delayed discharge from hospital. Delayed return of gut function is multifactorial: opioid analgesia side effects, host autonomic nervous system imbalance, anaesthesia, intraoperative gut handling and the operation itself have all been implicated. There is currently no remedy to induce return of gut function; treatment is supportive until gut function returns spontaneously (IV fluids, nasogastric tube insertion, analgesia). Affected patients can spend 1-10 extra days in hospital compared to those who have a straightforward recovery. IV lidocaine has been used in the past as an adjunct to anaesthesia. Its mode of action is poorly understood but it appears to have anti-inflammatory properties, is opioid-sparing (i.e. it reduces requirements for opioid analgesia and therefore reduces the chance of opioid-associated side-effects (nausea, constipation, hallucinations etc)) and induces a sense of well-being and even euphoria. There is also data suggesting it improves return of gut function after colorectal surgery, for example by reducing nausea and reducing time from surgery to first bowel movement. We wish to test the hypothesis that perioperative IV lidocaine will reduce delayed return of gut function after elective colorectal surgery. Minimally invasive colorectal surgery (laparoscopic and robotic) has short-term recovery benefits and is likely to become the default choice in >75% of resections in the next 10 years. Therefore, the study is powered to test the primary hypothesis in laparoscopic/robotic segmental colectomy (total sample size 562 patients). The primary study outcome will be return of gut function after surgery defined by the previously validated GI-3 endpoint; secondary outcomes will include other patient-reported aspects of recovery, analgesia, length of stay and safety endpoints

1. INTRODUCTION

1.1 BACKGROUND

Delayed return of gut function is the most common cause of delayed discharge from hospital after elective colorectal surgery. It is characterised by a temporary cessation of normal gut propulsive contraction and manifests as nausea, vomiting, constipation and abdominal distension. The pathophysiology is complex and involves interaction of endogenous factors (including pain pathways, host endocrine- and inflammation-mediated stress responses, exaggerated sympathetic autonomic activity and endogenous opioids) and exogenous factors (bowel handling during surgery, opioid analgesics, anaesthetic agents, immobility). “Postoperative ileus" is the most severe end of the spectrum. There is no specific therapy; treatment is supportive. Although self-limiting it prolongs hospital stay by a few days in most cases but can last up to 10 days if severe.(1) Affected patients cannot tolerate oral intake due to nausea and vomiting and require inpatient support with intravenous fluids and ongoing opioid analgesia. Although gut transit is absent, digestive fluid continues to be secreted (bile, gastric acid, pancreatic enzymes) causing ‘third space’ losses, dehydration and progressive abdominal distension. Many patients require decompression of the fluid-distended gut by insertion of a nasogastric tube, a very uncomfortable experience that some patients rate worse than the operation itself. Furthermore, in an increasingly elderly population with increasing frailty, the development of gut dysfunction can contribute to other major complications including pulmonary aspiration, pneumonia and acute kidney impairment.

There are no specific preventative or therapeutic interventions to induce return of gut function in current use. Alvimopan (Entereg®) is a selective μ-opioid receptor antagonist evaluated in a number of North American RCTs where it has been shown to be of benefit in reducing incidence of postoperative ileus.(2) However, it has not gained widespread use due to cost and concerns regarding its cardiac side-effect profile. It is not licensed for use in the UK.

In the previous era of open colorectal surgery, many surgeons regarded delayed return of gut function as a “normal” part of a prolonged post-operative recovery. Accordingly, the true prevalence was seldom recorded; best estimates suggest it affected up to 40% of cases. However, in the last decade a revolution has occurred in colorectal surgery. Minimally invasive “key-hole” surgical techniques (laparoscopic or robotic)() and evidence-based “Enhanced Recovery” peri-operative management care pathways have reduced average length of hospital stay from 9 days to 4-6 days, and have of themselves reduced the prevalence of delayed return of gut function. Paradoxically, these improved results have highlighted a group of patients for whom delayed return of gut function forms the main barrier to discharge. As a result of modern care, most patients are independently mobile, requiring no or only low dose oral analgesics and are free from IV fluids and invasive monitoring (e.g. urinary catheters) within 48-72 hours. However, only half will have regained gut function by this time-point (3, 4); furthermore, 10-20% will go on to develop prolonged postoperative ileus (PPOI), defined as gut function failing to return by the 5th postoperative day.(4-6).

It should be emphasised that minimally invasive techniques have not replaced open colorectal surgery entirely. A colectomy can be undertaken by either method and the choice is made by the operating surgeon according to a number of factors, including his/her training and experience, technical complexity of the planned procedure and patient comorbidity. There has been a steady increase in minimally invasive colectomy in the UK over the last 5 years: data from the National Bowel Cancer Audit indicate an increase from 25% in 2010 to >50% in 2016 although in specialist centres this figure is

>80%. The remainder are undertaken by open surgery, and it is estimated that a significant proportion of cases will be treated by open surgery for the foreseeable future. Furthermore, in the emergency setting minimally invasive colectomy is much more challenging and currently open surgery predominates.

How does the existing literature support this proposal?

Lidocaine (previously lignocaine in the UK) is in common use worldwide as a local anaesthetic. It can also be administered systemically by intravenous infusion, and was used extensively in the 1970s in North America to prevent post- myocardial infarction ventricular dysrhythmias (until meta-analysis showed it was ineffective). IV lidocaine is also a recognised treatment for chronic pain.(7) Recently, IV lidocaine has been repurposed as an anaesthetic adjunct in abdominal surgery. A Cochrane meta-analysis of 45 trials involving 2802 patients in open and laparoscopic abdominal and non-abdominal operations reported a benefit in reducing early postoperative pain scores and opioid requirements. Evidence of effect was also found for IV lidocaine on measures of gut function recovery, including time to first flatus (MD −5.49 hours, 95% CI −7.97 to −3.00), time to first bowel movement (MD −6.12 hours, 95% CI −7.36 to −4.89) and risk of postoperative ileus (risk ratio (RR) 0.38, 95% CI 0.15 to 0.99). Evidence of beneficial effects was also noted for secondary outcomes such as reduction in length of hospital stay and postoperative nausea.(8) A meta-analysis of IV lidocaine in open and laparoscopic abdominal surgery (21 trials, 1108 patients) supported evidence of benefit for analgesia and return of gut function (time to first flatus and bowel movement reduced by 6.9 (95% CI:-9.2,-4.6, I2=62.8%) and 11.7 hours (95% CI:-17.0,-6.5, I2=0) respectively) and reduced hospital length of stay (weighted mean difference: -0.71 days).(9) A further meta-analysis of IV lidocaine in laparoscopic abdominal surgery only (14 trials, 742 patients) confirmed analgesic benefit, reduced incidence of nausea and vomiting (OR = 0.52, 95% CI: 0.35,0.75, I2=0) and faster resumption of diet (WMD -6.2 hours, 95% CI:-12.37,-0.03, I2=93.8%).(10) However, the limitation of meta-analysis in this area is the considerable heterogeneity of studies included: a variety of surgical procedures, a mix of open and laparoscopic techniques, inconsistent lidocaine dose/treatment duration and inconsistent perioperative management protocols.

There are only 3 published RCTs of intravenous lidocaine in laparoscopic colectomy, comprising a total of 181 patients. Two of these were conducted in Europe(11, 12) and reported length of stay consistent with NHS practice for this procedure (3-5 days). Only Kaba et al reported a perioperative management protocol consistent with Enhanced Recovery principles. Both studies reported reduced analgesic requirements, faster return of gut function, and a 1 day reduction in median length of stay. The third study was conducted in South Korea and found a trend towards faster gut recovery but no statistically significant benefit. However, perioperative management practices were not consistent with NHS norms and the excessive median length of stay of 8 or 9 days makes this study difficult to interpret.(13)

Finally, IV lidocaine appears to improve postoperative recovery in general, as measured by Quality of Postoperative Recovery Scores (a relatively recent metric for assessing global recovery after anaesthesia based on assessment of physiologic, nociceptive, functional, cognitive, emotional recovery domains as well as overall patient perspective).(14) This observation is consistent with the known action of the drug causing a feeling of well-being/euphoria and is supported by the applicants' anecdotal experience in >2000 cases.

Although the systematic reviews indicate that IV lidocaine reduces post-operative pain severity and is hence opioid-sparing, and suggest that return of gut function is improved, the heterogeneity in the small RCTs included means we now need a high quality, multicentre pragmatic effectiveness study with an adequate sample size, in

NHS patients undergoing laparoscopic/robotic colectomy , to confirm these promising findings and quantify with sufficient precision the benefits from the patient and clinical perspectives. It would be important for example if IV lidocaine did not, in fact, deliver these benefits to then know that the search for effective interventions for what is by consensus a very important issue for patients and the NHS needs to develop in different directions. Equally, if as we hope, the promising benefits are confirmed, then that would give high-quality evidence- backed impetus to the widespread uptake of this intervention in routine clinical practice.

1.2 RATIONALE FOR STUDY

Scale of the problem in the UK and use of NHS resources

Delayed return of gut function is particularly prevalent after colorectal surgery but it can occur after other types of abdominal surgery and even in non-abdominal procedures, particularly spinal and orthopaedic operations. It is less prevalent where bowel is not resected (e.g. gynaecological surgery) and more prevalent in emergency compared with elective procedures, and in open compared with laparoscopic procedures. Colorectal surgery is common, being undertaken in every acute hospital throughout the world. Approximately 30,000 colorectal resections per year are undertaken in the UK (HES data 2013/14). Reducing the prevalence of delayed return of gut function and prolonged postoperative ileus would accelerate recovery, avoid some of the more unpleasant aspects of supportive treatment (nasogastric tube insertion, repeated venous cannulation for IV fluids) and allow more patients to get home more quickly. For the NHS there would be a cost saving associated with reduction in bed occupancy and reduced supportive treatments for what is a common complication of a common procedure. It is likely that any benefit found using the “model” of colorectal surgery would be applicable to other abdominal surgery procedures. The objective of the study aligns well with the current national dissemination of Enhanced Recovery after Surgery programmes (an evidence-based package of perioperative care measures shown to reduce length of stay and complications after surgery) by the UK Department of Health and Scottish Government. If as hoped IV lidocaine is effective in improving recovery from abdominal surgery it could be effective across a number of specialties and benefit many patients as an affordable, safe and easy-to-use treatment.

Patient and public involvement

The Association of ColoProctology of Great Britain and Ireland (ACPGBI) in collaboration with the Bowel Disease Research Foundation (BDRF) recently held a Delphi exercise to create a shortlist of research priorities in colorectal surgery. Following a patient consultation meeting in which research topics were prioritised, a group of interested stakeholders including patients, clinicians and specialist nurses met in April 2015 to discuss approaches to answering the question: “How can postoperative ileus be reduced?”. This topic received considerable attention from patients involved with the BDRF, many of whom had experienced the consequences of postoperative ileus (“the NG (nasogastric) tube is the worst thing ever. Worst complication. I still have nightmares about having that tube in my nose”). Following discussion of the evidence available, a trial of intravenous lidocaine was proposed. This was strongly supported by the ACPGBI and BDRF.

Discharge from hospital after colorectal surgery is inextricably linked to functional gut recovery.(4, 15, 16) With modern care most patients undergoing laparoscopic colectomy are independently mobile, requiring no or minimal oral analgesics and free from IV fluids and invasive monitoring (e.g. urinary catheters) within 48-72 hours. However, only half will have regained gut function by this time-point and 10-20% will go on to PPOI. The success of laparoscopic techniques and evidence-based perioperative care in accelerating recovery has highlighted that delayed return of gut function has become the main barrier to discharge for a significant proportion of laparoscopic colectomy patients. It is the main problem to be solved to exploit the full

benefits of modern colorectal surgery.

There are compelling reasons to include open colectomy cases in a parallel exploratory RCT: the prevalence of delayed return of gut function and PPOI after open colectomy is higher than in laparoscopic colectomy; open surgery continues to be used for a substantial minority of UK cases; findings would be more generalisable to other abdominal procedures most commonly performed by open surgery (e.g. liver and oesophagogastric surgery); and collecting data on such open surgery cases using the trial infrastructure would represent good value for money. The primary outcome event rate is likely to be higher in open cases, and there is some evidence to suggest that the effect size may be greater too, which would suggest a smaller trial is needed in open cases (which is fortuitous given there is likely to be 2-3 laparoscopic cases for every open case, although there is considerable uncertainty in that estimate). However, open cases are associated with more variation in anaesthesia, surgery and postoperative care and the signal to noise ratio will be different. We propose to use a group sequential interim analysis approach to the open study to maximise flexibility in achieving optimal evidence in this arm.
Update: June 2020. Recruitment to the parallel exploratory RCT of open surgery cases was closed in June 2020 because of slow accrual of such cases (see section 4.1 for further details).

Intravenous lidocaine is cheap, safe and easy to administer within existing NHS perioperative practice, and offers to accelerate return of gut function and hence shorten postoperative recovery. These benefits taken cumulatively could translate into a more rapid recovery with a shorter hospital stay for many patients; reduction in the incidence of PPOI; and a significant reduction in bed occupancy and complications consequent on gut dysfunction, potentially achieving a major cost saving for the NHS from a common (and resource-intensive) procedure.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary aim is an effectiveness analysis to measure whether perioperative intravenous lidocaine achieves faster return of gut function for more patients after minimally invasive colorectal surgery. The **primary outcome** will be the proportion of randomised subjects compared between IV lidocaine and placebo that have achieved return of gut function at 72 hours postoperatively. This will be measured by '**GI-3 recovery' -**a composite endpoint defined as achievement of both of the following two events: tolerating diet (defined as ingestion of food and drink without significant nausea or vomiting for 3 consecutive meals) and passage of flatus OR stool (whichever comes first).

2.1.2 Secondary Objectives

- to measure whether perioperative intravenous lidocaine is effective in achieving faster postoperative return of gut function measured by **GI-2 recovery** (defined as the time to achieving both of the following two events: tolerating diet (defined as ingestion of food and drink without significant nausea or vomiting for 3 consecutive meals) and passage of stool.[1, 2])
- to detect an absolute reduction of 10% (from 20% to 10%) in the rate of Prolonged Postoperative Ileus (PPOI= failure to establish GI-3 by postoperative

day 5)
- to detect a reduction in postoperative nausea and vomiting
- to measure any difference in analgesia requirements
- to assess quality of postoperative recovery using multi-dimensional patient-reported outcome tools and quality of life tools, as well as assessing time to medically-defined and patient-defined readiness for discharge from hospital
- To measure the impact on recovery of variation in perioperative care from Enhanced Recovery after Surgery guidelines
- To assess whether perioperative intravenous lidocaine during colorectal surgery is cost-effective relative to current standard of care (colorectal surgery without intravenous lidocaine).

2.1.3 Tertiary Objectives: exploratory/safety

- Total length of stay
- 30- and 90-day mortality
- Unplanned re-admissions within 30 days of hospital discharge
- Reoperation/major complications (defined by Clavien-Dindo classification grade 3 and above [31]) (see section 10.5)
- Qualitative analysis of recovery beyond hospital: GP visits, district nurse visits,
- Record linkage analysis of survival (most cases will be colorectal cancer) with consent to include analysis of survival and cancer-specific data in appropriate patients up to a maximum of 10 years. A separate, ethically approved protocol will cover this analysis.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Measurement variable: GI-3 recovery (a composite endpoint defined as the achievement of both of the following two events: tolerating diet without significant nausea or vomiting for 3 consecutive meals AND passage of flatus or stool) *Participant-level analysis metric:* a) Yes/No outcome at 72 hours after the start of operation; b) time to event
Method of aggregation: a) proportion of participants achieving GI-3 recovery by 72 hours postoperative; b) average/dispersion
Specific time-point: 72 hours after start of operation

2.2.2 Secondary Endpoints

Time to return of gut function using the GI-3 recovery definition (a composite endpoint defined as time from surgery to the later time to establish both of the following two events: tolerating diet without significant nausea or vomiting for 3 consecutive meals AND first passage of flatus or stool)
Measurement variable: GI-3 recovery
Participant-level analysis metric: time from start of operation to event
Method of aggregation: average/dispersion

Time to return of gut function using the GI-2 recovery definition (a composite endpoint defined as time from surgery to the later time to establish both of the following two events: tolerating diet without significant nausea or vomiting for 3 consecutive meals AND first passage of stool)
Measurement variable: GI-2 recovery
Participant-level analysis metric: a) Yes/No outcome at 96 hours after start of operation; b) time to event
Method of aggregation: a) proportion of participants achieving GI-2 recovery at 96 hours; b) average/dispersion

Specific time-point: 96 hours after start of operation

Prolonged Postoperative Ileus (PPOI= failure to establish GI-3 by 120 hours after surgery (postoperative day 5))
Measurement variable: GI-3 recovery
Participant-level analysis metric: Yes/No outcome
Method of aggregation: proportion of participants
Specific time-point: 120 hours after start of operation

Nausea and vomiting
Measurement variables: daily PONV score; number of episodes of vomiting (defined as episodes of expulsion of gastric content); total dosage of rescue antiemetic
Participant-level analysis metric: PONV questionnaire: total number episodes vomiting within 72 hours of operation; total dose rescue antiemetic within 72 hours of operation
Method of aggregation: average/dispersion
Specific time-point: daily until 72 hours after start of operation

Quality of analgesia
Measurement variable: OBAS score
Participant-level analysis metric: values
Method of aggregation: average/dispersion
Specific time-point: daily in-hospital up to and including postoperative day 7.

Total postoperative opioid consumption
Measurement variable: morphine equivalent doses
Participant-level analysis metric: final value
Method of aggregation: average/dispersion
Specific time-point: cumulative total until 72 hours after start of operation

Quality of Recovery
Measurement variable: Quality of recovery score (15-question patient-reported outcome measure)
Participant-level analysis metric: value
Method of aggregation: mean
Specific time-point: daily while in hospital up to 7 days; also days 7 and 30 days after date of operation.

Quality of life assessment
Measurement variable: EQ-5D
Participant-level analysis metric
Method of aggregation:
Specific time-point: daily in hospital up to 7 days, day 7, 30 days and 90 days after date of operation.

Measurement of specific enhanced recovery guideline variables that have been shown to impact GI recovery
Measurement variable: Enhanced Recovery After Surgery protocol compliance measured by recording specific variables relevant to return of gut function. These are:

Avoidance of long-acting opioids for maintaining anaesthesia
Prescribed PONV prophylaxis for 48 hours
Euvolaemic IV fluid policy- assessed by total IV fluid administration in 24 hours from start of anaesthesia and measuring patient weight pre- and 24 hours after operation.
Early feeding- carbohydrate supplement drink on day of surgery and solid food from postoperative day 1 onwards

Early mobilisation- patients should be out of bed for 2 hours on day of surgery and 4-6 hours every day thereafter AND walking
Routine postoperative laxative prescription
No NGT immediately after surgery

Participant-level analysis metric: graded proportion e.g 0-30% compliant; 30-60% compliant; >60% compliant
Method of aggregation: proportions
Specific time-point: end of inpatient admission

Time to achievement of medical criteria for discharge
Measurement variable: Time (days) to meeting medically-defined hospital discharge criteria (independent hydration/nutrition, adequate analgesia by oral route, independent mobilisation, return of gut function by GI-3 definition, no medical contraindication)
Participant-level analysis metric: time to event (days)
Method of aggregation: average/dispersion and time difference from actual length of stay (days)
Specific time-point: end of inpatient admission

Patient-reported assessment of readiness for discharge
Measurement variable: Time (days) to patient-reported readiness for discharge (must also have achieved medical criteria for discharge as noted above)
Participant-level analysis metric: time to event (days)
Method of aggregation: average/dispersion
Specific time-point: assessed daily from day 2 onward

Health economic evaluation
Cost-effectiveness over the observed within trial period of 90 days. End point(s) for longer term health modelling will be determined through the model scoping exercise, , though a 5 year duration is anticipated.

2.2.3 Tertiary Endpoints: exploratory/safety

Total length of hospital stay
Measurement variable: total duration of primary admission + any readmission within 30 days
Participant-level analysis metric: time to event (days)
Method of aggregation: average/dispersion
Specific time-point: as above

Complications/safety analysis:

Mortality
Measurement variable: death
Participant-level analysis metric: yes/no
Method of aggregation: proportion
Specific time-point: 30 days, 90 days after date of operation.

Unplanned re-admissions within 30 days of date of operation
Measurement variable: number of patients readmitted
Participant-level analysis metric: value
Method of aggregation: total
Specific time-point: 30 days from date of operation
Data collected from patient or hospital notes

Major complications
Measurement variable: Clavien-Dindo classification grading ≥3
Participant-level analysis metric: value
Method of aggregation: total
Specific time-point: up to 30 days from date of operation
Data collected from patient or hospital notes

Record linkage analysis of survival
Measurement variable: survival and cancer-specific outcome data in appropriate patients
Participant-level analysis metric: cancer-related death; cancer related recurrence
Method of aggregation:
Specific time-point: up to 10 years

3. STUDY DESIGN

U.K. multicentre double blind parallel group placebo-controlled randomised CTIMP of a 6 or 12-hour (see 6.3 Dosing Regimen) perioperative infusion of intravenous lidocaine in colorectal surgery. An initial internal pilot phase will be built into the trial to assess feasibility of recruitment.

The primary study will be in minimally invasive (laparoscopic or robotic) colectomy, and the sample size of 562 is calculated accordingly.

We will collect randomised data on an additional 100-200 open colorectal surgery patients using an adaptive design to assess recruitment and effect size as the trial proceeds. The patient cohort eligible for this exploratory trial will be those patients undergoing open elective colorectal resections for whom an epidural is not planned (co-administration of epidural local anaesthetic and IV lidocaine is contraindicated due to the increased risk of systemic lidocaine toxicity). We will use a group sequential interim analysis approach to this study to maximise our ability to generate sufficient evidence to estimate the effectiveness.
Update: June 2020. Recruitment to the parallel exploratory RCT of open surgery cases was closed in June 2020 because of slow accrual of such cases (see section 4.1 for further details).

3.1 Internal Pilot

Ahead of the expansion to the full site list we will first undertake an internal pilot RCT specifically to provide reassurance on all the trial processes, including recruitment, consent, randomization, delivery of treatment, and follow-up assessments to ensure that all run smoothly. In addition, the impact of the contraindication to co-administration of regional lidocaine infusion during the period of IV lidocaine/placebo infusion will be assessed during the internal pilot.

The internal pilot will run in at least 4 of the trial sites and will recruit 50 laparoscopic patients, at which point the TSC will review recruitment and other outputs on trial processes. During the pilot, open cases will also be recruited but there is no target number in place for this. The purpose of these pilot sites is to provide reassurance about all of the trial processes, including recruitment, consent, randomisation, delivery of the intervention, and measurement of the primary and secondary outcomes, before expansion to the full set of sites.

4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

The study will take place in at least 12-15 high-throughput UK colorectal surgery units. The number of NHS sites participating in the study was increased to 30. This was supported by the funder, Sponsor and the TSC members.

Planned minimally invasive stratum:
With a sample size of 562 randomised 1:1 to IV lidocaine or placebo the study will have 90% power at a 2-sided 5% level of significance to detect a relative reduction of 33% from 40% to 26.8% (absolute reduction of 13.2%) in non-return of gut function at 3 days post-op (or if the event rate is lower, the same power to detect a 40% relative reduction from 30% to 18% (a 12% absolute reduction)). There should be no missing primary outcome data (see section 6.5.4).

Planned open surgery stratum:
We estimate that for every 2-3 laparoscopic cases we expect to randomise one open case. However there is considerable uncertainty in this estimate as different units have different levels of laparoscopic expertise, and different attitudes to forgoing epidural anaesthesia for open cases. We have chosen 200 cases as the upper limit for analysis using a group sequential interim analysis approach to assess recruitment and effect size as the trial proceeds. However the DMC will assess the data after 100 patients to assess rate of recruitment and estimate effect size.
Update: June 2020. The DMC met in November 2019 and the TSC in February 2020. Following discussion, recruitment to the parallel exploratory RCT of open surgery cases was closed in June 2020 because of slow accrual of such cases.

4.2 INCLUSION CRITERIA

Patients scheduled for elective minimally invasive (laparoscopic or robotic) colorectal resection for colorectal cancer, benign polyps, benign stricture or diverticular disease at participating UK colorectal surgery units. Right hemicolectomy, extended right hemicolectomy, left colectomy, sigmoid colectomy, subtotal colectomy with ileosigmoid or ileorectal anastomosis and high anterior resection are eligible.

4.3 EXCLUSION CRITERIA

Planned epidural anaesthesia
Planned regional or local continuous infusion of lidocaine at the same time as lidocaine infusion (see section 6.7.3 for prohibited concurrent medication)
Planned open surgery
Current pregnancy*
Breastfeeding
Age <18 years
Patients lacking capacity to give informed consent.
Known or suspected allergy to lidocaine or amide-type local anaesthetics
Current complete heart block
Current severe liver dysfunction (Child's A or greater)
Current renal failure (eGFR<30)
Patients participating in the active intervention phase of another therapeutic clinical trial (or other interventional trial) unless a co-enrolment agreement is in place
Patients having surgery for indications other than those noted above
Rectal cancer below the peritoneal reflection in which total mesorectal excision is planned
Rectal cancer patients who have received any neoadjuvant radiotherapy
A preoperative surgical plan to form any new stoma during the primary procedure

*Women of child bearing age will have negative pregnancy test confirmed before inclusion to trial. Pregnancy test is part of routine preoperative assessment in women of child-bearing age hence this is not an additional test for trial purposes.

4.4 CO-ENROLMENT

Patients participating in the active intervention phase of another therapeutic clinical trial or other interventional trial will not be co-enrolled. Participants in long-term follow- up of an interventional clinical trial or participants in non-interventional research may be co-enrolled.

Arrangements for co-enrolment with another interventional trial (in long term follow up only), the co-enrolment checklist (POL008-F01) must be completed by the Sponsor(s) representative in conjunction with the CI prior to the co-enrolment proceeding.

Participants recruited onto the ALLEGRO study will be prohibited from enrollment onto other interventional research for 30 days following infusion of the IMP.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

At each site, members of the local clinical team will identify participants from hospital systems already in place to arrange surgery for patients: out-patient lists, local colorectal cancer multidisciplinary team meetings, planned operating lists for surgeons in each unit, waiting lists, and from promotion of the study amongst colorectal surgeons in each unit.

Medical or study staff will approach patients about study participation at existing points of contact with the surgical team prior to surgery. These may include any face-to-face or virtual outpatient consultation with the surgeon, by post or at the preoperative assessment of fitness for surgery and on the day of hospital admission.

Outpatient clinic: Investigators (Clinical team) will approach patients at the outpatient clinic or preoperative assessment clinic after the decision to perform colorectal surgery has been confirmed with the consultant surgeon responsible. At this appointment, a letter of invitation and a patient information leaflet will be provided to the patient. If the out-patient clinic is held virtually, then the investigator will send a copy of the patient information leaflet to the participant.

By post: Alternatively, after the decision to perform colorectal surgery has been confirmed, the consultant surgeon responsible or a member of their team will write to the patient, enclosing the patient information leaflet. This will give adequate time for patients to read the PIS before consent for participation is sought.

Day of hospital admission: Patients can also be approached about the study by the surgical team on the day of hospital admission and given information about the study. Patients will be able to consent prior to admission for surgery, or following admission prior to surgery.

In all instances, potential participants will be given adequate time to consider their participation in the trial.

Eligibility will be determined by the trained local medical or study team members (clinical team) and confirmed by the local study team at the time of consent.

5.2 CONSENTING PARTICIPANTS

Recruitment and consent will take place prior to surgery.

Where face-to-face consent is possible, a member of the trial team will explain the trial and time will be allocated for questions and discussion prior to surgery. The patient and a member of the local ALLEGRO trial team (delegated this activity) will both sign the consent form. The original will be retained in the site file. A copy will be given to the participant to keep. Copies will also be filed in the hospital notes and Trial Master File.

If face-to-face consent is not possible, the consent form will be sent to the potential participant along with the patient information leaflet (see above). A telephone number for the research team will be provided so that potential participants can ask any questions or seek clarification. A designated member of the ALLEGRO site team will contact the potential participant and conduct the consent discussion with them over the phone and ask the participant to initial, sign and date the consent form during the discussion – we are describing this as "verbal confirmation of written consent". The ALLEGRO team member will document the discussion in the patient medical notes. The participant will be asked to either return the consent form by post or to bring the consent form with them when they attend for surgery. When the consent form is returned, the member of the local site research team with delegated responsibility for consent and who conducted the consent discussion over the phone will countersign and date the consent form. If that person is not available to countersign before administration of the IMP, then another member of the ALLEGRO site team should have a further consent discussion with the participant and then countersign the consent form. The date of countersignature should not be earlier than the date of the participant signature, but may be later. To give sufficient time for the IMP prescription to be generated and signed, and for the pharmacy team to prepare and dispense the IMP prior to surgery, the participant may need to be randomised after verbal confirmation of written consent, but before the hard copy of the consent form is received back by the study team. Participant eligibility will be verified by a clinical trial physician prior to randomisation – this verification of eligibility will be done around the time of verbal confirmation of written consent or on receipt of the hard copy consent form. The consent form must be received by the site study team before administration of IMP. If the patient does not post it back or bring it with them when they attend for surgery, there should be a further consent discussion and a new copy of the consent form should be completed prior to administration of the IMP.

Throughout a participant's involvement in a study, consent is an on-going process, and should re-confirmed verbally prior to ANY research activity taking place.

A letter will be sent to the participant's GP to inform them of their participation.

5.3 SCREENING FOR ELIGIBILITY

As noted above, participant eligibility will be verified by a clinical trial physician (named on the trial delegation log to carry out this role) prior to randomisation. Confirmation of eligibility will be recorded within the participants' medical records and on the case report form.

As noted above, patients will be identified through a number of routes. This will involve members of the clinical team screening identifiable personal information within the existing hospital data systems.

Pregnancy testing on women of childbearing age is part of normal routine preoperative

assessment.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Ineligible and non-recruited patients will receive surgery and perioperative care according to normal participating unit standard practice.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

After either verbal confirmation of written consent (as described above) or the hard copy consent has been received from the participant and all eligibility criteria have been met, the member of the local research team will randomise the participant via the Clinical Trials Unit (CTU). The CTU is the Centre for Healthcare Randomised Trials (CHaRT) based within the University of Aberdeen. Participants will be randomised using either a telephone Interactive Voice Response (IVR) randomisation application or via the web based application. The CTU provides a 24 h randomisation web based service.

Randomisation for the study will be allocated on a 1:1 basis to either lidocaine or placebo.

Factors for **minimisation** :

Age (<50 years, 50-74 years, 75 years and older)
Gender
Trial centre

5.5.2 Treatment Allocation

Blinding: participants, medical staff and study staff/outcome assessors will all be blinded in this study. Both study drug and placebo are clear colourless liquids and will be packaged in identical containers. Upon randomisation the participant will be allocated a unique participant study number and assigned a numbered participant pack. Randomisation will trigger a notification email to pharmacy.

5.5.3 Emergency Unblinding Procedures

The treatment of systemic lidocaine toxicity is supportive treatment and lipid rescue.

In the event of characteristic symptoms in a trial patient (see section 6.6.1) it is appropriate to assume lidocaine toxicity, stop the infusion and treat side-effects as per current Association of Anaesthetists of Great Britain and Ireland guidelines without having to wait for code breaks/permissions etc. If necessary, the investigator can unblind a participant's treatment allocation via the trial database.

In the event of a SUSAR, the Sponsor will unblind treatment allocation (via access to the database) in order to comply with ethics and regulatory reporting requirements.

The trial office will be alerted in any cases of unblinding (but will not be unblinded) and a full audit trail will be maintained.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case record form, if possible. The participant will have the option of withdrawal from:

(i) study medication with continued study procedures and collection of clinical and safety data

(ii) all aspects of the trial but continued use of data collected up to that point or

(iii) all aspects of the trial with removal of all previously collected data

Participants who are randomised but do not receive any/all of infusion will undergo follow-up and be analysed as intention-to-treat.

Participants who decide that they do not want to continue contributing data: we will keep study data collected to that point unless the participant requests that all data be removed. We will continue to collect routine data to measure the primary endpoint unless they specifically request that they do not want routine data collected for study purposes. Data will be analysed as intention-to-treat.

Participants who do not survive/regain capacity following surgery or suffer a fatal postoperative complication will be analysed as intention-to-treat. In terms of the primary outcome data (GI-3 recovery – yes/no), they will classified according to whether gut function had returned by 72 hours – this data will be available from their medical notes. Those who die before return of gut function will be classified as no GI- 3 recovery.

5.7 INFORMING KEY PEOPLE

Following formal trial entry the Study Office will inform the participant's general practitioner of their involvement in the trial if the participant consents to this. This will be by letter and information about ALLEGRO and the Study Office contact details will be enclosed. GPs are asked to contact the Study Office if the participant moves, becomes too ill to continue or dies, or any other notifiable event or possible serious adverse event occurs.

6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

Sterile solution of Lidocaine 2% made isotonic with Sodium Chloride

6.1.1 Study Drug Identification

Lidocaine hydrochloride 2% solution for injection
Clear and colourless solution

6.1.2 Study Drug Manufacturer

Tayside Pharmaceuticals, (Ninewells Hospital & Medical School, Dundee, DD1 9SY) will manufacture the IMP under their MIAIMP number- 14076. The IMP dossier is prepared by Tayside Pharmaceuticals.

6.1.3 Labelling and Packaging

Tayside Pharmaceuticals will undertake the labelling and the manufacturing of the study drug. The study drug will be presented in 100ml glass DIN bottles with an injection bung and sealed with an aluminium over seal and each bottle will be overwrapped. Packs will be blinded before regulatory release to the site.

Medication labels will be in English and comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP). They will include

storage conditions for the drug and drug pack number but no information about the patient. All boxes and vials used for the IMP will be labelled.

6.1.4 Storage

The drug packs stored in pharmacy will be subject to routine temperature controls in place within pharmacy. Any drug pack subject to temperature deviation (>25°C) will be quarantined, pending a decision as to whether they can be returned to stock or need to be destroyed.
Drug packs have a shelf life of 24 months and should be protected from light. If a bottle is removed from the box the overwrap will continue to protect the contents from light.

Stocks will be temperature monitored at the manufacturer prior to dispatch.

6.1.5 Regulatory Release to Site

All required approvals for a site must be in place before regulatory release to a recruitment site can be authorised. Once these are in place, the Trial Office will order stocks to be released from Tayside Pharmaceuticals and sent to the recruitment site. Following confirmation of receipt of study medication at a site, the trial office will release drug packs onto the IVRS to allow for randomisation to take place.

The IVRS will include a low-stock notification to the Trial Office so that re-orders can be placed as appropriate.

6.1.6 Drug Accountability and Destruction of Trial Drug

Destruction of trial drug can take place at local recruitment sites or at the facilities of Tayside Pharmaceuticals.

At each site, the PI is responsible for ensuring drug accountability. In addition to recording the drug pack number on the inclusion form and in the medical records, an accountability log of the drug packs dispensed will also be maintained by the Clinical Trials Pharmacy at each site.

Throughout the trial expired medication will be destroyed at recruitment sites following local procedures. Clinical Trials Pharmacy staff will complete a destruction certificate confirming which packs have been destroyed – a copy will be retained in the Pharmacy file and a copy forwarded to the Trial Office. Any expired medication not released to recruitment sites will be destroyed by Tayside Pharmaceuticals. A destruction certificate will be completed - a copy should be retained by Tayside Pharmaceuticals and a copy forwarded to the Trial Office.

At the end of the recruitment phase of the trial, unused medication will be destroyed (and documented) at recruitment sites or Tayside Pharmaceuticals as described above.

There may be cases where a drug pack is dispensed at a recruitment site for a trial participant, collected by trial staff and the participant is not able to receive all or any of the infusion. Where possible, medication that is unused for this reason will be returned to the Clinical Trials Pharmacy for destruction. If this is not possible (for example the pack has been opened), the unused study medication can be safely discarded in theatre. A destruction certificate will be completed in such cases by trialstaff.

6.1.7 Summary of Product Characteristics (SmPC)

A simplified IMP Dossier has been produced by Tayside Pharmaceuticals to

summarise information related to the quality, manufacture and control of the IMP. A copy is filed in the TMF. A representative Lidocaine Summary of Product Characteristics (SmPC) is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Sponsor) and section 4.8 acts as the reference safety information for the trial IMP. Copies are held in the TMF and at site.

6.2 PLACEBO

0.9% sterile Sodium Chloride solution for injection.
Clear and colourless solution.
The placebo will appear identical to the IMP.

The placebo will be manufactured, labelled and packaged by Tayside Pharmaceuticals.

6.2.1 Labelling and Packaging

The placebo will be labelled as described in section 6.1.3

Medication labels will be in the local language and comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP). They will include storage conditions for the drug, but no information about the patient.

6.2.2 Storage

The placebo will be stored as described in section 6.1.4

6.3 DOSING REGIME

Intravenous bolus of 2% lidocaine at induction of anaesthesia (1.5mg/kg ideal body weight) over 20 minutes followed by intravenous infusion of 1.5 mg/kg/hour ideal body weight with a maximum rate of 120mg/hour (6ml/hour) for a minimum of 6 hours up to a maximum of 12 hours (see below).

Ideal body weight is used rather than actual body weight to prevent the possibility of toxicity by exceeding the upper therapeutic threshold of lidocaine in very overweight patients.[30]

*In patients whose weight is **less than** ideal body weight, actual weight should be used to calculate dose*.

Ideal body weight in Kg:
Men: Height in cm-100
Women: Height in cm -105

Height and weight are measured routinely as part of preoperative assessment.

Starting the infusion and calculation of the correct infusion rate will be undertaken by the responsible anaesthetist for the scheduled operation using a standard infusion pump (commonly used in every NHS hospital anaesthetic department). The study drug will be provided at 2% strength and will be infused directly via peripheral or central cannula, hence no preparation (dilution, reconstitution etc) will be required. The trial manual will contain a predetermined dosage table to indicate the correct range of dose. Drug will be manufactured at appropriate dose and delivered according to participant's Ideal Body Weight. The clinical research team will be responsible for calculating the dose required.

Placebo- 0.9% Sodium Chloride, infusion as above.

Table 1: Example dosing by ideal body weight

Ideal body weight	Bolus	Infusion rate of 2% lidocaine	Total volume for 6 hour infusion	Total volume for 12 hour infusion
40kg	3ml	3ml/hour	18	36
50kg	3.75ml	3.75ml	22.5	45
60kg	4.5ml	4.5ml/hr	27	54
70kg	5.25ml	5.25ml/hr	31.5	63
80kg or greater	6ml	6ml/hr	36	72

Planned duration of infusion will be determined pre-operatively by the participating unit's normal postoperative availability of continuous cardiac monitoring.

- Units where normal postoperative disposal is to the standard inpatient ward, where facility for reliable cardiac monitoring is not available, will aim to administer the infusion for a minimum of 6 hours (operating time plus theatre recovery suite time). Before the patient is moved to the ward, the infusion will be stopped. This means that (i) if the operating time plus theatre recovery suite time is less than 6 hours, the duration of the infusion will also be less than 6 hours; and (ii) if the operating time plus theatre recovery time is six hours or more, the duration of the infusion will be more than six hours, but will be stopped at 12 hours.

- Units where normal postoperative disposal is to HDU, or other clinical area where reliable cardiac monitoring is available, will aim to administer the infusion for up to12 hours. If the patient is moved to a ward before the 12 hour period has been completed, the infusion will be stopped.

The infusion may be stopped early if the treating surgeon or anaesthetist has clinical concerns.

For all patients, duration of infusion will be recorded.

6.4 DOSE CHANGES

No planned dose changes other than those described above in relation to planned duration of infusion.

In a very small number of patients there may be a failure to administer the full dose due to unforeseen intraoperative surgical complications or technical problems with the infusion kit (e.g. inadvertent disconnection of giving set or infusion pump failure). These patients will be included within the intention to treat analysis.

6.5 PARTICIPANT COMPLIANCE

Since this is an in-hospital study with short duration of study drug/placebo infusion it is unlikely that non-compliance will be an issue. Monitoring the infusion will be a documented part of normal nursing care. A single container dispensed by pharmacy will contain sufficient drug/placebo to avoid necessity for the infusion being changed/running out.

6.6 OVERDOSE

The following strategies are in place to minimise the potential for Lidocaine overdose:

- It is a hospital-based study with infusion rate calculation and administration overseen by senior anaesthetic staff;
- A limited amount of the drug will be provided for each patient;
- Patients with severe liver or renal impairment in whom lidocaine metabolism is impaired are specifically excluded;
- Co-administration of lidocaine via other routes which may increase systemic levels (e.g. epidural, regional or local infiltration) is specifically contraindicated and this will be emphasised in the trial operation manual.
- Overdose is most likely to occur through operator error (setting the infusion rate wrongly) or pump failure. Although the dose is calculated by ideal body weight there will in practice be a relatively narrow range of infusion rates and the trial operation manual will emphasise the appropriate range of values.

6.6.1 Symptoms of Lidocaine Acute Systemic Toxicity

Central nervous system toxicity presents with symptoms of increasing severity. Patients may present initially with circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual disturbance and muscular tremors or muscle twitching are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly following convulsions due to increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis increases the toxic effects of local anaesthetics.

Effects on the cardiovascular system may be seen in severe cases. Hypotension, bradycardia, arrhythmia and cardiac arrest may occur as a result of high systemic concentrations, with potentially fatal outcome.

Reduction of lidocaine levels occurs due to redistribution from the central nervous system and metabolism. Recovery will only occur with appropriate active management of the symptoms of toxicity up to and including cardiac arrest.

6.6.2 Treatment of Lidocaine Acute Toxicity

If signs of acute systemic toxicity appear, infusion of lidocaine should be stopped immediately. Participants should be reviewed urgently by a senior anaesthetist and closely observed for signs of progression of toxicity. Lipid rescue should be considered early if there are clinical signs of deterioration and the patient has received a significant dose of lidocaine.

Treatment will be required if convulsions and CNS depression occurs. The objectives of treatment are to maintain oxygenation, stop the convulsions and support the circulation. Lipid rescue should also be instituted as per the Association of Anaesthetists of Great Britain and Ireland guidelines (Management of severe local anaesthetic toxicity 2010, available at http://www.aagbi.org/publications/publications-guidelines/M/R).

A patent airway should be established and oxygen should be administered, together with assisted ventilation (mask and bag) if necessary. The circulation should be maintained with infusions of plasma or intravenous fluids. Where further supportive treatment of circulatory depression is required, use of a vasopressor agent will be required. Convulsions should be controlled by the intravenous administration of Diazepam or Thiopentone Sodium, bearing in mind that anti-convulsant drugs may

also depress respiration and the circulation. It is highly likely that the patient will need to be intubated and ventilated to control hypoxia and hypercarbia both of which exacerbate toxicity. If cardiac arrest should occur, standard cardiopulmonary resuscitation procedures should be instituted. Continual optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

There are no NIMPs specified in the protocol.

6.7.2 Permitted Medications

Standard analgesia regimes as per the normal practice in each participating unit.

Standard anti-emetic regimes as per the normal practice in each participating unit.

All other medications apart from those prohibited below will be permitted.

6.7.3 Prohibited Medications

Additional continuous infusion of any local anaesthetic agent is prohibited during IMP infusion.

The following single local infiltrations of local anaesthetic are acceptable in an individual study patient:

- **1-2ml lidocaine for local anaesthesia to insert spinal or venous access cannulae.**
- **Up to 3mls of 0.5% bupivacaine as part of the spinal diamorphine injection**
- **once-only abdominal wound infiltration with up to 20ml of 0.25% levo-bupivacaine (or 40ml of 0.125% levo-bupivacaine) at the end of surgery; if the patient weighs less than 50kg (actual weight) these doses should be reduced by 50%)**

Caution must be exercised if an epidural containing any local anaesthetic is deemed necessary for the participant during or in the 24 hours following the IMP infusion, due to the possibility of toxicity through additive effects.

There are no other prohibited medications.

7. STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

Safety will be assessed perioperatively and postoperatively for 30 days.

Safety will be assessed by recording the incidence of AE/SAEs attributable or possibly attributable to IV lidocaine toxicity based on its well-documented side-effect profile (neurological impairments, respiratory depression, convulsions, ventricular arrhythmia (complete heart block). Continuous cardiac monitoring during the period of IV lidocaine infusion is mandatory for trial participants because of the potential for cardiac arrhythmia at toxic levels- note that the dose and duration of infusion used in this study makes toxicity extremely unlikely.

In the event of signs or symptoms of Lidocaine toxicity (including seizures, cardiac ventricular arrhythmias/asystole) Lidocaine treatment will be stopped. As above, the treatment of systemic Lidocaine toxicity is supportive treatment and lipid rescue.

Colorectal surgery has inherent dangers of various well-recognised and significant complications. These will be specified and recorded as part of the specified tertiary end-points but will be distinguished from adverse events attributable to lidocaine. Section 11.0 details the adverse events that will be recorded and reported for ALLEGRO.

7.2 STUDY ASSESSMENTS

The schedule for study assessments is summarised in table 1. Clinicians and nurses will follow their local clinical guidance as per standard clinical care for their contact with participants or between each other. While physical distancing measures are in place, face-to-face contact with participants should be kept to a minimum; where face-to-face contact is required, a safe distance should be maintained and appropriate PPE worn.

7.2.1 Study Assessments

The following assessments will be made as per the schedule outlined below and summarised in table 1. Some of the following information will be captured routinely into medical notes. The Research Nurse will be required to extract information from medical records to CRF/eCRF, but also to record some trial-specific data directly to the CRF/eCRF.

Demographic data and contact details
Name, age, CHI/hospital number, gender, unique identifier, address, contact telephone number

Clinical history/past medical history
Significant current or previous medical and surgical conditions

p-POSSUM
Risk stratification tool to compare morbidity and mortality in a wide range of general surgical procedures in order to facilitate surgical audit and the comparison of units performance.

CRP
Blood test marker for inflammation in the body. Levels of CRP rise in response to inflammation. Measured in most units as part of routine care. Results to be obtained from medical notes.

OBAS Score
Patient-reported outcome measure (PROM) which assesses pain intensity and opioid-related adverse effects and patient satisfaction with analgesia. See Appendix 2

QoR Score

PROM to measure quality of recovery after surgery and anaesthesia. See Appendix 4

EQ-5D
Standardised PROM instrument for use as a measure of health outcome and used in Quality Adjusted Life Year (QALY) calculations for health economic analyses..

Intraoperative blood loss

As documented on anaesthetic record- recorded as part of routine documentation of the operation.

ERAS Protocol compliance
Assesses compliance with accepted best practice in perioperative care during the operation and during postoperative days 1-3. The key variables are detailed in section 2.2.2 secondary endpoints:

Avoidance of long-acting opioids for maintaining anaesthesia- *certain IV opioids are more likely to cause GI side-effects and these will be identified from the concomitant medication list, source data= anaesthetic record*
Prescribed PONV prophylaxis for 48 hours- *Y/N response on CRF, source data= patient prescription chart*
Euvolaemic IV fluid policy-

-total IV fluid administration from 24 hours from start of anaesthesia, source data=prescription chart
- Day 1 weight difference is the most accurate indication of fluid balance and is calculated from the difference between patient weight 24 hours after start of anaesthesia (+/-6 hours) and pre-operative weight (eCRF will calculate the difference)

Early feeding- *oral supplement on day of surgery and solid food offered from postoperative day 1 onwards -data obtained from medical record/prescription chart/ direct questioning of patient by CRN*
Early mobilisation- *patients should be out of bed for 2 hours on day of surgery and 4-6 hours every day thereafter source data= medical record /direct questioning of patient by CRN*
Routine postoperative laxative prescription- Y/N, *source data= medical record/prescription chart*
No NGT immediately after surgery- *any intraoperative insertion of a NG tube where one was not in place pre-operatively and which was left in situ postoperatively, source data= operation note or direct observation on day 1 by CRN.*

PONV Impact Score
PROM assessing severity and clinical importance of postoperative nausea and vomiting in general surgical population (see Appendix 3)

Time to first flatus
See Endpoints section 2. To be calculated and recorded by CRN and entered directly on eCRF as may not be recorded in medical notes.

Time to first bowel movement
See Endpoints section 2. To be calculated and recorded by CRN and entered directly on eCRF as may not be recorded in medical notes.

Time to tolerating solid food
See Endpoints section 2. To be calculated and recorded by CRN and entered directly on eCRF as may not be recorded in medical notes.

Pregnancy Test

Urinary beta HCG dipstick test – **undertaken as part of routine clinical care**

Total antiemetic dose
Antiemetic drugs administered up to 72 hours from start of anaesthesia.

7.2.2 Schedule of Assessments

Baseline assessment

The data is likely to have been captured at pre-assessment and can be transcribed into the CRF/eCRF. However, certain key variables should be confirmed at the time of admission for surgery (height, weight, pregnancy test, confirmation of eligibility).
Note that P-POSSUM depends on some data which can only be determined intra and postoperatively.
The following data will be recorded on case report form from the patient and their medical notes:

- Consent
- Confirmation of eligibility
- Pregnancy test (for women of childbearing potential)
- Demographic data, contact details
- Height
- Weight
- p-POSSUM
- CRP (if measured as part of routine care)

Participants will be asked to complete a questionnaire comprising:

- OBAS score
- QoR score
- EQ-5D.

Post-operative day 1(defined as the first calendar day after the day of surgery i.e. day of surgery =day 0)

On post-operative day 1, the following data will be recorded on case report form from the patient and their medical records.

- Weight (to be obtained by CRN if not recorded as standard care in participating unit, as close as possible to 24 hours following start of anaethesia)
- Operation
- Anaesthesia start time
- Knife to skin time
- Duration of operation (knife to skin to entry into operating theatre recovery suite)
- Duration of lidocaine/placebo infusion
- Intraoperative blood loss (mls)
- ERAS protocol compliance
- Adverse events

Participants will be asked to complete a questionnaire comprising:

- PONV Impact score
- QoR score
- OBAS score
- EQ-5D

It is acknowledged that participants may not complete questionnaires for example they may be too unwell. Non-completion of a participant questionnaire (at any time-point) will not be documented on a deviation log. Instead, questionnaire non-compliance will be collected through the ALLEGRO database

Post-operative day 2

On post-operative day 2, the following data will be collected via case report form from the patient and their medical records.

- CRP (if measured as routine care)
- Time to first flatus
- Time to first bowel movement
- Time to tolerating solid food
- ERAS protocol compliance
- Achievement of medical criteria for discharge (Y/N)
- Patient-reported readiness for discharge
- Adverse events

Participants will be asked to complete a questionnaire comprising:

- PONV Impact score
- QoR score
- OBAS score
- EQ-5D

Post-operative day 3

On post-operative day 3, the following data will be collected via case report form from the patient and their medical records.

- CRP
- Time to first flatus
- Time to first bowel movement
- Time to tolerating solid food
- antiemetic dose total for 72 hours
- Analgesic dose total for 72 hours
- Total number of episodes vomiting in 72 hours
- Achievement of medical criteria for discharge Y/N
- Patient-reported readiness for discharge
- Adverse events

Participants will be asked to complete a questionnaire comprising:

- PONV Impact score
- QoR score
- OBAS score
- EQ-5D

Daily from post-operative day 4 to discharge

If the participant has not been discharged, the following data will be collected daily up to and including day 7 via case report form from the patient and their medical records.

- Time to first flatus
- Time to first bowel movement
- Time to tolerating solid food
- Achievement of medical criteria for discharge Y/N
- Patient-reported readiness for discharge
- Adverse events

Daily up to and including day 7, participants will be asked to complete a questionnaire comprising:

- QoR score
- OBAS score
- EQ-5D

At discharge

At discharge, the following data will be collected from medical records/ prescription chart

- Length of stay (days)
- Complications
- Mortality
- Analgesic and anti-emetic medication

Post-Operative Day 7 (+/- 3 days)
On day 7, participants will be asked to complete a questionnaire comprising the OBAS, QoR and EQ-5D. Participants who have been discharged from hospital prior to day 7 will be contacted by telephone by the local CRN/study team to collect the data. If the patient cannot be contacted on day 7, further attempts will be made to contact the patient by telephone until day 10. Participants who have not been discharged by day 7 will be asked by a member of the research team (e.g. Research Nurse) to complete the questionnaire in hospital.

Day 30 (+/- 7 days)
At day 30 following the date of surgery, in hospital mortality will be confirmed from medical records. Participants who were discharged from hospital will be contacted by telephone by the local research team to collect the following data:

- QoR
- EQ-5D
- Complications
- Unplanned hospital readmissions
- Self-reported use of primary care services
- Adverse events

It is acknowledged that participants may not complete questionnaires for example they may be too unwell. Non-completion of a participant questionnaire (at any time-point) will not be documented on a deviation log. Instead, questionnaire non-compliance will be collected through the ALLEGRO database

Day 90 (+/- 7 days)
At day 90, following the date of surgery, in hospital mortality will be confirmed from medical records. Patients who were discharged from hospital will be contacted by telephone to collect the following data:

- EQ-5D
- Unplanned hospital admissions after day 30 up to day 90.

It is acknowledged that participants may not complete questionnaires for example they may be too unwell. Non-completion of a participant questionnaire (at any time-point) will not be documented on a deviation log. Instead, questionnaire non-compliance will be collected through the ALLEGRO database

Record Linkage
Participants will consent at onset of trial to allow access to their medical records/ data records for up to 10 years post-surgery. Data to be assessed will comprise mortality and cancer-survival data.

A separate, ethically approved protocol will cover record linkage.

Concomitant medications
We will record in the eCRF only those medications of relevance to the study endpoints.Information will be obtained from the medical record/prescription charts at discharge. These medications are:
Analgesia- total perioperative opioid prescription up to 72 hours.
Anti-emetics- total prescription up to 72 hours.

IV Dexamethasone- given at induction of anaesthesia in some units (not used recurrently thereafter)
Laxatives- Whether or not prescribed regularly as part of participating unit postoperative ERAS protocol.

In the event of an SAE or SAR, concomitant medications will be recorded on the SAE form.

Summary table – schedule of assessments

Assessment	Recruitment /Baseline	POD 1	POD 2	POD 3	Daily from POD 4 until discharge	POD 7	Discharge	30 days	90 days
Assessment of Eligibility Criteria	✓								
Written informed consent	✓								
Pregnancy Test (where applicable)									
Demographic data, contact details	✓								
Clinical history/ past medical history	✓								
Drug history esp. laxatives	✓								
Height	✓								
Weight	✓	✓							
p-POSSUM	✓	✓ (part)						✓ (part)	
Operation type		✓							
Duration of operation		✓							
Blood loss (mls)		✓							
OBAS score	✓	✓	✓	✓	✓	✓			
QoR score	✓	✓	✓	✓	✓	✓		✓	
PONV score		✓	✓	✓	✓				
EQ5D	✓	✓	✓	✓	✓	✓		✓	✓
CRP	✓		✓	✓					
Time to first flatus			✓	✓	✓				
Time to first bowel movement			✓	✓	✓				
Time to tolerating solid food			✓	✓	✓				
antiemetic dose total up to 72 hours							✓		
Total number of episodes vomiting		✓	✓	✓					
Total opioid consumption in-hospital up to 72 hours							✓		
ERAS protocol compliance		✓	✓	✓					

Assessment	Recruitment /Baseline	POD 1	POD 2	POD 3	Daily from POD 4 until discharge	POD 7	Discharge	30 days	90 days
Achievement of medical criteria for discharge Y/N				✓	✓				
Patient-reported readiness for discharge				✓	✓				
Length of stay (days)							✓		
Complications							✓	✓	
Unplanned readmissions								✓	✓
Use of primary care services								✓	
Mortality							✓	✓	✓
Adverse events		✓	✓	✓	✓	✓		✓	

7.3 COMPLIANCE ASSESSMENTS

Since this is an in-hospital study with short duration of study drug/placebo infusion it is unlikely that non-compliance will be an issue. Monitoring the infusion will be a documented part of normal nursing care.

7.4 LONG TERM FOLLOW UP ASSESSMENTS

Participants will be followed up using record linkage post-operatively to determine survival and cancer-specific outcomes. Consent for this will be sought at recruitment and a separate protocol will be prepared to detail the long term follow up.

7.5 STORAGE AND ANALYSIS OF SAMPLES

No trial specific samples will be collected for participants.

8. DATA COLLECTION

Outcome data up to the point of discharge will be entered into either paper or electronic CRFs, developed by CHaRT, by the local research team at each centre. If data is entered onto paper CRFs they must be inputted onto the database in a timely manner. The post-discharge paper-based questionnaires will be completed by participants by telephone or post, and again will be inputted into an electronic database by the local research team or staff at the central trial office. The trial manager and clinical site coordinator will liaise with local sites to address data completeness and data queries.

8.1 SOURCE DATA DOCUMENTATION

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first time.

8.2 CASE REPORT FORMS

CHaRT will develop the case report forms for the trial in collaboration with the Chief Investigator and Trial Statistician.

All case report forms must be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation).

NOTE: All electronic case report forms are subject to Sponsor approval (see section 8.3).

8.3 TRIAL DATABASE

A web-based trial database will be developed by the programming team in CHaRT. Individual users will be given unique log in details. Access to edit the database for recruitment site staff will be limited to the participants recruited at that site.

Recruitment site staff will be responsible for entering data collected at site; trial office staff will be responsible for entering any data collected by postal questionnaire and returned by participants to the trial office.

The Trial Website is SSL secured, ensuring links between server and browser client are always encrypted. Access to patient identifiable information is limited to key personnel only and has appropriate user level access across a secure network, personal identifiable data held in the database will be encrypted to AES_256 encryption standard.

At the end of the trial, electronic data will be archived at The University of Aberdeen.

9. DATA MANAGEMENT

9.1.1 Personal Data

The following personal data will be collected as part of the research:

- Name
- Address
- NHS number (England only)
- CHI number (Scotland only)

Participants are allocated an individual trial number. Participant's details are stored on a secure database under the guidelines of the 1998 Data Protection Act. To comply with the 5th Principle of the Data Protection Act 1998. The CHaRT senior IT development manager (in collaboration with the CI) manages access rights to the data set.

Personal data is not kept for longer than is required for the purpose for which it has been acquired.

Transfer of Data

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s). Data collected or generated by the study will be accessed by CHaRT, University of Aberdeen to manage on behalf of the sponsors.

9.1.2 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site)

9.1.3 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

10. STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

We have interrogated the literature for the most relevant data to inform our estimates of the minimal clinically important difference, and the untreated event rate for the primary outcome, and hence required sample size. Data from the applicants' pilot study (referred to here as the Targinact study) in laparoscopic colectomy is highly relevant since it was conducted under real-world NHS conditions on NHS patients typical of the

recruitment cohort proposed in this application. It showed that 22 of a total of 50 patients (44%) failed to achieve return of gut function (GI-3 endpoint) by the third postoperative day.(4) Ten patients (20%) went on to develop PPOI. Interpretation of data from other healthcare systems is made complex by reporting of various endpoints, but control arm data support the event rate measured in the Targinact study: Delaney et al (3) in a prospective analysis of laparoscopic colectomy found the mean time to GI-2 recovery was 4.4 days, 53% achieved GI-2 by 3 days, with PPOI in 10%. Adam MA et al in a prospective analysis examining the drug Alvimopan in 660 participants, of which about 3 in 5 were laparoscopic, 16% of controls had PPOI(17). Estimated effect size is also beset by varying endpoints: from the Sun et al meta-analysis of IV lidocaine (9) , there was about a 20% (open) and 13% (laparoscopic) improvement in mean time to bowel movement. The Kranke et al Cochrane meta-analysis (8) reported a risk ratio of 0.38 for PPOI in favour of IV lidocaine vs placebo with an event rate of around 14% in controls. A small (n=40) RCT by Kaba et al(11) showed around 40% relative risk reduction in time to first flatus and time to first stool, whereas the Herroeder et al(18) RCT of a similar size (n=60) showed smaller relative risk reductions (~25%) for similar outcomes, as did the Tikuisis study(12)(n=60), ~20%.

So although the evidence base specifically for IV lidocaine in laparoscopic (and open) surgery is not extensive, there do seem to be consistent signals of benefit across a range of outcomes. Therefore, with a sample size of 562 randomised 1:1 to IV lidocaine or placebo the study will have 90% power at a 2-sided 5% level of significance to detect a relative reduction of 33% from 40% to 26.8% (absolute reduction of 13.2%) in non-return of gut function at 3 days post-op (or if the event rate is lower, the same power to detect a 40% relative reduction from 30% to 18% (a 12% absolute reduction)). Given the day 3 measure is in hospital there should be no appreciable loss to follow up (the perioperative death rate is ~1% for the whole duration of hospital stay and the very few discharged before 3 days can be assumed to have achieved return of gut function). This size of study would also give us similar power to detect a difference of 10% (from 20% to 10%) in the important secondary outcome of PPOI.

The sample size of 562 refers to only minimally invasive surgery cases, and is fully powered for this group.

Open cases will be analysed entirely separately. We will use a group sequential interim analysis approach to maximise our ability to generate sufficient evidence to estimate the effectiveness. The details of this approach will be specified at a first scoping meeting of the iDMC after around 100 open surgery participants with mature data – this will allow us to estimate (a) the likely number of open recruits we will get while fully randomising to the definitive laparoscopic stratum, and (b) get a reasonable idea about what the aggregate event rate for the primary outcome in the open surgery cases is, so enabling us to calibrate the group sequential plans.
Update: June 2020. Recruitment to the parallel exploratory RCT of open surgery cases was closed in June 2020 because of slow accrual of such cases. Revisions to the planned analysis of data from the open cases will be documented in the Statistics Analysis Plan.

10.2 PROPOSED ANALYSES

All baseline and outcome data will be described using appropriate summary statistics, e.g. frequency and proportions for dichotomous data, mean and standard deviation for continuous data, and graphical methods. The primary outcome will be analysed using a generalised linear model with a logit link function and including minimisation covariates. Secondary outcomes will analysed in a similar manner using a statistical model appropriate for the outcome (Cox regression for time-to-event outcomes, linear

regression for continuous outcomes). All treatment effects will be presented with 95% confidence intervals. Statistical analysis for . subgroups include:

Operation (right/extended right colectomy v “left-sided” colectomy (=left colectomy, sigmoid colectomy, high anterior resection))
ERAS protocol compliance for elements known to impact gut function (see section 3.2.2 above)

Potential moderating of subgroups on the treatment effect will be estimated by repeating the analysis of selected outcomes including treatment-by-subgroup interactions. Analysis will be by intention-to-treat. We do not anticipate any missing data due to the low-risk nature of the surgery and short time-frame of the primary outcome. However, should we observe substantial missing data we will use multiple imputation and pattern mixture methods to explore the robustness of treatment effect estimates.

10.3 HEALTH ECONOMIC ANALYSIS

Full details of these analyses will be specified in a comprehensive Health Economic Analysis Plan, authored by the study health economist(s), and signed off by the PI prior to analysis. However, to summarise:

To maximise UK policy relevance, health economic analysis will follow NICE reference case recommendations[20] including: Adoption of an NHS and PSS (personal social service) costing perspective for primary analyses; cost-utility approach (results presented in terms of incremental cost per quality adjusted life year (QALY), with QALYs derived from EQ-5D-5L); discount rate of 3.5% for both costs and QALYs (if applicable); use of probabilistic sensitivity analysis; and provision of value of information analysis to inform future research.

Data Collection & Variable Derivation

Where possible healthcare resource use (for cost generation) are being extracted from electronic records. This will include direct surgery time and treatments used, lidocaine infusion, cardiac monitoring, details of time spent recovering in hospital wards, and any re-admissions within the 90 day trial period. Additional top up self-report surveying of primary care resource use will be performed at the 30 day follow up to check for unanticipated offsetting of resource use for example increased GP/A&E contacts following early discharge. Each of these NHS resource use elements will then be converted to cost estimates using standard UK price weights [21,22] and summed to estimate total NHS costs per patient.

Self-reported EQ-5D-5L data are being recorded daily between baseline and discharge (inclusive), and at day 7, day 30 and 90 day follow up. This data will be converted to health utility scores using the standard algorithm [23], unless at the time of analysis and alternative algorithm has been developed which has policy support. QALYs will then be generated using an area under the curve approach. [24]

Analysis

Within trial period comparisons of costs and QALYs between trial arms will be undertaken via generalised linear modelling to account for any skewed

distributions,[25,26] with both univariate assessment and multivariate assessments controlling for all minimisation variables. Means per trial arm and differences in means

with accompanying standard errors will be reported to provide parameter estimates for use in future research.

Within trial cost-utility analysis will be undertaken via the recycled predictions method detailed by Glick et al. [26]

It is anticipated that any observable impacts on QALYs will be confined to the first few days post-surgery, hence the daily data collection prior to discharge. However given the low weighting of a single day in QALY terms, even large differences during this period may have limited impact on overall cost-effectiveness. As such early convergence of health utilities is expected to be an important explanatory factor when undertaking cost-utility analysis, the QALY profiles of the two arms up to discharge will be presented graphically.

To determine if there is a need for economic modelling of longer term cost-efficiency, and if so details such as relevant model structure(s) and potential sources of parameter inputs, a consultation process with clinical experts and examination of the literature will be undertaken. In particularly low frequency high severity events of colorectal surgery or lidocaine toxicity will be considered. Complications of surgery to be considered will include but not be limited to: anastomotic leak, abdominal sepsis, wound healing problems, cardiorespiratory (MI, PTE, DVT, pneumonia etc), acute kidney injury, CVA, multi-organ failure, death. Lidocaine toxicity effects to be considered will include: seizures, cardiac ventricular arrhythmias/asystole, and death. Where necessary this process will make use of the recent Cochrane review [28] topped up with an additional literature search towards the end of the trial to capture new literature published in this period with additional searches for any required variables identified which are not available from either of these. In absence of empirical data, parameters may be elicited from expert opinion using established techniques if appropriate. [29]

Where possible and reasonable to do so, incremental cost effectiveness ratios (ICERs) in terms of cost per QALY will be presented and compared to established UK thresholds. [20] Uncertainty will be presented in the form of probabilistic sensitivity analysis (PSA) using cost effectiveness acceptability curves (CEACs) [26] with deterministic sensitivity analysis around key assumptions or where a probabilistic approach would be inappropriate.

We initially planned to carry out sensitivity analysis to model changes in proportions of patients receiving laparoscopic surgery vs open surgery. Closure of the parallel exploratory RCT of open cases means that such analysis is unlikely to be possible.

Value of Information Analysis
The value of further research will be determined and compared using value of information analysis to identify the parameters which are most likely to change the decision recommended by the model such as: those with a high degree of uncertainty; high weighting; or, an important structural role in the model. This information can be used to make recommendations for efficient future research.

11. PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the current, approved Summary of Product

Characteristics (SmPC).

Participants will be instructed to contact their Investigator at any time after consenting

to join the trial if any symptoms develop. Adverse events (AE) that occur after informed consent until 30 days after surgery should be recorded in the AE log that is part of the Case Report Form (CRF). In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

11.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- □ results in death of the clinical trial participant;
- □ is life threatening*;
- □ requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- □ results in persistent or significant disability or incapacity;
- □ consists of a congenital anomaly or birth defect;
- □ results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where 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.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SmPC).

11.2 IDENTIFYING AEs AND SAEs

In this study, AEs will be identified and recorded from the time a participant signs the consent form to take part in the study until the 30th postoperative day.. In addition, all appropriate SAEs will be recorded from the time a participant signs the consent form to take part in the study until the 30th postoperative day.

Participants will be asked daily about the occurrence of AEs/SAEs during admission and then again during the 7 day (if discharged) and 30 day follow up telephone calls. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories. Patient hospital records will be labelled to alert medical staff to clinical trial participation and reporting of unplanned admissions to the study team.

11.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably

qualified physician in the research team who is delegated to record AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the AE log and on the SAE form (if the event meets the criteria of serious).

For SAEs, information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

11.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as adverse events if medically judged to have worsened during the study specifically as a result of the study drug.

11.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and recorded on the AE log if medically judged to have unexpectedly worsened during the study specifically as a result of the study drug, particularly as some conditions are transiently worsened by abdominal surgery (e.g. COPD). Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

11.3.3 Common AEs after surgery

The following events are common after surgery and are typically self-limiting:

- pyrexia
- anorexia, nausea, vomiting, constipation, pain
- raised inflammatory markers
- minor wound infections
- dizziness
- transient biochemical derangement eg hypokalaemia, hyonatraemia, hypomagnesaemia, hypophosphataemia, hypocalcaemia
- transient self-limiting confusional state.

11.4 ASSESSMENT OF AEs AND SAEs

AEs will be captured on the AE log that is part of the CRF. Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator or other medically qualified delegate. For randomised double blind studies, AEs will be assessed as though the participant is taking active IMP. Cases that are considered serious, and possibly, probably or definitely related to IMP, and unexpected (i.e. SUSARs) will be unblinded by the Sponsor.

The Investigator is responsible for assessing each AE.

This may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting AEs.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

11.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 11.1.

11.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the

IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.

- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. The assessment of causality will be made against the reference safety information found in the reference safety information of the SmPC (section 4).

The trial protocol does not specify non-Investigational Medicinal Products. However, participants will receive standard analgesia and anti-emetic regimes as per normal practice in each participating unit. If an AE is considered to be related to an interaction between the IMP and any concomitant medication, or where the AE might be linked to either the IMP or the concomitant medication but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

11.4.3 Assessment of Expectedness

If the event is an AR/SAR the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC.

The event may be classed as either:

Expected: the AR/SAR is consistent with the toxicity of the IMP listed in the SmPC

Unexpected: the AR/SAR is not consistent with the toxicity in the SmPC.

11.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AR log or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

11.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance **within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 11.4.2, Assessment of Causality and 11.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on **+44 (0)131 242 9447** or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner. ACCORD will forward all SAEs and related correspondence to the ALLEGRO trial office by email to allegro@abdn.ac.uk within 24 hours of receipt.

The sponsor will report all SUSARs to Tayside Pharmaceuticals (Tay-UHB.tptrials@nhs.net) within 7 days of becoming aware of them.

All reports transmitted to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

11.5.1 SAEs within ALLEGRO

Toxicity due to lidocaine is well described (see section 6.6.1). Any of these symptoms/signs occurring **during or within 2 hours of completion of the IV lidocaine infusion** should be recorded as an AR on the AE log and, if it meets the criteria for serious, also recorded and reported as an SAR following the process described in 11.5 above.

Death of any patient within the study should be recorded as an SAE and reported to the sponsor within 24 hours as described in section 11.5, whether or not thought to be related to the study IMP.

As noted in 11.3.3, colorectal surgery is unavoidably associated with a variety of 'complications', which may range in severity from trivial to life-threatening, and occur in at least 40% of cases. Most are self-limiting or treatable with oral medications, and will be recorded as adverse events.

Complications of surgery reaching grade 3 and above on the Clavien-Dindo scale will be recorded as secondary/tertiary outcome measures and not as SAEs, unless they are considered to be related to the study drug. Such events will not be reported to the sponsor in the expedited fashion described in section 11.5 even if they reach the criteria for seriousness. The exception to this is deaths as a result of complications of surgery, which should be reported as an SAE.

Prolongation of hospital admission for social reasons will not be recorded or reported as a SAE, but captured as part of the outcome data for the trial.

In summary:

Event	If the event is thought to be an adverse reaction	If the event is not thought to be an adverse reaction
Lidocaine toxicity within 2h of infusion	Record on adverse event log (SAR if meets criteria for serious)	n/a
Transient events common after surgery (section 11.3.3)	Record on adverse event log	Recorded on adverse event log
Complications of surgery Clavien-Dindo grade 1/2	Record on adverse event log	Recorded on adverse event log
Complications of surgery Clavien-Dindo grade 3+	Record as SAR/SUSAR	Record as outcome data on CRF
Prolongation of admission for social reasons	n/a	Record as outcome data on CRF
Death	Record as SAR/SUSAR	Record as SAE

11.6 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the co-sponsors (The University of Edinburgh and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction. ACCORD will inform the trial office by emailing allegro@abdn.ac.uk and CI of all SUSARs and any other arising safety information.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

11.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the AE log or additional information section of SAE form.

11.8 PREGNANCY

Pregnancy is an exclusion criteria and is confirmed at time of surgery. Pregnancy post-intervention is not considered an AE or SAE; however, the Investigator will collect pregnancy information for any female participants who become pregnant during the 30-day follow-up period post-intervention. The Investigator will record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

All pregnant female participants will be followed up until following the outcome of the pregnancy.

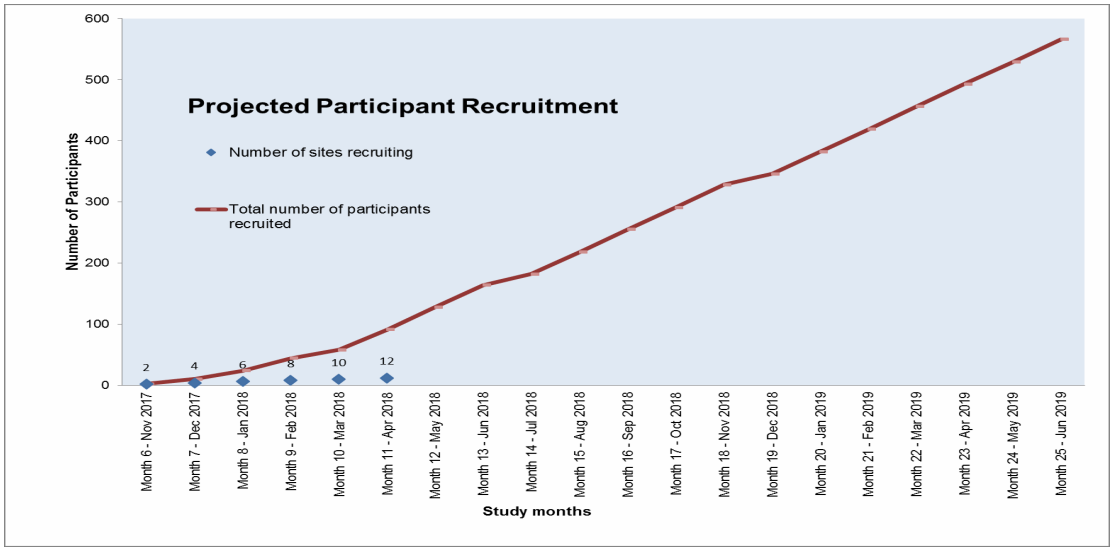
There is no teratogenic effect of lidocaine on the male reproductive system; therefore pregnancies in female partners of male participants will not be recorded or followed up.

12. RECRUITMENT PROJECTIONS & TIMETABLE

12.1 Recruitment rates and expected throughout per centre

Pilot study data and literature review has suggested that at a conservative estimate approximately a third of patients will suffer from delayed return of gut function in an estimated 90 to 250 cancer resections per unit per year (National Bowel Cancer Audit Project 2015). Our Targinact study(4) showed that patient interest and participation was high (only 2 out of 82 patients declined to participate, 62 randomised of 82 approached). Therefore we would expect that with 12 centres open and 11 of these recruiting 3.3 participants per month per centre (36 to 37 in total per month) we would expect to achieve our target of 562 participants over a 20 month recruitment period. The 20 month recruitment period allows for a staggered site set up, lower recruitment during peak holiday times (Christmas and summer) and in the first month of site set up. At the outset of the study, the projected recruitment was modelled as below in Figure 1.

Figure 1 – Recruitment projections



The projected recruitment was reprofiled in2019. Due to delays in study and site set-up, and lower than anticipated recruitment rates, an extension application to the recruitment period was approved by the funder, extending recruitment to June 2021. COVID-19 had impacted on these projections (recruitment paused on xx March 2020) and the ongoing impact is, as yet, unclear. Figure 2 shows the revised projected participant recruitment which has been updated to take account of the current pause in recruitment – the projections may be further revised depending on how quickly recruitment restarts at the sites.

Figure 2: Revised projected participant recruitment

12.2 Internal pilot study

We will include an internal pilot study with the sole purpose of demonstrating that recruitment is feasible. We have assumed that we can recruit 562 participants in 12 sites over 20 calendar months of recruitment. This equates to 3.3 recruits per centre per month. We will recruit 2 centres in each calendar month from study month 6 (see graph above), reaching the full 12 sites by end of month 11. By the beginning of calendar month 12 i.e. 6 months after recruitment has begun, with 14 months of recruitment at full capacity to run), we would expect to have aggregated 36 centre months of recruitment, with an expected randomised total of 119. See section 11.3 below for the associated stop-go criteria,

12.3 Stop/go criteria

If we assume that each centre month follows an identical independent distributed Poisson with mean (and variance) 3.3, then the expected total at the end of month 12 will follow an approximate Normal distribution with mean 119 and SD 11. We therefore propose an 'abandon/modify/continue' algorithm in which we abandon if the number randomised is >4 SD lower (i.e. 119-44 = 75), we modify (e.g. more centres, and/or improved recruitment techniques) if between 4 and 2 SD (i.e. 75 – 97); and we continue if within 2 SD i.e. total >97. Progress will be discussed at this milestone with the HTA as funder, taking into account all relevant information including any interim safety data, on the recruitment process to date.

12.4 Project timetable and milestones

The projected start date for study funding is 1 June 2017: the study duration was initially designed to be 36 months (See figure 3) and was extended by 24 months to 60 months in total. Milestones are: prefunding: multicentre research ethics and central R&D approvals; month 1-5: Study set-up authorisations; months 6-25: patient recruitment; months 7-30 (plus extended recruitment period of 24 months): patient follow up at 90 days (plus 2 months for data retrieval); months 55-60: analysis of data, interpretation of results, report writing and dissemination. The trial will continue to 31 May 2022. The Gantt chart was updated based on the approval of the recruitment extension of 24 months. The updated Gantt chart is shown below in Figure 4. The planned record linkage is not included in this time-table.

Figure 3 – Gantt chart

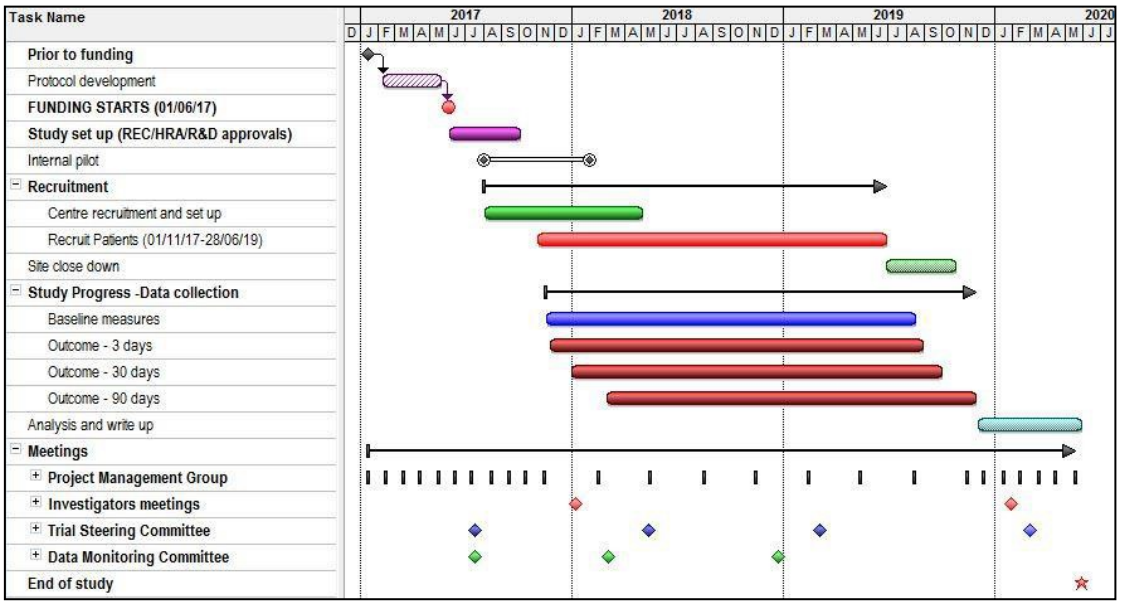
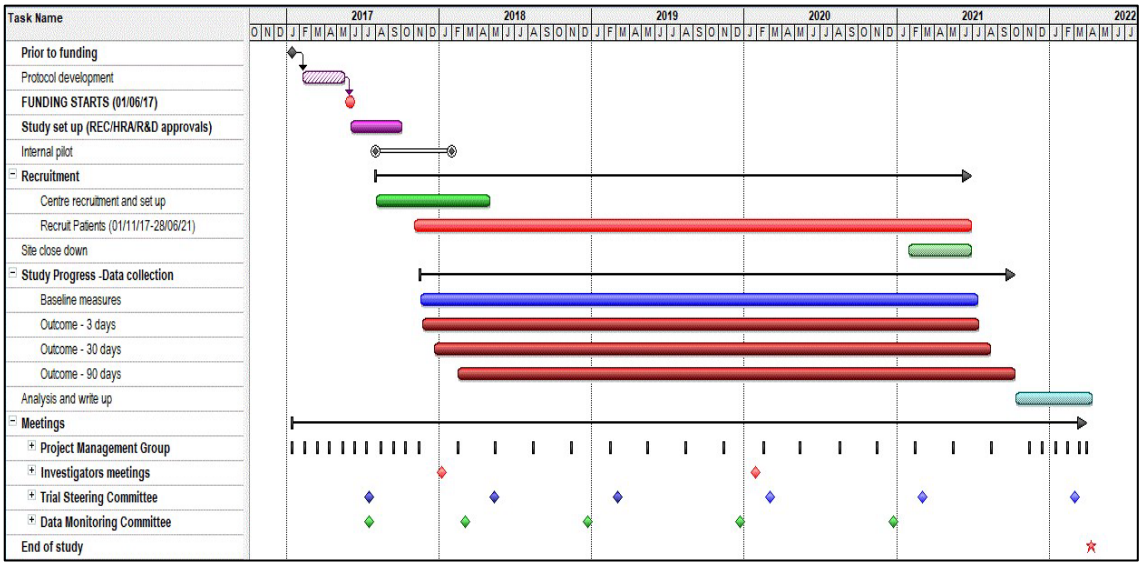


Figure 4 – Updated Gantt chart



13. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), a Trial Manager and coordinating nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Clinical Trial Site Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

The trial management group will meet quarterly to review trial progress, address issues etc. Grantholders and trial staff will be invited to these meetings.

13.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the names and contact details of the members, the roles and responsibilities of the committee and frequency of their meetings are detailed in CR0015 TSC Charter. The TSC charter will be filed in the Trial Master File.

13.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee, the names and contact details of the members, the roles and responsibilities of the committee and frequency of their meetings are detailed in CR0015 DMC Charters.

The DMC Charter will be signed by the appropriate individuals prior to the trial commencing.

13.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

13.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co- sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

13.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote

monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary.

14. GOOD CLINICAL PRACTICE

14.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met. A favorable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior tocommencement of the study.

14.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

14.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

14.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must begiven sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will retain a copy and a copy will

be filed in the participant medical notes. A copy will also be held in the TMF.

14.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

14.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site. The source data plan identifies which source data correspond to CRF data and states which data are recorded directly into the CRF.

14.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files (ISFs). Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

14.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training or training commensurate with their role.

14.3.6 Confidentiality

All evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

15. STUDY CONDUCT RESPONSIBILITIES

15.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Sponsor for classification and authorisation.

Any amendments concerning modification of the intended use of the IMP or placebo will be notified to Tayside Pharmaceuticals for review and comment.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

Following approval, ACCORD will provide Tayside Pharmaceuticals with a copy of the amended protocol and associated documents.

15.2 PROTOCOL NON-COMPLIANCE

15.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

15.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

15.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.

Deviation logs / violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on **+44 (0)131 242 9447** or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

15.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

15.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

15.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 10 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

15.6 END OF STUDY

The end of study is the last clinical follow-up which is defined as the last participant's last clinical data collection (day 90).

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@ed.ac.uk.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.

Upon completion of the study, the Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gov.uk) once the result-related information has been uploaded to EudraCT, with 'End of trial: result-related information: EudraCT 2017-003835-12 as the subject line. The Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

15.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Not applicable – participants will be given a single infusion of lidocaine (or placebo) at the time of their colorectal surgery.

15.8 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

□ The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

□ Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.

□ Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

□ The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

16. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

16.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

16.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

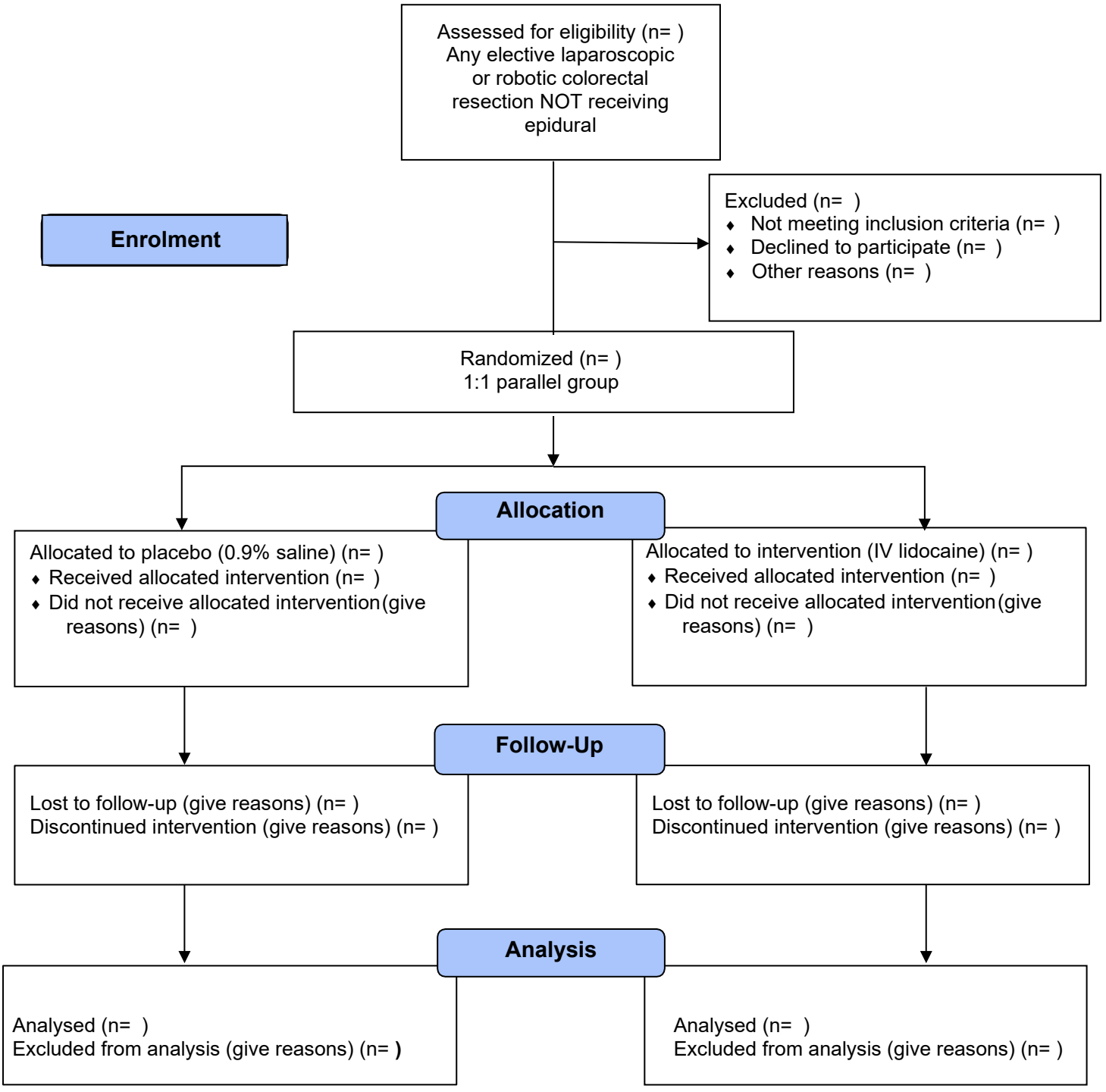
16.3 DATA SHARING

Consent will be sought from participants to permit sharing of anonymised data with funders and collaborators or published on publically available resources as appropriate.

17. PEER REVIEW

The protocol/trial design has been peer reviewed by all authors (HMP, AB, SN, IF, JN, DS); by the CHaRT study team (GM, SC, SC, AM); and by the funder (NIHR-HTA).

APPENDIX 1: Study Algorithm Flow chart



APPENDIX 2: Overall Benefit of Analgesia Score (OBAS)

To calculate the OBAS score, compute the sum of scores in items 1–6 and add [4-score in item 7]. For example, a patient with minimal pain (NRS1⁄4), severe vomiting (NRS 4/4), and no itching, sweating, and freezing who is slightly dizzy (NRS1⁄4) and is not very satisfied with his postoperative pain treatment (NRS1⁄4) has an OBAS of 8. Note that a low score indicates high benefit

1. *Please rate your current pain at rest on a scale between 0⁄4 minimal pain and 4⁄4 maximum imaginable pain*
2. *Please grade any distress and bother from vomiting in the past 24 h (0⁄4 not at all to 4⁄4 very much)*
3. *Please grade any distress and bother from itching in the past 24 h (0⁄4 not at all to 4⁄4 very much)*
4. *Please grade any distress and bother from sweating in the past 24 h (0⁄4 not at all to 4⁄4 very much)*
5. *Please grade any distress and bother from freezing in the past 24 h (0⁄4 not at all to 4⁄4 very much)*
6. *Please grade any distress and bother from dizziness in the past 24 h (0⁄4 not at all to 4⁄4 very much)*
7. *How satisfied are you with your pain treatment during the past 24 h (0⁄4 not at all to 4⁄4 very much)*

APPENDIX 3: PONV impact scale score

1. Have you vomited or had dry-retching*?

0. No
1. Once
2. Twice
3. Three or more times

Q2. Have you experienced a feeling of nausea ("*an unsettled feeling in the stomach and slight urge to vomit")?* If yes, has your feeling of nausea interfered with activities of daily living, such as being able to get out of bed, being able to move about freely in bed, being able to walk normally, or eating and drinking?

0. Not at all
1. Sometimes
2. Often or most of the time
3. All of the time.

To calculate the PONV Impact Scale score, add the numerical responses to questions 1 and 2. A PONV Impact Scale score of ≥5 defines clinically important PONV.

**count distinct episodes: several vomits or retching events occurring over a short time frame, say 5 min, should be counted as one vomiting/dry-retching episode; multiple episodes require distinct time periods without vomiting/dry-retching.*

See Miles P. and Wengzrtizky R. Simplified postoperative nausea and vomiting impact scale for audit and post-discharge review. British Journal of Anaesthesia 108 (3): 423–9 (2012)

APPENDIX 4: The QoR-15 Quality of Recovery Scale

reproduced from Stark PA, Myles PS, Burke JA. Anesthesiology. 2013 Jun;118(6):1332-40

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____ ____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time

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