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Ileus Management International (IMAGINE): Protocol for a multicentre, observational study of ileus after colorectal surgery

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Abstract

Aim: The management of postoperative ileus (POI) following colorectal surgery remains controversial. It is the commonest complication after elective colorectal resection and is associated with an increased incidence of postoperative adverse events. The prevention and management of POI remains unstandardised. This study aims to describe an international profile of gastrointestinal recovery after colorectal surgery and will assess the role of non-steroidal anti-inflammatory drugs (NSAIDs), when used as postoperative analgesia, in expediting the return of gastrointestinal function.

Methods: A multi-centre, student- and trainee-led, prospective cohort study will be conducted across both in Europe and Australasia. Adult patients undergoing elective colorectal resection during two-week data collection periods between January and April 2018 will be included. A site-specific questionnaire will capture compliance to Enhanced Recovery After Surgery (ERAS) components at participating centres. The primary outcome is time to gastrointestinal recovery, measured using a composite outcome of bowel

function and oral tolerance. The impact of NSAIDs on gastrointestinal recovery will be evaluated along with safety data with respect to anastomotic leak, acute kidney injury and complications within 30 days of surgery

Discussion: This protocol describes the methodology of an international, observational assessment of gastrointestinal recovery after colorectal surgery. It discusses key challenges and describes how the results will impact on future investigation. The study will be conducted across a large student- and trainee-led collaborative network, with prospective quality assurance and data validation strategies.

Introduction

Post-operative ileus (POI) is common after colorectal surgery, with an estimated incidence of 10-20% following elective colonic resection [1]. Numerous groups have attempted to distinguish “normal” return of gastrointestinal function from “prolonged”, or “pathological” POI. Pathological POI is characterised by delayed gastrointestinal recovery and is associated with an increased risk of postoperative adverse events which include malnutrition, pneumonia, acute kidney injury (AKI) and even death [2]. POI has a major impact on health resources as it prolongs the duration of hospital stay which has major financial implications. In the United States (US), these account for USD \$1.47 billion (£1.15; €1.24 and AUD \$1.86 billion according to 2017 exchanges) in additional healthcare expenditure per year [3].

A number of individual and multimodal interventions to reduce or prevent POI have been proposed including chewing gum, epidural analgesia, mu-opioid antagonists and intravenous lidocaine. However, complex interactions between interventions and unstandardised outcome measures have limited their translation into clinical practice [4-6]. Enhanced recovery protocols employ multimodal strategies to optimise postoperative recovery [7]. These are associated with improvements in gastrointestinal recovery, but compliance to individual components (and subsequent outcomes) are variable [8,9]. Consequently, POI has been recognised as a key area of unmet clinical need in colorectal surgery [10].

The causes of POI are incompletely understood. Current evidence describes a complex relationship between inflammatory, neurogenic, and vagal mechanisms, which are exacerbated by the effects of opioid analgesia and other homeostatic imbalances [11, 12]. RCTs of non-steroidal anti-inflammatory drugs (NSAIDs) have demonstrated significant improvements in gastrointestinal recovery, likely through their anti-inflammatory and opioid-sparing properties [13,14]. Although NSAIDs appear to offer effective postoperative analgesia, concerns remain over their safety, including the risk of AKI and anastomotic leak [15-17].

This manuscript describes a protocol for an international prospective cohort study on POI following colorectal surgery. The safety and impact of NSAIDs on gastrointestinal recovery will be explored. Key methodological features are discussed, as well as strengths and limitations of the study design.

Methods

In the absence of more appropriate reporting guidelines, the content of this protocol is described according to relevant items of the SPIRIT Checklist (Standard Protocol Items: Recommendations for Interventional Trials) [18]. Its design has been guided by the results of a pilot study performed in a comparable patient cohort across ten centres in the United Kingdom [19]. Although patients have not been involved in the design of the study, patient and public involvement will be a key feature in the dissemination of results. The study was prospectively registered on the Research Registry Service (www.researchregistry.com) prior to commencement of data collection (UIN: 3072).

Study Objectives

The primary aim of this study is to profile postoperative gastrointestinal recovery following elective colorectal surgery. The secondary aim is to assess the efficacy and safety of NSAIDs in shortening the time to gastrointestinal recovery when administered as postoperative analgesia in the first three days after surgery. This will inform the design and delivery of future interventional studies aimed at reducing the incidence, duration and impact of POI.

Study Design

A snapshot, multicentre, prospective international cohort study will be delivered by the EuroSurg Collaborative and its partners. EuroSurg is a student- and trainee-led collaborative group with active networks in multiple European and Australasian countries [20]. It is coordinated by a steering committee of student and trainee surgeons, supported by the European Society of Coloproctology (ESCP) [21]. The model of student- and trainee-led collaborative groups has been described in detail elsewhere [22]. This comprises small teams of collaborators collecting data across multiple hospitals over short periods of time, typically several weeks.

Study Setting

Any centre within a member nation of the ESCP or the Royal Australasian College of Surgeons (RACS) performing elective colorectal surgery will be eligible to participate. Each centre may contribute data in up to three pre-determined data collection periods between January and April 2018. Each period will have a duration of 14 consecutive days (Box 1). All patients will be followed for 30 days.

Centre-specific Questionnaire

A centre-specific questionnaire will be distributed. This will determine adherence to Enhanced Recovery After Surgery (ERAS) criteria at each participating hospital [7]. Responses will be anonymised and no centre-specific comparisons will be performed. The questionnaire is provided in Supplementary Document 1.

Eligibility Criteria

Patients undergoing elective colorectal resection, or reversal of colostomy or ileostomy, will be eligible.

Each of the following criteria must be satisfied for inclusion in the study:

- Adult patients (18 years or above)
- Elective colorectal resection procedures. These should be planned and booked in advance of routine hospital admission. A full list of eligible procedures is described in Box 2.
- Procedures performed using any surgical approach, including open, laparoscopic, and robotic surgery.

Patients who fulfil any of the following criteria will be excluded:

- Procedures performed on an emergency or unplanned basis
- Appendectomy (emergency or elective)
- Transanal surgery not involving an external skin incision (including transanal endoscopic microsurgery and transanal minimally invasive surgery)
- Procedures for primary gynaecological, hepatobiliary, urological or vascular pathologies
- Diagnostic procedures (including laparoscopy or laparotomy) which does not subsequently lead to colorectal resection or reversal of stoma.

Outcomes

The primary outcome is time to gastrointestinal recovery (GI-2). This is defined as the time when the following two events are met [23]:

- (1) tolerance to oral intake (solid or soft food) in the absence of vomiting
- (2) first passage of stool

In order to determine the GI-2 outcome, patients will be reviewed daily for 10 days following surgery. In patients discharged before satisfying these criteria, the day of discharge from hospital will be accepted as a GI-2 outcome. This surrogate endpoint will be explored in a sensitivity analysis. The secondary outcome is the rate of postoperative adverse events occurring within 30 days of surgery. These will be measured using the Clavien-Dindo classification, with the highest graded complication recorded for each patient (minor: Grades: I-II; major: Grades III-V) (Table 1) [24]. Specific recorded adverse events will include the rate of anastomotic leak, postoperative pneumonia and AKI (Table 2) [25].

Other Variables

The main variable of interest is postoperative NSAID administration in the first three days after surgery. Other variables which will be collected are those known to significantly impact on the rate of gastrointestinal recovery, and that are readily accessible within the limitations of an observational study. These include: previous abdominal surgery; cardiovascular or metabolic comorbidities (including chronic obstructive pulmonary disease, ischaemic heart disease, peripheral vascular disease and diabetes mellitus); open surgical approach; transfusion of red blood cells and postoperative opioid administration [26].

Data Collection & Management

A full list of data points is provided in Table 3. All data will be collected prospectively and stored via the Research Electronic Data Capture (REDCap) service [27], hosted by the Birmingham Clinical Trials Unit at the University of Birmingham. REDCap is a secure online service used widely by academic organisations throughout the world. All data transmissions and storage via REDCap are encrypted and no patient

identifiable information will be collected. Anonymous data will be pooled and analysed, with no surgeon- or centre-specific comparisons performed.

Power Calculation

The study is powered based on the comparison of GI-2 between patients that receive NSAIDs and those that do not. Preliminary data for gastrointestinal recovery were available in 207 patients over 10 days of postoperative follow-up in a similar patient cohort [19]. The distribution of gastrointestinal recovery in this study (measured in days) was heavily skewed so values were $\log_{10}$ -transformed. This gave a mean $\pm$ standard deviation of $\log_{10}[\text{days}]$ of 0.47 ± 0.25 and, hence, a geometric mean of 2.9 days. Minimal detectable differences were calculated according to this assumed distribution and an NSAID administration rate of 15%, as demonstrated by a previous study in a comparable population [28]. The calculation was based on an independent samples t-test on the $\log_{10}$ -transformed data, with 5% alpha and 80% power. The minimal detectable difference in gastrointestinal recovery between both groups were found to be 8.0% and 6.6% for total sample sizes of 3,500 and 5,000, respectively (i.e. differences of 0.033 and 0.028 in $\log_{10}[\text{days}]$). This is equivalent to a difference in the average time to gastrointestinal recovery between groups of approximately 0.2 days. In the current study, a difference of 1 day is the smallest recordable difference and the minimum for which is considered clinically meaningful.

Statistical Analysis

Initial analyses will be performed to evaluate differences between patients that receive NSAIDs, and those that do not. Continuous variables will be assessed for normality, prior to analysis, and will be compared between groups using independent samples t-tests if normally distributed, and Mann-Whitney tests otherwise. Ordinal variables will be assessed using Mann-Whitney tests, with χ^2 -tests applied to nominal variables.

Associations between these variables and patient outcomes will be performed using univariable analyses, followed by multivariable models to identify independent predictors of outcomes. Assessment of the primary outcome of time to GI-2 is complicated by the fact that this will remain unknown in two groups of patients: 1) those where the time to GI-2 is greater than 10 days and 2) those who die in hospital or are discharged before it occurs. Although these groups are expected to be small, excluding these patients would result in selection bias. As such, the analyses of time to GI-2 will be performed using two approaches. The primary approach will treat time to GI-2 as a continuous variable. Univariable analyses will be performed using Mann-Whitney or Kruskal-Wallis tests for nominal factors, and Spearman's rho for comparisons with ordinal or continuous factors. Multivariable analyses will use general linear models, with the time to GI-2 being $\log_{10}$ -transformed prior to analysis, in order to reduce skew in the distribution. Those patients where the time to GI-2 is unknown will initially be excluded from the analysis, but sensitivity analyses will be performed with these patients considered as having a "long" time to GI-2, arbitrarily set at 11 days. The results of the primary and sensitivity analyses will be compared to check for consistency, with further investigation performed where discrepancies are identified. The second approach will use a time-to-event methodology, with patients censored at the point of death or discharge, or at the end of 10 days. Univariable analyses will use Kaplan-Meier curves, with comparisons across groups performed using log-rank tests. Multivariable analyses will be performed using Cox regression models.

Analyses of complication rates will treat complications as a binary variable, with the outcome of interest being either a complication of any grade, or Clavien-Dindo classification grades III-V. Univariable analyses will be performed using independent samples t-tests, Mann-Whitney tests and χ^2 -tests, whilst multivariable analyses will use binary logistic regression models. Throughout the analysis, p-values less than 0.05 will be deemed to be indicative of statistical significance.

Study Delivery & Quality Assurance

National student- and trainee-led committees will lead the study in participating countries, with overall coordination provided by a study steering committee. The study protocol will be disseminated through country specific channels, organisations and social media platforms, including the #colorectalsurgery hashtag following via Twitter [29]. A team of students and trainees at each participating centre will be responsible for data collection with support from a nominated senior surgeon. All collaborators will be required to complete an online e-learning package relating to the REDCap data capture service and the assessment of study outcome measures. A process of data validation by independent assessors will be performed on a sample of participating centres in each country.

Governance & Ethics

The study will proceed through appropriate country-specific governance and ethical approval processes. Where formal approval processes are required, confirmation of this will be required from national or local collaborators prior to the commencement of data collection. As an observational evaluation of normal clinical practice, with no planned change to routine care, the authors consider that there are no ethical issues. In the United Kingdom, ethical review by the South-East Scotland Research Ethics Service and the NHS Health Research Authority has confirmed IMAGINE does not require formal ethical approval, and it can be registered at eligible centres as a clinical audit.

Discussion

Recent evidence suggests that the management of POI should be a research priority in patients undergoing colorectal surgery. [10]. This study will produce a generalisable profile of gastrointestinal recovery, and its management across diverse, international settings, supporting the design of future interventional trials. The study will also explore the impact of NSAIDs on gastrointestinal recovery and their safety profile.

Student- and trainee-led studies empower experiential learning in research methods and IMAGINE will extend this platform across multiple countries [30]. This will build and sustain an already established network of international junior surgeons and promote multinational collaboration. Prospective quality assurance and data validation methods will attempt to maximise internal validity.

POI remains one of the commonest complications after elective colorectal surgery [1]. Epidural analgesia and mu-opioid receptor antagonists (such as Alvimopan®) have been successful in reducing the duration of POI and preventing delayed hospital discharge in previous, high quality RCTs [5, 31]. Conversely, the role of chewing gum (sham feeding) and pro-kinetic agents, when used as targeted postoperative therapies, remain contentious [4, 31]. NSAIDs have been recommended for the prevention and reduction of POI and are included in some enhanced recovery protocols for postoperative analgesia [7]. They are readily available and offer favourable opioid-sparing and anti-inflammatory properties. However, concerns over their safety profile after colorectal surgery persist [32]. The nephrotoxic effects of NSAIDs after non-cardiac surgery are well understood, and whilst commonly mild, these are associated with 1-year postoperative mortality [17]. More recently, data from large, prospective databases have identified an association between NSAIDs and anastomotic leak, although this finding is inconsistent [15, 16]. Previous RCTs assessing the role of NSAIDs in reducing POI have demonstrated favourable outcomes for gastrointestinal recovery, but these are not powered to evaluate the risk of serious adverse events [13, 14].

A number of challenges are recognised in the design and delivery of this study. Firstly, the definition and choice of outcome measure for POI is poorly standardised. In 2017, Wolthuis and colleagues identified five unique definitions used in previous colorectal RCTs and four used in non-randomised studies [33]. This is despite previous efforts to reach international consensus on standard endpoints and definition [34, 35]. Such heterogeneity is problematic for performing reliable comparisons between studies and translating meaningful results into clinical practice. Measurements of gastrointestinal recovery using composite outcomes such as GI-2 (time to first stool and food tolerance) or GI-3 (time to first stool and/or flatus and food tolerance) avoid arbitrary assessment criteria and may produce more meaningful outcomes [23]. In a

pilot study performed in a comparable U.K. cohort, measurements of GI-3 provided a feasible assessment of gastrointestinal recovery, but challenges related to the measurement of flatus persisted [19]; passage of flatus can occur at night or remain unnoticed in the presence of a stoma. In the current study, the GI-2 outcome has been chosen as it provides an outcome which is simple to collect in an observational setting. It is hoped that this will provide a widely applicable and easy translatable outcome across diverse healthcare settings.

Secondly, due to the study's "snap-shot" design, a pragmatic decision was made to rationalise the volume and accuracy of data points in order to maximise its feasibility across an international network. Although compliance to enhanced recovery protocols is closely related to POI, per-patient compliance is beyond the scope of this study. Instead, a centre-specific survey of ERAS items will be administered and the results incorporated into statistical models [7, 8]. The collection of per-patient opioid doses also represents a challenge. Although these are significantly associated with delayed gastrointestinal recovery [36], their bioavailability according to dynamic changes in renal function presents difficult to control factors in determining morphine equivalent doses. In the current study, the need for weak versus strong opioid analgesia will be used as a surrogate marker for analgesic requirements. This is informed by the World Health Organisation recommendations for cancer pain, with definitions for strong versus weak opioids derived from guidelines by the Scottish Intercollegiate Guidelines Network [37].

Finally, the model of collaborative, student- and trainee-led research is established throughout Europe and Australasia [22]. This network facilitates the inclusion of large numbers of patients in "snap-shot" research studies across short study periods, generating hypotheses for future interventional studies. The accuracy and completeness of data collected using this methodology must be monitored. In the IMAGINE study, a package of quality assurance measures will be disseminated to ensure methodological rigour and uphold the quality of resulting data: (i) a structured network of senior support will give supervision for students and trainees for quality assurance and compliance with local governance and ethical requirements; (ii) a programme of e-learning will provide training in assessment of primary and secondary outcome measures,

eligibility criteria and data collection; (iii) a prospectively considered process of data validation will be performed by independent assessors in participating centres in each country.

Dissemination of this protocol across international settings will maximise the study's uptake and improve recognition of gastrointestinal recovery as an unsolved problem after colorectal surgery. The study is open to new registrations until the commencement of the final data collection period.

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Box 1: Data Collection Periods

Data Collection Periods:

- **Period 1:** 22 January 2018 – 5 February 2018
- **Period 2:** 12 February 2018 – 26 February 2018
- **Period 3:** 5 March 2018 – 19 March 2018

Each data collection period is followed by 30-days of follow up. The latest day of follow up (30 days after the final included patient) is 17 April 2018

Box 2: Included Procedures

All of the following colorectal procedures are eligible for inclusion:

- Ileocolic resection
- Right hemi-colectomy
- Extended right hemi-colectomy
- Transverse colectomy
- Left hemicolectomy
- Sigmoid colectomy (including Hartmann's Procedure)
- Anterior Resection
- Sub-total colectomy
- Total colectomy
- Pan-proctocolectomy
- Completion colectomy
- Abdominoperineal resection (APER)
- Reversal of ileostomy or colostomy

Table 1 – Clavien-Dindo Classification

Grade	Description
I	Any deviation from the normal postoperative course without the need for pharmacological (other than the 'allowed therapeutic regimens'), surgical, endoscopic or radiological intervention. Allowed therapeutic regimens are: selected drugs (anti-emetics, anti-pyretics, analgesics, diuretics and electrolyte replacement), physiotherapy and wound infection opened at the bedside but not treated with antibiotics.
II	Requiring pharmacological treatment with drugs beyond those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
III	Requiring surgical, endoscopic (must be therapeutic) or radiological intervention
IV	Life-threatening complications requiring critical care management, neurological adverse events including brain haemorrhage and ischaemic stroke (exclude transient ischaemic attack)
V	Death of a patient

Table 2 – Secondary Outcome Measures

Adverse Event	Description
Anastomotic leak	Defined according to leakage detected radiologically or at the time of re-operation
Pneumonia	Defined radiologically (plain film or cross-sectional)
Acute kidney injury	Defined according to Kidney Disease Improving Global Outcomes (KDIGO) Guidelines [25]

25: Kidney Disease Improving Global Outcomes. KDIGO Clinical Practice Guideline for acute kidney injury. Kidney Int. 2012;2(Suppl 1):1–138.

Table 3 – Data collection points

Preoperative data points			
1	Age	[Years]	
2	Gender	Male, Female	
3	ASA grade	I, II, III, IV, V	
4	Smoking status	Smoker, Non-smoker	
5	Body Mass Index	Underweight (<18.5); Normal range (18.5-24.9); Overweight (25-29.9); Obese (30+)	
6	History of any abdominal surgery	Yes, No	
7	Pre-existing abdominal stoma	Yes – colostomy, Yes – ileostomy, No stoma	
8a	History of ischaemic heart disease	Yes, No	
8b	History of peripheral vascular disease	Yes, No	
8c	History of chronic obstructive pulmonary disease	Yes, No	
8d	History of diabetes mellitus	Yes (insulin controlled), Yes (tablet/diet controlled), No	
9a	Preoperative administration of ACEi/ARB	Yes, No	
9b	Pre-operative creatinine (most recent pre-op)	[Value]	
Operative data points			
10	Underlying pathology/indication	Malignancy, Inflammatory bowel disease, Diverticular disease, Other benign	
11	Operative approach	Open, Laparoscopic, Lap-assisted, Robotic	Converted open? Converted to Laparoscopic?
12	Primary operation performed	ileocolic resection, right hemi-colectomy, extended right hemi-colectomy, transverse colectomy, left hemi-colectomy, sigmoid colectomy, anterior resection, sub-total colectomy, total colectomy, pan-proctocolectomy, completion colectomy, reversal of ileostomy/colostomy, abdominoperineal resection (APER)	
13	Formation of new stoma	Yes – colostomy, Yes – ileostomy, No stoma	
Daily postoperative data points (Data collected each day for up to 10 days)			
14	Passage of stool At least one episode per rectum or stoma	Yes, No	

15	Vomiting At least one episode of vomiting	Yes, No
16	Oral Intake Record greatest status per day	Yes - <i>Solid Diet (including soft)</i> , Yes - <i>fluids only</i> , No
17	Nasogastric tube in situ For drainage (not feeding)	Yes, No
Once only postoperative data points		
18a	NSAIDs administration on POD 1-3	Low Dose, High Dose, None *
18b	NSAIDs administration on PO 4-7	Low Dose, High Dose, None *
19a	Opioid administration on POD 1-3	Yes – <i>strong</i> , Yes – <i>weak</i> , No Ψ
19b	Opioid administration on POD 4-7	Yes – <i>strong</i> , Yes – <i>weak</i> , No Ψ
20	Postoperative adjunctive analgesia on POD 1-10	Epidural, Spinal, IV PCA, Wound catheter, None
21	Postoperative chewing gum on POD 1-10	Yes, No
22	Postoperative Mu-opioid antagonist on POD 1-10	Yes, No
23	Postoperative pro-kinetic drug use on POD 1-10	Yes, No
24	Transfusion of red blood cells on POD 1-10	Yes, No
Outcome data points		
25a	Anastomotic leak Radiological or intra-operative diagnosis	Yes, No
25b	<i>If yes, POD of diagnosis</i>	[Value]
26	Intra-abdominal/pelvic collection Radiological or surgical diagnosis	Yes, No
27	Bronchopneumonia Radiological diagnosis	Yes, No
28	C-reactive Protein <i>Highest value recorded between POD 1-3</i>	[Value]
29	Creatinine (Daily day 1-7)	[Value]
30	Length of hospital stay (days)	[Value]
31	30-day readmission	Yes, No
32	Highest Clavien-Dindo Grade	I, II, III, IV, V

* Scottish Intercollegiate Guidelines Network (SIGN) [37]

Ψ Comparative Effectiveness Reviews, No. 4. [38]

ASA: American Society of Anesthesiologists; ACEi: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin II Receptor Blocker; IV: intravenous; NSAID: non-steroidal anti-inflammatory drug; PCA: patient-controlled analgesia; POD: postoperative day;