IMAGINE: Ileus MAnaGement INtErnational

An international, observational study of postoperative ileus and provision of management after colorectal surgery

Study protocol v2.1

28th August 2017 [Final]

Ileus MAnaGement INtErnational

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	#IMAGINE #colorectalresearch #colorectalsurgery

Key Study Dates:

Study registration opens:	1st Sep 2017
Study launch at ESCP Annual Meeting	21st Sep 2017 (20-22nd Sep 2017)
Data collection starts	22nd Jan 2018

Collaborative Partners

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Study co-ordination

Representatives to Management Group

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Viktoria Schaeff	Latvia		**Ross Goodson**	UK & ROI
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National network committees

In each participating country, a national network committee is responsible for disseminating and running the study. Consultant (attending) surgeons act as a link between participating students in their country and their national colorectal or surgical association.

Students and trainees from other ESCP or RACS member countries are also welcome to participate in EuroSurg. Please contact us at info@eurosurg.org for further information.

Key contacts:
For matters relating to mini-team setup and study registration, please contact your local or national lead (details at www.eurosurg.org). For general enquiries concerning the protocol, please contact the study management group by email (info@eurosurg.org) or on Twitter (@EuroSurg).

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Study timeline

Jul 2017	• Provisional IMAGINE protocol released
Aug 2017	• National committees established • Collaborators can register IMAGINE at their hospital
Sep 2017	• Final IMAGINE protocol released • EuroSurg Collaborators Meeting, ESCP (Berlin)
Oct-Dec 2017	• Application for REDCap Logins open • Participating sites seek governance/ethical approvals
Jan 2018	• **Study Inclusion Period 1:** 0800AM 22 Jan 2018 – 0800AM 5 Feb 2018
Feb 2018	• **Study Inclusion Period 2:** 0800AM 12 Feb 2018 – 0800AM 26 Feb 2018
Mar 2018	• **Study Inclusion Period 3:** 0800AM 5 Mar 2018 – 0800AM 19 Mar 2018
Apr 2018	• Completion of 30-day follow up Last patient followed up on 17th April 2018
May 2018	• Deadline for REDCap data uploads: 31 May 2018
Jul 2018	• Manuscript writing
Sep 2018	• Results presented at EuroSurg Session, ESCP 2018

About EuroSurg

The EuroSurg collaborative is an international audit and research group led by students and surgical trainees (1). It was founded at the European Society of Coloproctology (ESCP) meeting in 2015 and has evolved quickly with active members in over 10 European and International countries. EuroSurg aims to build a new generation of research active, internationally-linked surgeons.

Details of previous EuroSurg studies may be found on our website, eurosurg.org

The model for trainee-led research collaboratives was pioneered in the UK by local networks of trainee surgeons (2). These networks were successful in delivering major surgical research initiatives, including multicentre cohort studies and randomised controlled trials (RCTs). The feasibility of students conducting similar projects was first demonstrated by the Student Audit & Research in Surgery (STARSurg) group, which delivered several national cohort studies in the UK (3,4).

Collaboration across international surgical communities produces transferable results which may inform the design of future RCTs and drive changes in clinical practice. Through participating in the EuroSurg project, students and trainees will acquire essential skills in surgical research methodology (5). EuroSurg will replicate previous groups' successful authorship policy, which designates PubMed-citable co-authorship to all student and trainee collaborators. An example of this authorship model can be found here: https://www.ncbi.nlm.nih.gov/pubmed/27321766.

Postoperative Ileus: Background

Post-operative ileus (POI) is common after colorectal surgery, with an estimated incidence of 12% (6). It is characterised by a delayed return of bowel function and is associated with increased postoperative complications. Whilst once regarded as an obligatory component of postoperative recovery, the resulting delays in hospital discharge are burdensome for patients and the subsequent costs are substantial for healthcare systems ($1.47 billion in the United States [£1.15; €1.24; AUD 1.86)] (7).

Enhanced recovery protocols and targeted interventions (such as chewing gum and epidural analgesia) have been tested in efforts to reduce POI but the evidence for many of these remains contentious (8,9). Non-steroidal anti-inflammatory drugs (NSAIDs) may improve the return of bowel function through their anti-inflammatory and opioid sparing properties (10,11), however concerns over their safety (such as the risk of acute kidney injury and anastomotic leak) persist. Recent evidence from large prospective cohort studies have introduced renewed equipoise in the use of NSAIDs after elective colorectal surgery and they remain recommended for use by enhanced recovery guidelines (3, 12, 13).

The IMAGINE study will be launched at a dedicated EuroSurg parallel session during the ESCP conference in Berlin (20-22 September 2017). It will aim to produce a profile of postoperative ileus and its management across an international cohort of patients undergoing colorectal surgery. Additionally, it will assess the safety and impact of NSAIDs on the return of bowel function when used as postoperative analgesia.

Methods

01
Postoperative ileus
Throughout this study, postoperative ileus will be assessed according to the time taken for return of bowel function after surgery (measured in whole days). Return of bowel function is defined by the following two criteria:

- The patient has tolerated solid intake (no vomiting) for 24 hours
- The patient has passed stool

This composite outcome measured is commonly known as "GI-2" and is an accepted measure of postoperative bowel function (14).

02
Summary
"Mini-teams" of collaborators (medical students and trainees/residents) will participate at each hospital. They will prospectively collect data on consecutive patients undergoing elective colorectal surgery over a 14-day period.

03
Study Aims
- To characterise the incidence of postoperative ileus and its clinical management after elective colorectal surgery in an international cohort.
- To assess the effect of NSAIDs on postoperative ileus when administered within the first three days after elective colorectal surgery.
- To assess the safety of NSAIDs after elective colorectal surgery, including the risk of acute kidney injury and anastomotic leak.

04
Project Timeline
Data collection will take place between 22th January 2018 and 19th March 2018 during the following three pre-defined data collection periods:

Details about follow up data collection is found in Section 11

- Period 1: 0800 22 Jan 2018 – 0800 5 Feb 2018 (+ 30 Day Follow-up)
- Period 2: 0800 12 Feb 2018 – 0800 26 Feb 2018 (+ 30 Day Follow-up)
- Period 3: 0800 5 Mar 2018 – 0800 19 Mar 2018 (+ 30 Day Follow-up)

Each mini-team will collect data on eligible patients undergoing surgery over a 14-day data collection period. Follow-up data will also be collected for up to 30 days after surgery. The final date for follow up data collection is 17th April 2018.

▲ Multiple teams of students/trainees can participate at each centre, collecting data on patients operated during distinct 14-day periods. ▲

05

Centres

Detailed guidance for participating centre is available in Appendix D

- Hospitals in the member nations of the European Society of Coloproctology (ESCP) and the Royal Australasian College of Surgeons (RACS) that perform elective colorectal surgery may participate.
- All participating centres are required to register the study according to local regulations. Evidence of successful registration should be sent to your national network committee prior to commencement of data collection.
- Following conclusion of the study, it is a requirement that mini-teams at each centre **present their local findings** to their hospital's surgical department.

▲ Providing feedback on the project's findings to your department's clinicians is an essential step for improving care. Presenting local results will help you to develop your presentation skills & CV ▲

06

Centre-specific survey

The centre-specific survey will be made available upon study launch

Prior to study launch, a short survey will be completed by the consultant lead at each centre. This will collect data regarding enhanced recovery protocols. Completion is essential and responses will be anonymous.

07

Inclusion & exclusion criteria

▲ You should collect data on **all** consecutive patients who undergo eligible procedures at your hospital during collection periods ▲

Strategies to identify consecutive patients could include:

Daily review of elective theatre lists.
Daily review of handover sheets and ward lists.
Daily review of theatre logbooks

- **Inclusion criteria**
  - Summary: All consecutive patients undergoing colonic or rectal resection, or reversal of stoma (colostomy/ileostomy) should be included.
  - Age: Age 18 years or above.
  - Timing: Elective procedures (these should be planned and booked in advance of admission to hospital).
  - Technique: Open, robotic, laparoscopic, laparoscopically-assisted, or laparoscopic converted to open.

- Returns to theatre: Each individual patient should only be included in the IMAGINE study once. Return to theatre during the same admission or follow up should be collected as a complication
- Included procedures: Any colorectal resection **(See Appendix B)** Reversal of stoma (colostomy/ileostomy)

- **Exclusion criteria**
  - Emergency and 'unplanned' procedures
  - Appendicectomy (unless procedure involves a right hemicolectomy)
  - Transanal surgery - *e.g. TEMS, TAMIS, Altemeier's procedure.*
  - Primarily urological procedure - *e.g. ileal conduit.*
  - Primarily gynaecological procedure - *e.g. Hartmann's during ovarian surgery*
  - Primarily vascular procedure - *e.g. bowel resection during AAA repair.*
  - Diagnostic laparoscopy/laparotomy without resection of colon/rectum
  - Inguinal, incisional or femoral hernia, without resection of colon/rectum
  - Surgery involving multi-visceral surgery – *e.g. pelvic exenteration*

08
Outcome Measures

Primary outcome measure
- Time (measured in whole days) until return of bowel function (GI-2). This is a composite measure of tolerance to solid intake for 24 hours (no vomiting) AND passage of stool (14).

Information about the Clavien-Dindo scale is found in Appendix C

Secondary outcome measures
- Overall 30-day adverse event rate according to the Clavien-Dindo scale of postoperative complications (15).
- Incidence of anastomotic leak, defined according to leakage detected radiologically or during surgery
- Incidence of acute kidney injury, defined according to KDIGO (16).

09
Measuring return of bowel function
The composite outcome for return of bowel function (GI-2) should be assessed daily for the first ten days after surgery (Day 0; day of surgery – Day 10). This requires daily recordings of:

- Oral tolerance (eats solid/soft food with no vomiting in the same day)

AND

- Presence of bowel motions (at least one stool)

Strategies to record bowel function

- Speaking to ward staff, including doctors and nurses
- Reviewing patient medical and nursing notes/charts daily, particularly for events occurring at night
- Participating in daily ward rounds and doctor reviews

Remember: recordings of bowel function must correspond to the entire day. It is advised that you consider these symptoms one day in retrospect to capture all relevant data.

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Covariates

In addition to demographic, procedure and outcome data, the following data will be collected on confounding variables to permit accurate risk adjustment of outcomes. These are consistently shown to independently predict postoperative ileus after colorectal surgery in previous literature (17):

- The American Society of Anesthesiologists (ASA) score
- Cardiorespiratory and metabolic co-morbidities (includes chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), peripheral vascular disease (PVD) and diabetes mellitus
- History of previous abdominal surgery
- Transfusion of red blood cells

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Follow-up

- Patients will be followed for 30 days after surgery. All secondary outcome measures will be recorded if they occurred at any point from post-operative day 0 (day of surgery) to Day 30.
- No change to normal follow-up should take place. Collaborators should be proactive in identifying follow-up data, but this should be done according to the limits of normal follow up at their hospital.

Strategies for follow-up include:

- Regularly reviewing patient notes to identify in-hospital complications
- Participating in daily ward rounds and doctor reviews
- Reviewing clinic notes and clinic letters, if seen in clinic by 30 days
- Checking electronic systems and handover lists for re-admissions
- Checking for emergency department re-attendances

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Dataset

A full list of data fields is provided in Appendix A

Data domains that relate to the patient, operation, operative method and postoperative period will be collected. In order to maximise completion of data recording, the dataset includes only those variables that are needed to

accurately risk adjust outcomes relating to the primary study question. Without adjusting for pre-operative risk, it is likely that any findings would be biased.

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Data Analysis & Sample Size

Expert statisticians have been consulted regarding the planned analysis of this study. The data will be analysed using descriptive statistics and regression models on SPSS v21.0. If a large proportion of data are missing from specific fields, a process of imputation using the Markov Chain Monte Carlo method is planned. No surgeon-, hospital- or country-specific comparisons will be performed. The study is anticipated to include 150 centres in the UK and 150 centres in Europe and Australasia. With consideration to recent figures provided by the UK National Bowel Cancer Audit 2016, we estimate that, on average, three patients will undergo colorectal resection per week at each participating centre. Provided all centres complete at least two of three data collection periods, a sample size of 3500-5000 patients is anticipated.

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Data Collation and Governance

Printable data proformas can be found on the online study hub

Data will be collected and stored online through a secure server running the Research Electronic Data Capture (REDCap) web application. REDCap allows collaborators to enter and store data in a secure system. It is widely used by academic institutions throughout Europe and all storage of web-based information by this system is encrypted and compliant with HIPAA-Security Guidelines in the United States. The service is managed by the University of Birmingham, UK. Collaborators will be given secure REDCap server login details, allowing secure data storage on the REDCap system. No patient identifiable information will be uploaded or stored on the REDCap database. All anonymous data will be held for a total of three years, after which it will be permanently removed from the server space. Paper copies of data should be destroyed as confidential waste within the centre once uploaded to REDCap.

It will **not** be possible to store patient identification numbers (hospital numbers) on REDCap. A unique 'REDCap ID' will be generated by the system for each patient. If needed, you may wish to keep a local cross-reference of hospital numbers and REDCap IDs at your hospital. This should be kept in a secure, encrypted spreadsheet on a hospital, password-protected computer.

One REDCap login will be issued per mini-team. It will be issued to a nominated collaborator in each mini-team and **only** that person may use the login. If you experience problems, please email info@eurosurg.org.

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Local Project Registration & Data Governance

If the option is available, this project may be registered as clinical audit or service evaluation. In some countries, it may be necessary to obtain formal research ethics approval. It is the responsibility of the local mini-team at each

hospital to ensure the study is registered appropriately, according to local regulations. This should be supervised by a local consultant surgeon.

▲ Check with your supervising consultant how the study should be registered at your hospital. If you encounter difficulties **seek advice** from your national committee ▲

In the UK, the study may be registered as a clinical audit or "service evaluation". The gold standard is based on ERAS® Guidelines for Colonic Surgery, found below (13).

NSAIDs should be used as postoperative pain relief after colorectal surgery. Whilst low level evidence has suggested a link with anastomotic dehiscence, there is insufficient evidence to stop using NSAIDs.

UK collaborators should also seek their NHS trust's Caldicott Guardian's approval to submit data to the REDCap system. When registering the study, the following points should be made clear:

- All data collected will measure current practice.
- No changes to normal patient pathways/ treatment will be made.
- This is an international audit.

▲ Collaborators should complete the data governance e-learning module which will be made available on the online project hub: www.EuroSurg.org or via bit.ly/learn.IMAGINE ▲

You **must** have confirmation of successful study registration prior to commencing data collection. REDCap accounts cannot be issued until evidence is sent to your national network committee that you have successfully registered the study at your centre.

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Quality assurance

For further information about mini-teams, see Section 17.

- **Mini-teams**
  Each mini-team should include three individuals, including at least one medical student and one trainee/resident. The study should also be registered with a supervising consultant (attending) surgeon at each site.

Modules found at: bit.ly/ learn.IMAGINE

- **IMAGINE E-learning**
  To maximise the educational value of IMAGINE, and to ensure understanding of key steps, all collaborators will undertake a series of short e-learning modules. These will be evidenced by a certificate of completion. The following modules will be mandatory for participation:

    - Study set up and governance (5 minutes)
    - Measurement of bowel function (5 minutes)

- Clavien-Dindo Classification System (5 minutes)
- REDCap User Guide (5 minutes)

- **Data completeness**
  Following data collection, only data sets with >95% data completeness can be accepted for pooled international analysis. Unfortunately, centres with >5% missing data points cannot be included in the study and collaborators from those centres must be withdrawn from the publication list.

▲ Ensure complete datasets of at least 95% by collecting data prospectively. If unsure, **seek advice** from your national committee. ▲

- **Validation**
  Data validation will be performed in five hospitals in each participating country. For smaller volume countries, validation requirements may be agreed with the study management group. Data validators should be a student or a trainee/resident who were not involved in the initial data collection.

Details about validation will be available on the online study hub.

The validator will select a single 14-day study period at a local centre to validate and will take place after completion of data collection. The validator will send a summary of how many records were reviewed and error rates to the study management group. There are two components of validation:

- *Case ascertainment*
  Validators will independently identify all patients eligible for inclusion over one 14-day study period. The target for data ascertainment is >95%.

- *Data accuracy*
  Validators will independently collect data for 10 key data fields relating to risk-adjustment and outcome measures. The selection of fields will only be made available to validators. Conflicts with the data originally submitted by the relevant mini-team will be resolved by discussion between the validator and mini-team. The target for accuracy of collected data is >98%.

The outcome of data validation (case ascertainment and data accuracy) and error rates will not affect the inclusion of data in the pooled analysis.

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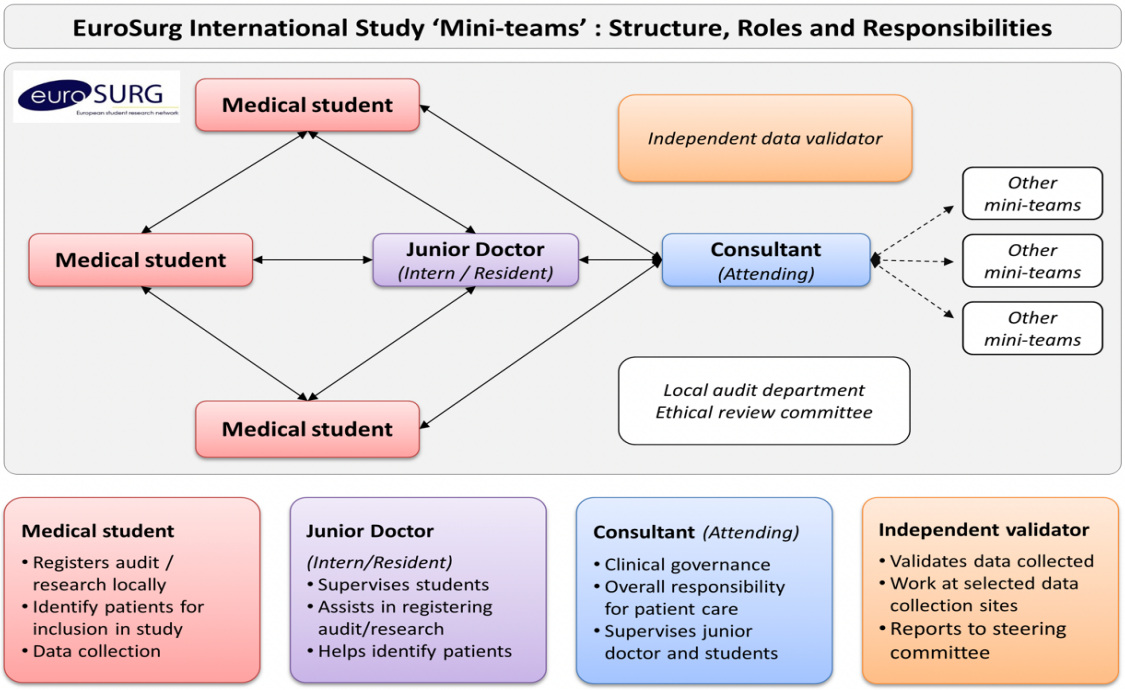
Project team structure
Medical students and trainees/residents will take the lead in disseminating and delivering this study, which is supported by national committees and supervising consultant surgeons:

- **Study management group**: a core group of medical students and trainees/residents responsible for protocol design, data handling and management, analysis and drafting of the paper.



- **National network committees**: a core group of medical students and trainees located in each participating country responsible for study dissemination, protocol translation and supporting students to correctly register and run the study at each participating centre.

- **Local leads**: a network of students/trainees at participating hospitals:
  - Responsible for co-coordinating mini-teams at their local hospital.
  - Act as a link between mini-teams and the national network committee.
  - First point of contact for local collaborators.
  - Ensure local study outcomes are reported back to clinical teams.

- **Mini-teams**: a team of three students/trainees responsible for data collection over one specific data collection period at one hospital:
  - A mini-team is formed by a medical student collaborating with a qualified trainee/resident. An additional student or trainee makes the mini-team up to three people.
  - Each mini-team will work with their local lead to ensure that the results are reported back to their clinical teams.

- **Consultant surgeons**: each mini-team must be supervised by a consultant (attending) surgeon. One consultant may supervise multiple mini teams at an individual hospital. The consultant sponsors registration of the study and ensures collaborators act in accordance with governance guidelines. They should assist with ethical/local approvals and facilitate presentation of local results.

For an example of this authorship style, search PubMed with PMID: 27321766

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Authorship

Mini-team collaborators, consultant surgeons, data validators, local leads, national committee members & the study management group are eligible for PubMed-citable co-authorship. Some specific requirements exist:

Mini-teams

A maximum of three collaborators per data collection/ follow-up period will be listed as 'PubMed' citable authors. Validators at each site are also eligible for authorship.

Each mini-team collaborator should participate in gaining local approval, identifying patients, collecting data and follow-up, ensuring >95% data completeness. Unfortunately, centres with >5% missing data will be excluded from the analysis and the contributing mini-team will be removed from the authorship list.

For more information, see www.ICMJE.org

Consultant Surgeons

In line with the International Committee of Medical Journal Editors authorship guidelines, one consultant per centre is eligible for collaborative PubMed citable co-authorship **if** they meet the following criteria:

(i) Supports local study registration.
(ii) Circulates information about the study to consultant colleagues.
(iii) Facilitates presentation of local results at a departmental meeting.

Local leads

To qualify for authorship, Local Leads must recruit **at least 2** mini-teams at their hospital. The maximum number of mini-teams per hospital is 3 (one per data collection period) (Section 04: Project Timeline).

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Dissemination & Impact

The impact of the IMAGINE study will be measured using the following criteria:

- Presentation of local results to clinical teams and local research meetings
- Presentation of international results at the EuroSurg Session at ESCP 2018
- Dissemination of results via academic and professional bodies with audiences related to surgery or colorectal surgery
- Dissemination of results in peer-reviewed journals
- Dissemination of results to patient and public interest groups

Appendix A: Required data fields

Patient Demographics		
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 (BMI)	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 respiratory disease (COPD)	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]
Operation Details		
10	Underlying pathology/indication	Malignancy, Inflammatory bowel disease, Diverticular disease, Other benign
11	Operative approach	Open, Lap, Lap-assisted, Robotic | Conversion?
12	Primary operation performed	**See Appendix B**
13	Formation of new stoma	Yes – colostomy, Yes – ileostomy, No stoma
Postoperative Gastrointestinal Function (Data collected each day for up to 10 days)		
14	Passage of stool **(Daily POD 1-10)** At least one episode per rectum or stoma	Yes, No
15	Vomiting **(Daily POD 1-10)** At least one episode of vomiting in 24 hours	Yes, No
16	Oral intake **(Daily POD 1-10)** Record greatest status per day	Yes - *Solid Diet (including soft),* Yes - *fluids only*, No
17	Nasogastric (NG) tube in situ **(POD 1-10)** For drainage (not feeding)	Yes, No
Postoperative Medication		
18a	NSAIDs administration on POD 1-3	Yes, No - **See Appendix B**
18b	NSAIDs administration on PO 4-7	Yes, No - **See Appendix B**
19a	Opioid administration on POD 1-3	Yes – *strong*, Yes – *weak*, No - **See Appendix B**
19b	Opioid administration on POD 4-7	Yes – *strong*, Yes – *weak*, No - **See Appendix B**
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 - **See Appendix B**
23	Postoperative pro-kinetic drug use on POD 1-10	Yes, No - **See Appendix B**
24	Transfusion of RBCs on POD 1-10	Yes, No
Outcomes		
25a	Anastomotic leak Radiological or intra-operative diagnosis	Yes, No
25b	*If yes, POD of diagnosis*	[value]
26a	Intra-abdominal/pelvic collection Radiological or surgical diagnosis	Yes, No
26b	*If yes, POD of diagnosis*	[value]
27a	Pneumonia Radiological diagnosis	Yes, No
27b	*If yes, POD of diagnosis*	[value]
28	C-reactive Protein (CRP) *Highest value recorded between POD1-3*	[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

Appendix B: Procedures & Drug Descriptions

The following procedures should be included:

- Ileocolic resection
- Right hemicolectomy
- Extended right hemicolectomy
- Transverse colectomy
- Left hemicolectomy
- Sigmoid colectomy (includes Hartmann's)
- Sub-total colectomy
- Total colectomy
- Pan-proctocolectomy
- Completion colectomy
- Closure/reversal of stoma
  includes ileostomy & colostomy

Included pro-kinetic drugs include:

- Metoclopramide
- Bisocodyl
- Ghrelin agonist (ipramorelin, ulimorelin)
- erythromycin
- gastrografin
- mosapride
- magnesium oxide
- choline citrate

Included mu-antagonist drugs include:

- Alvimopan
- Methylnaltrexone
- Naloxegol

NSAIDs and Opioids:

These may be administered via oral, rectal, intravenous, intramuscular, subcutaneous or epidural routes	
NSAIDS *(brand names in brackets)*	**Opioids** *(brand names in brackets)*
• Ibuprofen (Advil)	• Strong Opioids:
• Selective Cox-2 inhibitors:	Morphine sulphate (Oramorph, Zomorph)
Celecoxib (Celebrex)	Diamorphine
Parecoxib (Dynastat)	Oxycodone (Oxycontin)
Etoricoxib (Arcoxia)	Buprenorphine (Bupeaze, Sevodyne)
• Others:	Alfentanil (Alfenta)
Etodolac (Etopan, Lodine, Lodine XL)	Fentanyl (Fencino, Duragesic, Fentalis)
Ketorolac (Sprix)	Hydromorphone (Dilaudid)
Meloxicam (Mobic, Vivlodex)	• Weak Opioids:
Nabumetone (Ralifex, Relafen)	Codeine: *Includes co-codamol*
Diclofenac (Voltarol, Fenactol)	Tramadol (Maxitram, Tilodol, Zamadol)
Fenoprofen (Fenopron)	Dihydrocodeine: *Includes co-dydramol*
Flubriprofen (Froben, Ansaid)	
Ketoprofen (Orudis, Oruvail)	
Naproxen (Naprosyn, Naproxen Actavis)	
Sulindac (Clinoril)	
Piroxicam (Brexidol, Feldene)	

Appendix C: Clavien-Dindo classification system

Adverse post-operative events may be divided up into treatment failures, sequelae and complications. **Failure of treatment** occurs when the original surgery fails to achieve its intended benefits; for example, persistent pain following laparoscopic cholecystectomy or tumour recurrence following cancer surgery. **Sequelae** are the recognised consequences of a given procedure; for example, gut malabsorption following a large small bowel resection or immune deficiency following splenectomy. Any deviation from the normal post-operative course that has an adverse effect on the patient and is not either a treatment failure or sequel, is a **complication**.

In the Clavien-Dindo classification, the factor determining the severity of a complication is the treatment required. Consequently, a given complication may be graded differently depending on how it has been managed. For example, an anastomotic leak may be managed just with antibiotics if it is contained (grade II) or it may require re-operation under anaesthetic (grade III).

Some other considerations:

- Intra-operative complications are not considered unless they have an adverse effect on the patient post-operatively. The only exception to this is **intra-operative death**; this is classified as grade V.
- **All post-operative adverse events** are included, even when there is no direct relationship to the surgery.
- **All adverse events within the follow-up** period (30 days) are included, even if they occur following discharge.
- **Diagnostic procedures** are not included. For example, a diagnostic oesophagoduodenoscopy (OGD) to look for a source of bleeding without any intervention would not be considered a complication, but a therapeutic OGD with clipping of a bleeding vessel would be considered a grade III complication. Since **negative exploratory laparotomies** are considered to be diagnostic procedures, they should not be recorded as complications.

Grade	Definition (examples listed in italics)
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 (antiemetics, antipyretics, analgesics, diuretics and electrolyte replacement), physiotherapy and wound infections opened at the bedside but **not** treated with antibiotics. *Examples: hypokalaemia treated with K; nausea treated with cyclizine; acute kidney injury treated with intravenous fluids.*
II	Requiring pharmacological treatment with drugs beyond those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. *Examples: Surgical site infection treated with antibiotics; myocardial infarction treated medically; deep venous thrombosis treated with enoxaparin; pneumonia or urinary tract infection treated with antibiotics; blood transfusion for anaemia.*
III	Requiring surgical, endoscopic or radiological intervention *Examples: Therapeutic endoscopic therapy (do not include diagnostic procedures); interventional radiology procedure, return to theatre*
IV	Life-threatening complications requiring critical care management, neurological complications including brain haemorrhage and ischemic stroke (excluding TIA). *Examples: Single or multiple organ dysfunction requiring critical care management, e.g. pneumonia with ventilator support, renal failure with filtration; stroke.*
V	Death of a patient

Appendix D: Key steps for successful inclusion of your centre

☐ Contact your **local lead** about participation in the study at the centre of your choice. They will connect you to any other interested medical students and trainees at your centre.

☐ Form a **mini-team** of **up to three collaborators**. If possible a **medical student** should co-ordinate the team and lead study registration/data collection. They must be supported by at least one motivated trainee. This can be a trainee of any grade, but should preferably a junior doctor/resident.

☐ Choose a **14-day data collection period** within the data collection period to suit your availability. Multiple teams of students can participate at each centre, collecting data during distinct one-week periods. A single mini-team is permitted to collect data for more than one period if they have capacity.

☐ Ensure that you secure **formal study approval** from your hospital according to local regulations.

- This must be done prior to commencing data collection. UK collaborators should seek their NHS Trust's Caldicott Guardian's approval to upload data to REDCap. Non-UK collaborators should seek guidance from your national committee on your country's specific approval processes.
- Ensure that your centre is aware that this is study is **international** and data will be uploaded to **REDCap**. For more details on REDCap & data security see Section 12 of the study protocol. **No changes** to normal follow-up should be made.

It is essential that you begin this process immediately; approval can take up to 2-3 months. If you have any difficulties or are unsure what is required contact your local lead, your supervising surgeon, or your national network committee.

☐ Once the study is registered, forward evidence of this to your national network committee**.** REDCap accounts will not be issued until proof of study registration is received.

☐ Ask you supervising consultant surgeon to complete the centre-specific questionnaire. This is a short survey related to the presence of enhanced recovery protocols at your centre and will take less then 5 minutes to complete.

☐ Complete IMAGINE e-learning, including short modules on: Data Governance, Clavien-Dindo Classification System, Measurement of Bowel Function and REDCap user guide. These are mandatory and modules may be found via: bit.ly/learn.IMAGINE

☐ Arrange to **meet** with the other members of your mini-team, including the trainee/resident and, if possible, supervising consultant. If possible meet up with the **preceding mini-team** at your centre also. They will have a lot of helpful advice regarding what worked well. In you mini-team agree in advance who will be responsible for each stage of the project, e.g. identifying patients, collecting baseline data, completing follow-up, data entry to REDCap. Talk through how you will identify patients and collect required data, it will be particularly helpful if the consultant is present to offer guidance regarding this.

☐ **Identify** all patients meeting **inclusion criteria** within your 14-day period.

☐ Collect data on bowel function daily for the first 10 days (unless the patient is discharged before postoperative day 10 – In some centres, this may be the majority).

☐ Regularly **follow-up** for information on complications over the **30-day post-operative period.** This study is **prospective,** so you should not wait until the end of the post-operative period to follow-up patients. Discuss the best way to follow up patients with the consultant supervising you, as this will vary from centre to centre.

☐ Ensure all data has been uploaded to the **REDCap** system and you have completed all fields, avoiding **missing data points**. If more than 5% of patients at your centre are missing data, your centre unfortunately cannot be included and your name must be withdrawn from the author list.

☐ Following completion of the study at your centre, **present** your local results to your hospital's surgical department.

Appendix E: Glossary

- AAA abdominal aortic aneurysm
- ASA American Society of Anaesthesiologists
- BMI Body Mass Index
- CRP C-reactive protein
- CV curriculum vitae
- ERAS enhanced recovery after surgery
- ESCP European Society of Coloproctologists
- GI-2 (A composite outcome for *Gastrointestinal Recovery*)
- IV intravenous
- KDIGO Kidney Disease Improving Global Outcomes
- NG nasogastric
- NZ New Zealand
- NHS National Health Service (UK)
- NSAID non-steroidal anti-inflammatory
- OGD oesophagoduodenoscopy
- PCA patient-controlled analgesia
- POD postoperative day
- POI postoperative ileus
- RACS Royal Australasian College of Surgeons
- RBC Red Blood Cells
- RCT randomised controlled trial
- REDCap Research Electronic Data Capture
- SPSS Statistical Package for the Social Sciences
- TAMIS transanal minimally invasive surgery
- TEMS transanal endoscopic microsurgery
- UK United Kingdom
- US United States

Appendix F: References

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