The Role of Laxatives in Improving Recovery of Gastrointestinal Function After Colorectal Surgery

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ABSTRACT

Postoperative ileus (POI) is characterised by impairment of bowel motility leading to a delayed return of gastrointestinal (GI) function. It is a common complication after major abdominal surgery, and its clinical features include nausea, vomiting, abdominal distension, and delayed passage of flatus and stool. It predisposes patients to malnutrition, wound failure, and pneumonia, and often requires invasive interventions that significantly impact patient recovery and experience. The occurrence of POI is one of the most important determinants of adverse patient outcome after surgery, often surpassing both preoperative comorbid risk profile and intraoperative factors in the magnitude of its effect on short and long term survival. Delayed return of GI function as a single complication has the largest overall impact on healthcare costs. We do not have cost figures for Australia, but the estimated annual cost in the United States of this complication is approximately $1.5 billion.

POI or delayed return of gastro-intestinal function is not a normal or routine part of recovery after abdominal surgery. It arises in around 10-30% of patients and is increasingly regarded as a potentially preventable or treatable problem, the management of which is currently suboptimal. Most published and in-press research on this topic is almost exclusively focused on novel therapeutic medications to treat and prevent ileus. While some of these medications, such as Alvimopan and Prucalopride, may be promising in this regard, they tend to be quite expensive and currently not funded (nor approved) for use in Australia for this indication. There is a major knowledge gap, and significant variability, in the use of readily available “off the shelf” medications and techniques to improve the return of normal GI function. In particular, the use of simple laxatives has been largely overlooked and not subjected to scientific testing despite sporadic worldwide use.

This thesis aims to examine the available evidence for laxative use in this clinical setting, document usage patterns in routine clinical practice, and establish their clinical effectiveness and safety profile. A five-step process was adopted to answer these questions. Firstly, a systematic scoping review of Enhanced Recovery After Surgery (ERAS) protocols used in colorectal surgery worldwide was conducted. Second, a systematic review of randomised trials evaluating the safety and efficacy of laxative use after major abdominal surgery was conducted. Third, a global survey to gauge surgeons' preferences and practice regarding laxative use was undertaken to understand the reasons behind the varied uptake rates of these medications in routine clinical practice. Fourth, a retrospective cohort study was conducted in the colorectal unit at the Royal Adelaide Hospital (RAH), to document the safety and efficacy profile of laxative use in these patients. Finally, an open label randomised controlled trial (RCT) of the combination of simple stimulant and osmotic laxatives to reduce the duration of postoperative Ileus (POI) in patient's undergoing colorectal surgery (STIMULAX trial) was conducted.

Our research found that ERAS protocols commonly recommended laxatives as an intervention targeting POI and return of GI function, but the type and dose were inconsistent, and the evidence quoted was limited. The systematic review of RCT data revealed that while laxative use may result in an earlier passage of a stool after major abdominal surgery, it did not influence other postoperative recovery parameters. There was insufficient data to evaluate the safety profile of laxatives in this setting. Furthermore, this lack of high-quality evidence appeared to be the main reason why most surgeons do not routinely prescribe laxatives after elective colorectal surgery, as shown by the global survey we conducted. This survey also showed that there is wide variability in the type of laxatives used amongst those surgeons who do use laxatives. We then conducted an RCT on the risk-benefit of laxative use after elective colorectal surgery (STIMIULAX trial) to

address the knowledge gap. The trial showed that patients receiving multimodal laxatives achieved earlier recovery of GI function after surgery, compared with a control group. There was no difference in major complications, length of stay, or any other key recovery parameters. This paved the way for our final Phase II study (PyRiCo-P). We investigated whether we could safely circumvent the autonomic dysfunction caused after surgery by administering oral Pyridostigmine to reduce the duration of postoperative Ileus after colorectal surgery. Fifteen patients were recruited, and none of the patients had any adverse events. We suggest the next step is to conduct a double-blinded randomised controlled trial to assess the efficacy of Pyridostigmine in this setting.

This thesis contributes new evidence on therapeutic effectiveness of laxatives to reduce the duration of ileus after major abdominal surgery and has established a baseline framework upon which future trials of novel medications can be assessed.

STATEMENT OF DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Nagendra Naidu Dudi-Venkata

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DEDICATION

To my Gurus, whose support all through my life made me what I am today.

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Impact of STIMUlant and osmotic LAXatives (STIMULAX trial) on gastrointestinal recovery after colorectal surgery – a randomized controlled trial. Oral presentation, Royal Australasian College of Surgeons, 89th Annual Scientific Congress, May 2021.

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Multi-modal stimulant and osmotic laxatives to improve recovery of gastrointestinal function after colorectal surgery – the STIMULAX randomised controlled trial.
Oral Presentation (rated in Top 20 abstracts). European Society of Coloproctology, Sept 2020

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AWARDS RECEIVED

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Florey Postgraduate Conference, Adelaide Medical School

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GLOSSARY

Symbols

%	Percentage
χ^2	Chi squared (Chi 2) test
I2	Inconsistency (Index of Heterogeneity)

A

ACS	American College of Surgeons
ACTRN	Australian New Zealand Clinical Trials Registry number
ACIs	Acetylcholinesterase inhibitors
ANZCTR	Australian New Zealand Clinical Trials Registry
APR	Abdominoperineal
AR	Anterior Resection
ASA	American Society of Anaesthesia

B

BMI	Body Mass Index

C

CAIP	Cholinergic anti-inflammatory pathway
CALHN	Central Adelaide Local Health Network
CCI	Comprehensive Complication Index
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CD	Clavien-Dindo

CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COX-2	Cyclooxygenase-2
CT	Computed Tomography
CRS	Colorectal surgery
CSSANZ	Colorectal Surgical Society of Australia and New Zealand

D

d	Days
D0	Day of Surgery
D-1	Day before Surgery
D3	Day three after Surgery
DAMPs	Damage-Associated Molecular Patterns
DM	Diabetes Mellitus

E

eGFR	Estimated Glomerular Filtration Rate
ENS	Enteric Nervous System
EOD	End-organ dysfunction
ERAS	Enhanced Recovery After Surgery
ERP	Enhanced Recovery Protocol

G

GI	Gastrointestinal
GCP	Good Clinical Practice
GDFT	Goal-directed fluid therapy

GRADE	Grading of Recommendations, Assessment, Development and Evaluations

H

h	Hours
HREC	Human Research Ethics Committee

I

IBD	Inflammatory Bowel Disease
ICC	Interstitial Cells of Cajal
IDEAL	Idea, Development, Exploration, Assessment, Long-term Follow-up
IHD	Ischemic Heart Disease
iNOS	Inducible nitric oxide synthase
IQR	Inter-Quartile Range
IV	Intravenous

L

LOS	Length of stay or Length of Hospital Stay

M

M2	Muscarinic-2
M3	Muscarinic-3
MD	Mean Difference
MEDD	Morphine Equivalent Daily Dose
MeSH	Medical Subject Heading
Mg	Magnesium

MgO	Magnesium Oxide
MgOH	Magnesium Hydroxide
Min	Minutes
MRI	Magnetic Resonance Imaging

N

NCT	Non-central T
NGT	Nasogastric Tube
NO	Nitric Oxide
NSQIP	National Surgical Quality Improvement Program
NTS	Nucleus Tractus Solitarius
NYHA	New York Heart Association

O

OR	Odds Ratio
ORMIS	Operating Room Management Information System

P

PAD	Peripheral Arterial Disease
PAF	Population attributable fraction
PAMPs	Pathogen-Associated Molecular Patterns
PCA	Patient Controlled Analgesia
PO	Per Oral
POD	Postoperative day
POI	Post-Operative Ileus
PONV	Postoperative nausea and vomiting

PPOI	Prolonged Post-Operative Ileus

R

RAH	Royal Adelaide Hospital
RCT	Randomised Controlled Trial
REDCAP	Research Electronic Data Capture application
RLI	Reversal of Loop Ileostomy
ROH	Reversal of Hartmann
Rt	Right

S

SD	Standard Deviation
SP	Substance P
SPSS	Statistical Package for Social Sciences
SRS	Surgical Recovery Score
STIMULAX	Stimulant and Osmotic Laxatives
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

T

T test	Students T test
TC	Total Colectomy

V

VIP	Vasoactive Intestinal Peptide
Vs	Versus

CHAPTER 1: DELAYED RECOVERY OF GASTROINTESTINAL FUNCTION - POSTOPERATIVE ILEUS (POI)

1.1 Introduction

In patients who undergo abdominal surgery, there is often a delay in the return of normal bowel function due to reduced or uncoordinated intestinal transit. This delayed recovery of gastrointestinal function or postoperative ileus (POI) is distressing for patients. The primary features of POI include nausea and vomiting, inability to tolerate an oral diet, abdominal distension and delayed passage of flatus and stool. This condition lasts for a variable period, ranging from 2 to 4 days postoperatively (which is often termed “Physiologic POI” or “POI not further specified”) to lasting ≥ 4 days after surgery (often referred as “Prolonged POI (PPOI))”.[1] PPOI frequently requires the insertion of a nasogastric tube, leading to a significant increase in postoperative complication rates and length of stay.[2, 3]

This chapter presents an account of the aetiology of post-operative gut dysfunction, focusing on its clinical correlates and potential management challenges.

1.2 Incidence

POI occurs in 10%–30% of patients undergoing major gastrointestinal surgery. This broad range reflects the difficulty in reliably and consistently estimating its incidence, and the variability in assessment criteria.[4-8] A recent systematic review of randomised controlled trials (RCTs) by Chapman et al. found 73 different outcome measures were used to report return of bowel function after gastrointestinal surgery.[9]

POI occurs most frequently following intra-abdominal surgery but may also appear after procedures like orthopaedic spinal procedures, with an incidence of around 5-12%.[10-12] Intestinal resection and subsequent anastomosis have been shown to more profoundly impact post-operative gastrointestinal function than surgery of similar severity not involving resection.[5, 13, 14] Once regarded as an obligatory response to surgery, recent evidence has challenged this concept of postoperative gut paralysis, suggesting that previous

assumptions about gut motility and neurohormonal mechanisms involved in it may need to be reconsidered.[15, 16] POI is now thought to be a defined complication, albeit one that arises frequently in patients following elective intestinal surgery.[3]

1.3 Impact of POI on patient outcomes

POI can have a significant negative impact on patient outcomes in terms of a short-term recovery, long-term survival, and quality of life.[3, 17]

POI can lead to abdominal hypertension due to distension, which can impair deep breathing and reduce tidal volume. This, as well as the risk of aspiration with vomiting, is postulated to cause an increased incidence of atelectasis and pneumonia in patients having POI.[18-20] Delayed wound healing has also been linked to poor oral intake and malabsorption, resulting in nutritional and electrolyte deficiencies.[20-22] External drainage of gastric and intestinal contents is often necessary in patients with ileus after abdominal surgery. Insertion of a nasogastric tube (NGT) is a common management strategy, which aims to decompress the stomach and reduce the risk of vomiting. However, the procedure is distressing for patients, and may itself lead to vomiting through stimulation of the palatal 'gag' reflex. Aspiration pneumonitis and pneumonia are frequent reasons for critical care admission after surgery and are commonly life-threatening.[23] Other complications such as anastomotic leak have consistent associations with POI.[5, 24, 25] POI and its consequences as a complication thus contribute to the single largest overall effect on length of postoperative hospitalization for patients after colorectal surgery.[3, 4] Data from the Colectomy-Targeted American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) showed that POI as an index complication was associated with a significant adjusted relative risk of end-organ dysfunction (EOD) (3.80, 95% CI 3.23-4.45, $P < 0.05$) and mortality (2.57, 95% CI 1.94-3.41, $P<0.05$). This

essentially meant that if one could completely prevent POI in a patient, the incidence of EOD and death would decrease by 32% and 23% respectively.[3]

POI, when prolonged, also significantly impacts the psychological aspect of patient recovery. Prolonged postoperative inpatient stay is often associated with increased patient fatigue, decreased satisfaction with care, and negative self-perception of clinical progress.[26-28] In addition, associated complications and the presence of an uncomfortable nasogastric tube, significantly affect the QoL of these patients and contribute to the development of psychological barriers to recovery.[26-30] Studies have also documented the effects of stress on immune function and wound healing which has important implications in postoperative recovery.[27, 31-33] Current ERAS protocols recommend routine comprehensive preoperative counselling to allay surgery-related anxiety in patients and help alleviate these psychological barriers to recovery.[34-40] Interestingly, patients with POI experience reduced QoL which is not limited to the immediate postoperative period, but remains evident 3 and 6 months after surgery, emphasizing the long-term impact of the burden of POI.[41, 42]

1.4 Impact of POI on healthcare services

POI imparts a significant financial and resource-intensive burden on healthcare institutions.[5] This increase in the cost is primarily attributed to two key aspects – firstly due to POI per se as an individual complication and secondly, the costs accrued because of the secondary complications after the development of Ileus.

Goldstein et al. estimated that the cost of management of POI as a single complication in the USA alone approaches $US1.5 billion annually.[5] Several large retrospective studies have shown that the healthcare system spends somewhere between 50% and 100% more on patients who develop POI than those who do not and that 91% of those increased

costs are directly related to the patient's immediate postoperative stay.[5, 43, 44] A study by Iyer et al. similarly found that patients with ileus also had a 15% increase in health cost on multivariate analysis when adjusting for patient age, sex, incidence of complications, and type of admission (elective or emergency).[43] The rise in costs for patients who developed POI resulted from an increased need for nursing care, blood tests and laboratory work, radiology, and allied health input. Additionally, the number and cost of readmissions was greater in the PPOI group,[5] and secondary complications further increases the cost of care significantly.[42]

1.5 Pathophysiology

Traditionally, two distinct phases are recognised in the pathogenesis of postoperative ileus: a short-acting neurogenic phase marked by exaggerated inhibitory reflexes, and a longer inflammatory phase. However, recent studies have shown that gastrointestinal dysfunction following abdominal surgery is multifactorial.[45-48] This includes the role of altered local hormonal activity, action of exogenous narcotics on gut opioid receptors, and electrolyte derangements all being implicated in its pathophysiology, (Figure 1). These factors are outlined in detail below.

1.5.1 Inflammatory cascade

Mesothelial cells and local peritoneal immune cells respond to peritoneal injury and bowel handling by secreting inflammatory mediators. This early pro-inflammatory response is responsible for the local and systemic inflammatory and repair processes that define the injury response and its clinical implications including POI.[49-51] Although there is good evidence to point to the role of inflammatory transcription factors, cytokine and chemokine up-regulation, and leucocyte recruitment in the pathophysiology of POI, the cell types triggering this inflammatory response leading to a direct inhibitory effect on the muscularis

externa of the bowel are less defined. [51-55] Mast cells and macrophages residing in the muscularis externa of the intestinal wall, seem to play a pivotal role in the genesis of the inflammatory cascade.[56-58] Indeed, a murine model of POI revealed that animals pre-treated with mast cell stabilisers experienced reduced manipulation-induced inflammation and improved gastric emptying and mast-cell deficient animals likewise exhibited a diminished inflammatory response to surgery.[56] This also explains the decreased response in mast cell activation witnessed during laparoscopic surgery due to a reduced degree of intestinal handling.[51] Activation of these cells within the bowel wall is believed to be in part caused by macromolecules such as damage-associated molecular patterns (DAMPs) which are released in response to the handling of the bowel, and pathogen-associated molecular patterns (PAMPs) found on commensal intestinal flora that translocates through the gut wall during increased permeability associated with inflammation.[16]

This inflammatory cascade initiates the dysmotility through three different pathways. One of them is the release of potent smooth muscle relaxants, especially the COX-2 dependent prostaglandin E2 and inducible nitric oxide synthase (iNOS) which mediates the blunted contractile response of the inflamed bowel wall.[16, 59-61] Local inflammatory responses leading to bowel wall oedema adds further to this blunted contractility by affecting the myosin light chain apparatus central to smooth muscle contraction, and intestinal transit.[16, 62] Finally, relative intestinal ischemia occurring as a by-product of the inflammatory cascade or via the direct reduction in the arterial blood flow also plays a role in POI.[63, 64] This is further corroborated by clinical studies which have found hyperbaric oxygen therapy conferring a potential benefit in POI.[65-67]

While minimally invasive surgery has reduced the burden of the skin and abdominal wall wound in major intestinal surgery, the intra-peritoneal component of the injury has remained largely unchanged, owing to the inherent requirement for controlled damage to remove the target organ.[68]

1.5.2 Neural dysregulation

Manipulation of the intestine results in activation of mechanoreceptors and nociceptors, which play a significant early role in the gut dysfunction after surgery.[54] This response extends through the somatic, autonomic, and the enteric nervous system.[16] Neural derangement during this phase is also thought to be closely coupled with the immunological and inflammatory response outlined above, and this neuro-inflammatory activation is collectively termed as the “surgical stress response”.[69] Both afferent and efferent pathways contribute to this neural response leading to POI.

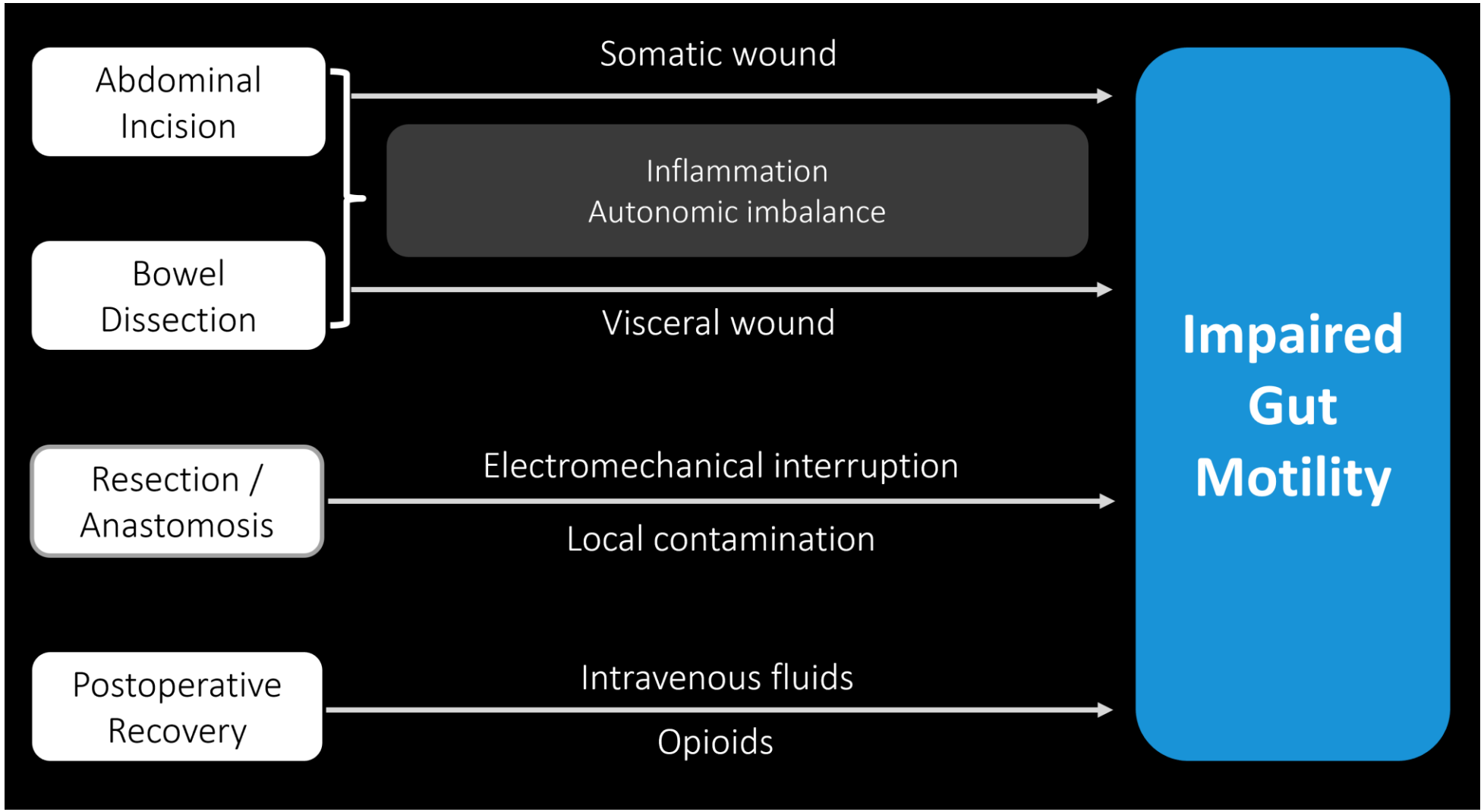

Fig. 1 Pathophysiologic basis for the development of post-operative ileus

1.5.2.1 Afferent pathways

During abdominal surgery, there are two types of wounds created, the “somatic wound’ representing the abdominal wall incision, and a ‘visceral wound’ representing the incision in the peritoneum and the resection / handing of the gut and intra-abdominal organs.[70]

i. Somatic wound – Nociceptive stimuli after the abdominal skin incision are carried via sensory neurons through the anterior and lateral branches of the ventral rami of the lower intercostal and upper lumbar nerves to synapse in the posterior column of the spinal cord.[16, 71] Activation of this site by the release of the excitatory neurotransmitter glutamate invokes the perception and localisation of pain, and this further incites a local autonomic response mediated by sympathetic efferents with cell bodies in the lateral horn.[70, 72]

ii. Visceral wound – To approach the intestinal viscera, the surgeon must breach the parietal peritoneal lining of the abdominal wall, and the visceral peritoneal envelope covering the viscera. The peritoneum lining is active metabolically and can activate a cascade of inflammatory and immunological mediators on injury as described above.[68] In addition, the intestinal viscera have a densely interconnected network of neurons contained within its wall – the enteric nervous system (ENS) – that derives information from various mechanoreceptors and chemoreceptors.[16, 73] Approximately 80% of this sensory information from viscera and peritoneum is conveyed by the vagus nerve.[74] Besides the neural response from nociceptors, the vagus nerve is also sensitized by upregulation of interleukin-1 receptors by its paraganglia cells forming the common bridge of the neuro-humoral response to injury-related inflammation.[75, 76] The major relay centre of the neuro-immuno-humoral response to injury is considered to be the nucleus tractus solitarius (NTS)

of the brain stem.[75] Experiments in animal models following vagotomy have shown blunting of this supraspinal response to intestinal manipulation, independent of presence or absence of any sectioning of the spinal cord.[76-78]

1.5.2.2 Efferent pathways

Efferent pathways of neural regulation of gut motility include both sympathetic and parasympathetic outflows but in the setting of abdominal surgery, the local reflex response with further stimulation by activation of supraspinal centres paves the way for an autonomic shift favouring sympathetic over parasympathetic flow. This neural shift underpins the gastrointestinal dysmotility which occurs following surgery. The delicate balance between excitatory parasympathetic and inhibitory sympathetic input which usually regulates bowel motility is deranged. Key sites implicated in the central inhibition of gut motility are the hypothalamus and NTS,[79-81] with counteracting excitatory parasympathetic efferent stimulus traveling via the vagus and pelvic splanchnic nerves, which meet at the splenic flexure of the colon, creating a “watershed” area at this location.[71] Activation of M2 and M3 muscarinic receptors, through release of acetylcholine by these postganglionic neurons then leads to an increase in smooth muscle excitability and contractility.[75, 82]

Sympathetic efferents in the thoracolumbar region originating from the lateral horn of the spinal cord release catecholamines within the gut as part of the reflex adrenergic response to nociception and supraspinal excitation.[73, 83-85] This release of catecholamines further activates α-2 adrenoceptors which act on presynaptic parasympathetic cholinergic nerves to inhibit the release of acetylcholine and directly on myocytes to stimulate the production of NO. These pathways serve to reduce myocyte tonicity and contractility.[86-88] In addition,

a non-adrenergic non-cholinergic vagally-mediated path impairing motility via the local release of NO and vasoactive intestinal peptide is also evident in rat studies.[89, 90]

It should be noted that the epidural blockade often used in the peri-operative setting can take advantage of the same interplay between the sympathetic and parasympathetic nervous system. An epidural can block sympathetic gut innervation at a spinal level thus creating a relative parasympathetic predominance which then helps to accelerate the gastrointestinal recovery after surgery.[91-94] However, impracticalities with routine epidural blockade and frequent issues with post-operative hypotension have resulted in a general reduction in their use worldwide.[95, 96]

1.5.3 Gastrointestinal hormones and neuropeptides

During the inflammatory and neural derangement phase after surgery, there is also an associated surge release of gastrointestinal hormones and neuropeptides. Some of the well-known peptides are substance P (SP), vasoactive intestinal peptide (VIP), and ghrelin.[97, 98] Studies using centrally penetrant ghrelin receptor agonists in animal models and humans have shown that the agonists stimulate colorectal motility and cause defecation through the receptors in the lumbosacral spinal cord.[99, 100]

Conversely, the role of SP and VIP mechanisms of action and their degree of involvement in the pathogenesis of ileus is unclear as they can act both as anti- and pro-inflammatory mediators.[101-104] VIP is a smooth muscle relaxant, and its antagonism by agents acting specifically on VIP receptors possibly have a role in accelerating postoperative gut recovery.[105, 106] SP, on the other hand, is involved in excitatory neurotransmission of visceral afferents and is believed to play a crucial role in mediating the neuro-immuno-humoral inflammatory response to tissue injury.[107, 108]

1.5.4 Disruption of intestinal continuity

Interstitial cells of Cajal (ICCs) are the pacemaker cells of the alimentary tract, generating and propagating slow waves, acting as mediators of inputs from the enteric nervous system to GI smooth muscle, thus playing an essential role in the regulation of GI motility.[82, 109, 110] Clinical studies indicate that ICCs are implicated in some specific GI motility disorders.[111-113] Resection of gut viscera and subsequent end-to-end anastomosis has been shown to profoundly impair downstream intestinal motility in the post-operative period leading to a higher incidence of POI compared to non-anastomotic surgery of similar severity.[6, 7, 14] Recent animal and human studies indicate that this could be because of functional and morphological alterations of ICCs at the site of transection/anastomosis in the intestine causing a physical barrier to electro-mechanical coupling.[14, 114, 115]

1.5.5 Recto-sigmoid brake

Traditionally, it has been taught that gastrointestinal motility after surgery recovers at varying speeds, with the small intestine first (<24 hours), followed by the stomach (24-48 hours), and then the colon last (>48 hrs).[116] This colonic delay in function was considered to be because of atony after surgery, however recent studies using colonic manometry have proven this to be more likely due to increasing cyclic motor patterns in the distal colon commencing soon after the induction of anaesthesia.[117, 118] These circular muscle contractions in the large intestine, commonly referred to as propagating motor complexes, have also been shown to increase in healthy controls in response to consumption of calorie-rich meals, morning waking and electrical stimulation.[119-123] The contractions propagate in a retrograde direction, occur predominantly in the sigmoid and descending colon, and appear to last for a long period after surgery.[118, 124] Another recently coined term for this phenomenon is the “rectosigmoid brake”, and it could be the reason why

recovery of intestinal function is quicker after left-sided resections than right sided resections (as the break is removed with the resected specimen in left-sided cases).[125, 126]

1.5.6 Iatrogenic mechanisms: intravenous fluid and opioids

The optimization of intraoperative fluid management in colorectal surgery has always been difficult and solutions controversial.[22] Historically, it has been argued that excessive fluid administered in the peri-operative setting can impair the function of key organ systems including the gut and cardiorespiratory system. Excess fluid can cause oedema of the gastrointestinal membranes thus impairing recovery of gastrointestinal function.[127, 128] This mechanism has been demonstrated in rodent models and replicated in human studies.[128-131] In general, Enhanced Recovery Protocols (ERPs) now recommend a focus on fluid restriction to achieve euvolaemia. However, given that urine output and basic haemodynamic parameters are known to be unreliable measurements of volaemic status in the peri-operative setting, euvolaemia can be difficult to achieve with any degree of precision.

To address this problem, goal directed fluid therapy (GDFT) using transesophageal doppler monitoring has been proposed. However, a recent clinical meta-analysis has demonstrated that in patients undergoing elective colorectal surgery there was no difference seen in postoperative clinical outcomes between conventional euvolaemic intraoperative fluid therapy and GDFT.[132] It has been suggested that the U-shaped relationship between fluid volume infused and perioperative morbidity postulated previously may not be as pronounced, as long as major the fluid overload and deficits are avoided.[133-135]

Administration of opioids postoperatively for pain relief significantly impacts GI recovery by acting on peripheral μ2–opioid receptor in the GI tract.[7, 46] Activation of these receptors

occurs at the level of the myenteric plexus, and serves to inhibit the release of acetylcholine from nerve endings, thereby decreasing smooth muscle tone and impairing gut motility.[136] The importance of narcotic-related dysmotility is demonstrated by the drug Alvimopan's success in accelerating postoperative gastrointestinal recovery.[137] Alvimopan is a synthetic, orally-administered, peripherally-acting μ-opioid receptor antagonist with limited systemic bioavailability. It has a polar molecular structure which prevents movement across the blood-brain barrier, thereby preserving the analgesic effect of opioids but mitigating opioid-induced bowel dysfunction.[138, 139] Unfortunately, Alvimopan is not available or funded for use in Australia, and its role in the context of recent opioid minimisation strategies is unclear.

1.6 Clinical features of delayed recovery of GI function or Ileus

Ileus is often recognised by a cluster of characteristic GI signs and symptoms occurring within the first few days after surgery. These usually reflect the abnormal motility patterns affecting different segments of the gut, and even though the clinical features are typically described as occurring in synchrony, symptom clusters can often be confined to either the upper or lower gastrointestinal tract.[119, 121]

Ileus typically leads to distention, nausea and/or vomiting, and consequently, the inability to tolerate an oral diet. Vomitus is of variable volume but is frequently bright green, indicating reflux of bile from the duodenum to stomach.[140] This may be accompanied by the absence of flatus and stool. Pain out of keeping with distention is an infrequent feature but can be present in the context of recent surgery or another primary intra-abdominal complication. Abdominal plain film or computed tomography (CT) can help to exclude another primary complication and diagnose ileus radiologically as characterised by generalised gut dilation with air-fluid levels and the absence of a transition point. However,

these findings can be non-specific and need to be cautiously interpreted within the appropriate clinical context.

1.7 Challenges in the management of ileus

The word ‘ileus’ is from Ancient Greek εἰλεός eileós, “intestinal obstruction”. However, over several decades it has been used more selectively for abnormal pathological motility patterns seen in the gut after surgery.[141, 142] One of the key ongoing challenges in its management is the lack of internationally accepted standardised clinical definition for POI.[1, 9, 143] There are two key components to defining POI , firstly the cut-off point at which there is a transition from normal physiological postoperative gut dysmotility to the pathological prolonged gut dysfunction, and secondly, the clinical features that are considered to be the endpoints for the return of bowel function after gastrointestinal surgery. The literature is widely divided in these two vital aspects of defining ileus.

1.7.1 POI vs PPOI

Studies analysing risk factors for ileus have variably defined the cut-off point for prolonged ileus to be between three to seven days. This has led to an imprecise appreciation of the true incidence of ‘prolonged’ POI,[7] and is the main reason for the vast discrepancy in incidence rates of POI (10-30%) described in the literature for patients undergoing abdominal surgery.[4, 6, 144-146] Artinyan et al. demonstrated in a retrospective study that with an early feeding regimen and an otherwise uncomplicated clinical course, almost 80% of their patients tolerated a solid diet by postoperative day (POD) six, and they suggested that ileus longer than six days appears to be a better definition of an abnormally prolonged ileus.[144] Interestingly, there are a few studies based in international consensus and Delphi processes which stop short of defining any cut-off points for ileus. In a study conducted by Gero et al.[143] experts did not differentiate POI and prolonged POI, and Venara et al.[147]

classified ileus into grades A-E based on their clinical consequences. Another systematic review and meta-analysis conducted by Wolthius et al. proposed ‘reinsertion of the nasogastric tube’ as the most relevant definition of PPOI after colorectal surgery, as this study considered it as a straightforward therapeutic act postoperatively which could be easily recorded in prospective trials in the future.[148]

Based on the findings of a systematic review of 52 trials on the definition of POI and a global survey, Vather et al. suggested using the terminology “POI” until the 3rd POD when the passage of flatus/stool and tolerance of an oral diet is not experienced and advocated for the use of the term “PPOI” from the 4th day if two of the following five criteria were met: nausea/vomiting, inability to tolerate an oral diet over the last 24 h, absence of flatus over the last 24 h, abdominal distension and radiologic confirmation.[1] Given the comprehensiveness of the data collected and presented, this is currently the best definition for PPOI and is gaining acceptance in academia as the accepted standard.

1.7.2 Outcome measures for recovery of GI function after surgery

Outcome measures used to assess recovery of postoperative GI function are also variable, comprising numerous clinical, physiological, and radiological measures which are often used interchangeably.[149] A recent systematic review characterising the extent of variation in current outcome measures for the return of GI function showed a total of 784 outcomes identified across all published RCTs. These comprised 73 discrete outcome measures. Overall, the most frequently reported measures were ‘time to first passage of flatus’ (64·5 per cent), ‘time to first passage of stool’ (31·8 per cent) and ‘time to first bowel movement’ (30·0 per cent).[9] Most of these published RCTs (86%) favoured clinical outcome measures (clinical scales, instruments, and consultations) with only a smaller number of studies using radiological modalities (radiographic, nuclear and MRI

assessments of GI transit) and physiological measures (acetate breath-testing, paracetamol (acetaminophen) absorption and gastric manometry) in 8% and 5% cent, respectively.[9] Without a single consensus definition and agreed outcomes, evaluations of new treatments in RCTs and data synthesis in meta-analyses are unsurprisingly difficult.

Currently, the most representative assessment of return of GI function after surgery is offered by the validated composite outcome measure GI-2 (defined as time to tolerance of oral diet and passage of stool) with the area under the curve of 0.9. This composite measure is based on scintigraphy recording of GI transit and correlating it with clinical symptoms to identify the most reliable clinical markers of bowel function recovery.[146] GI-2 is considered a much more reliable criteria than GI-3. GI-3 is a composite measure which in addition to GI-2 includes time to first passage of flatus, and this factor limits the interpretability of this measure for GI recovery as time to flatus is not significantly associated with recovery of colonic transit as shown in scintigraphic studies.[146]

1.7.3 Limitations of enhanced recovery protocols (ERPs)

ERPs are standardized perioperative care programs that utilize a multimodal, team-based approach to reduce the physiologic stress of surgery and improve the quality of perioperative care and surgical outcomes. In the last two decades, these programs, which were first implemented for patients undergoing colorectal surgery, have shown significant improvements in recovery of patients after surgery by reducing postoperative complications, length of hospital stay and readmissions.[150-152]

One of the fundamental principles that underlie the success of ERPs is their multimodal approach to resolving issues that delay recovery and cause complications.[153] While each component of perioperative care may have a modest benefit to the patient when applied alone, the multimodal, integrated care, across the continuum of the perioperative setting

offers a synergistic advantage over the implementation of individual elements in isolation.[154] This aspect has been well exemplified in real-life practice in patients using multimodal interventions for dealing with postoperative pain and nausea or vomiting (PONV) prophylaxis.[155]

Currently, ERPs recommend few interventions besides early enteral feeding after surgery to improve GI function recovery.[156] This may be because of a dearth of available evidence on how to prevent and treat POI, with limited published data providing varied and conflicting results.[157-160] One such recommendation is using laxatives to improve recovery of GI function after surgery, however, these laxatives again vary depending upon where the ERP guidelines originate from and are only backed by weak evidence to support their efficacy.[149, 155] In addition, published data on the safety of these laxatives in the postoperative setting are limited, particularly concerning anastomotic leak, which makes all these recommendations difficult to implement in practice.[156]

There are 4 main types of laxatives. Bulk-forming laxatives work by increasing the "bulk" or weight of stool, which in turn stimulates the bowel (ispaghula husk). Osmotic laxatives draw water from the rest of the body into the bowel lumen to soften stool and this leads to increasing distention which then potentially stimulates the bowel motility (polyethylene glycol, fleet enema). Stimulant laxatives as the name suggests, stimulates the bowel motility by its action on enteric nervous system to initiate muscular activity (bisacodyl, senna). Stool-softener laxatives work by letting water into stool to soften it and make it easier to pass (docusate sodium).

1.7.4 Paucity of research on laxatives

In a setting where physiological mechanisms are inadequately understood, and methodological prerequisites are absent, progress in POI research has been predictably

slow. Studies on gut motility and neurohormonal mechanisms have identified new avenues of research which may lead to novel treatments to prevent postoperative gut dysfunction.[16, 118] Currently, most of the published research on interventions to prevent POI are focused on novel therapeutic drugs like Alvimopan and prucalopride which are not funded nor easily available in Australia for this indication.[161-163] Furthermore, there appears to be a major knowledge gap and significant variability in the use of readily available, “off the shelf” and common medications such as simple gut stimulants and laxatives which require further exploration.

1.8 Summary

POI is one of the most common complications after abdominal surgery with a significant impact on patient recovery. Healthcare costs are substantially increased by this complication. POI is multifactorial in pathophysiology with key factors contributing to its development being the generation of an inflammatory response, autonomic dysfunction, disturbances in gastrointestinal hormone activity, and administration of opioids. The ambiguity surrounding the definition of POI has made it difficult to estimate its incidence reliably and consistently. Several trials have examined interventions for POI but there is considerable heterogeneity concerning the outcomes being measured as surrogate markers of its occurrence and resolution. Furthermore, most studies have focused on novel therapeutic targets, and there remains a dearth of evidence on the role of simple interventions like laxatives in this setting.

CHAPTER 2: PRECIS

The following chapters present an account of the current evidence on the role of laxatives in improving the recovery of gastrointestinal function after colorectal surgery, followed by a measure of local and global experience with regards to their use amongst colorectal surgeons, and further clinical investigation of the laxatives with contribution of original data on efficacy and safety.

The first chapter (**Chapter 3**) is a systematic review of the literature to categorize and summarize management recommendations targeting postoperative ileus (POI) and delayed return of gastrointestinal function after colorectal surgery in published ERPs. Thirty-seven published ERPs were identified from 37 studies (18 cohort, seven historical-control, five guidelines, four randomized controlled trials, one randomized controlled trial protocol, one case series and one narrative review). This study highlighted the lack of uniformity in ERPs with regards to these interventions. Geographical trends were also noted for the various interventions used in the ERPs. While laxatives were the most recommended intervention, only weak evidence was reported to support this practice.

The second chapter (**Chapter 4**) is a systematic review that updates the available evidence on the safety and efficacy of laxative use after major abdominal surgery, including abdominal colorectal surgery. While ERPs recommended laxatives to reduce the duration of POI, the evidence for this is shown to be relatively weak. Five RCTs with a total of 416 patients were included in this review. Laxatives reduced the time to passage of stool, but there was significant heterogeneity between studies for this outcome measure. There was no difference in time to passage of flatus or length of hospital stay. There were insufficient data available on postoperative complications for conducting a meta-analysis. Overall, this study showed a potential role of routine postoperative laxative use after major

abdominal surgery in helping patients pass the stool earlier, however, higher quality studies with better definitions are required.

In **Chapter 5**, a global survey of colorectal surgeons was conducted with the aim to gauge surgeons' preferences and practice regarding laxative use after elective colorectal surgery. A total of 852 surgeons, representing 28 surgical societies completed the survey. Twenty-seven per cent of the respondents routinely prescribed laxatives after colorectal surgery. There was a wide variation in the type of laxatives used, with magnesium-based laxatives, macrogol and lactulose being the most common. Geographical location was also correlated with the choice of laxative. Those not routinely using laxatives stated the reasons as being no evidence for benefit and potential of adverse events, however, the majority (93%) of these non-users suggested that they would consider using laxatives if better evidence was available.

To gather additional evidence and establish our local experience, in **Chapter 6**, a single-centre retrospective cohort study was conducted at the Royal Adelaide Hospital to assess the safety and efficacy of laxative use after elective colorectal surgery. Of 173 eligible patients, 67 (38.7%) had routine laxatives prescribed, and 106 (61.3%) did not. On raw analysis, there were significantly fewer anastomotic leaks in the laxative group (0 vs 10.7%, P 0.013), but otherwise, there were no differences in any other outcome measures. Propensity score matching was then done based on known risk factors for ileus, with 48 patients in each group. Time to GI-2, anastomotic leak, and readmission rates showed a trend favouring the laxative group though none were statistically significant. This study showed that postoperative laxative use following CRS appeared safe in our setting; however, their efficacy required further investigation.

Chapter 7 describes a level 1 open-labelled randomised controlled trial of STIMUlant and osmotic LAXatives (STIMULAX) to investigate the impact of these on recovery of gastrointestinal function after colorectal surgery. This study was designed from the outset to address the knowledge gap identified in the previous chapters. The primary outcome used was GI-2, a validated composite measure of time to tolerance of solid intake for 24 hours without vomiting and passage of stool. Secondary outcomes were the incidence of prolonged post-operative Ileus (PPOI), length of hospital stay (LOS), and postoperative complications. Of a total of 170 participants, 85 were randomized to each group (STIMULAX (laxatives) and Control). Baseline characteristics were evenly distributed. Median GI-2 was one day shorter in the STIMULAX compared with the Control group (2 days vs 3 days, P = 0.029). Incidence of PPOI was lower in the STIMULAX group (22% vs 38%, relative risk reduction 42%, P = 0.030). There was no difference in the LOS or 30-day postoperative complications (including anastomotic leak) between the STIMULAX and Control groups. The conclusion from these results is that routine postoperative use of multimodal laxatives after elective colorectal surgery resulted in the earlier recovery of gastrointestinal function and reduces the incidence of PPOI.

Despite some positive findings, the STIMULAX trial did not show any decrease in the length of stay, or in any other key recovery parameters using multimodal laxatives. The multifactorial pathophysiological mechanism behind the development of ileus is one explanation for this, and we hypothesized that autonomic dysfunction, which could not be counteracted by laxatives should serve as the next target for investigation.

In **Chapter 8**, we describe a safety and feasibility study to investigate the effectiveness of oral pyridostigmine after elective colorectal surgery. This study was conducted as a phase 2 trial and aimed to determine the possibility of conducting a future randomised controlled

trial using oral pyridostigmine to improve GI recovery after colorectal surgery. Fifteen consecutive patients undergoing elective abdominal colorectal resections for any indication or having formation or reversal of stoma at the Royal Adelaide Hospital (RAH) received oral pyridostigmine tablet twice a day from the day of operation till they opened their bowels. The primary outcome was 30-day postoperative complication rate, adverse events, and GI-2. All patients tolerated the study drug with no complications or serious adverse events at 30 days.

The following chapters provide a detailed account of the above findings, followed by a synopsis with final conclusions, and a description of potential areas of future research.

CHAPTER 3: SYSTEMATIC SCOPING REVIEW OF ENHANCED RECOVERY PROTOCOL RECOMMENDATIONS TARGETING RETURN OF GASTROINTESTINAL FUNCTION AFTER COLORECTAL SURGERY

Statement of Authorship

Title of Paper	Systematic scoping review of enhanced recovery protocol recommendations targeting return of gastrointestinal function after colorectal surgery
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
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Contribution to the Paper	Conception and design of the project Acquiring research data Analysis and interpretation of research data Drafting significant parts of the article and critically revising it
Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 26/11/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Name of Co-Author	Tarik Sammour		
Contribution to the paper	Conception and design of the project Analysis and interpretation of research data Contribution of knowledge, where justified Drafting significant parts of the article and critically revising it		
Signature		**Date**	26/11/2020

3.1 Introduction

Post-operative Ileus (POI) and delayed return of gastrointestinal (GI) function are common complications after colorectal surgery. The incidence of POI is reported to be around 10–25% depending upon which definition is used in the literature.[3, 4, 6, 7] More importantly, irrespective of what definition is used to define POI, it is evident that it has a significant effect on the post-operative recovery of patients leading to significant discomfort, delaying enteral nutrition, and predisposing to wound failure and pneumonia.[2] POI as a complication has the single largest overall effect on length of post-operative hospitalization after colorectal surgery,[3] and substantially increases the costs of surgical care. The estimated annual cost in the USA of POI is approximately $1.5 billion.[164]

With the advent of enhanced recovery protocols (ERPs), there has been general improvement in the management of patients undergoing colorectal surgery, with an overall reduction in complications.[165-167] However, while these protocols use multimodal strategies to optimize post-operative recovery, the incidence of POI has been largely stable and recalcitrant. This may be because of a dearth of available evidence on how to prevent and treat POI, with published data providing varied and conflicting results.[157-160] This probably also explains the lack of uniformity in recommendations targeting POI in different ERPs published worldwide.

The aim of this systematic review is to categorize and summarize management recommendations available from published ERPs.

3.2 Methods

3.2.1Search strategy

A comprehensive systematic review of the literature was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.[168] Ovid MEDLINE, Embase, Cochrane Library and PubMed databases were searched by two authors (NNDV and HMK) for all publication types, including conference papers and abstracts, from January 1990 to May 2018. The following medical subject headings (MeSH) and keyword search terms were used: ‘enhanced recovery after surgery’, ‘eras’, ‘fast track protocols’, ‘multimodal pathway, ‘multimodal rehabilitation’, ‘protocols’, ‘recommendations’, ‘guidelines’, ‘prevention’, ‘ileus’, ‘gastrointestinal motility’, ‘bowel function’, ‘gastrointestinal recovery’, ‘intestinal pseudo-obstruction’, ‘colon’, ‘rectum’, ‘colorectal’, ‘surgery’, ‘colorectal surgery’, ‘colectomy’ and ‘general surgery’ (Tables 1 and 2). The search was limited to studies published in the English language. Additional studies were identified on inspection of the reference lists of reviewed articles.

Database: EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Central Register of Controlled Trials , Embase Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, fx, dq, nm, kf, px, rx, an, ui, sy]	
ERAS	1. ERAS.mp 2. Enhanced Recovery After Surgery.mp 3. Or/ 1 - 2
Recommendations	4. Protocols.mp 5. Guidelines.mp 6. Recommendations.mp 7. Or/ 4 - 6
Prevention	8. Prevention.mp
Ileus	9. Ileus.mp 10. Gastrointestinal motility.mp 11. Bowel function.mp 12. Gastrointestinal recovery.mp 13. Intestinal pseudo-obstruction.mp 14. Or/ 9 – 13
Colorectal	15. Colorectal.mp 16. Colon.mp 17. Rectum.mp 18. Or/ 15 - 17
Surgery	19. Colorectal surgery.mp 20. Colectomy.mp 21. Surgery.mp 22. Or/ 19 - 21
	23. AND/ 3, 7, 8, 14, 18, 22

Table 1 Search strategy for scoping review (A)

Database: EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Central Register of Controlled Trials , Embase , Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, fx, dq, nm, kf, px, rx, an, ui, sy]	
ERAS	1. ERAS.mp 2. Fast track Protocols.mp 3. Multimodal pathway.mp 4. Multimodal rehabilitation.mp 5. Or/ 1 - 4
Recommendations	6. Protocols.mp 7. Guidelines.mp 8. Recommendations.mp 9. Or/ 6 - 8
Colorectal	10. Colorectal.mp 11. Colon.mp 12. Rectum.mp 13. Or/ 10 - 12
Surgery	14. Surgery.mp 15. Colorectal surgery.mp 16. General surgery.mp 17. Or/ 14 - 16
	18. AND/ 5, 9, 13, 17

Table 2 Search strategy for scoping review (B)

3.2.2 Eligibility criteria

All studies specifying enhanced recovery or fast-track or multimodal pathway protocols (ERPs) for colorectal surgery in their full text, abstract, or conference paper were eligible for inclusion. Studies were excluded if they were review articles, but further articles were identified from reference lists of reviews before exclusion.

3.2.3 Study selection

The titles and abstracts of studies identified in the search were read to identify potentially relevant articles, conference papers and abstracts falling within the eligibility criteria. The full texts of potentially relevant studies were reviewed, and articles were included if they

fulfilled the eligibility criteria along with a description of ERP interventions directed towards stimulation of bowel motility, prevention of POI or reducing its duration, or facilitating return of GI function after surgery. If multiple studies were found to be using the same reference ERP, then the latest study with the published protocol was included for analysis. Excluded studies were recorded with the reason for exclusion. The full text of all eligible studies were assessed independently by two authors (NNDV and HMK), and any disagreements over inclusion and exclusion were resolved by consensus.

3.2.4 Data extraction and quality assessment

The first author (NNDV) extracted the following data from the selected articles: first author, country of origin, year of publication, type of study, recommended intervention for ileus prevention or bowel motility, route of administration, dosage, frequency, duration of administration and grade of recommendation based on evidence in guidelines. The second reviewer verified the data extraction. The goal of this review was a qualitative summary description of the interventions used in ERPs and not the actual values or effect sizes of these measures. Similarly, the included papers were not evaluated for quality or assessment of bias as methodological soundness and validity of any reported results were not the objective of this review.

3.2.5 Statistical analysis

Data were analysed using descriptive statistics and presented as frequency and percentages.

3.3 Results

3.3.1 Study characteristics

Of 481 manuscripts screened, 37 individual ERPs were published in 37 studies including 41 centres as shown in Figure 2. There were 18 cohort studies,[169-186] seven historically

controlled studies,[154, 187-192] five guidelines,[155, 193-196] four randomized controlled trials (RCTs),[39, 197-199] one RCT protocol,[200] one case series[201] and one narrative review.[202] Institutions in Europe were the most frequent study locations (25 of 37, 67.6%), followed by North America (10 of 37, 27%), Asia (4 of 37, 10.8%) and Oceania (2 of 37, 5.4%), respectively. All the guidelines found in the review were published between 2013 and 2018; however, the timeline of the patient cohorts published (and their surgery) ranged from the years 1999 to 2017. Full study characteristics are shown in Table 3.

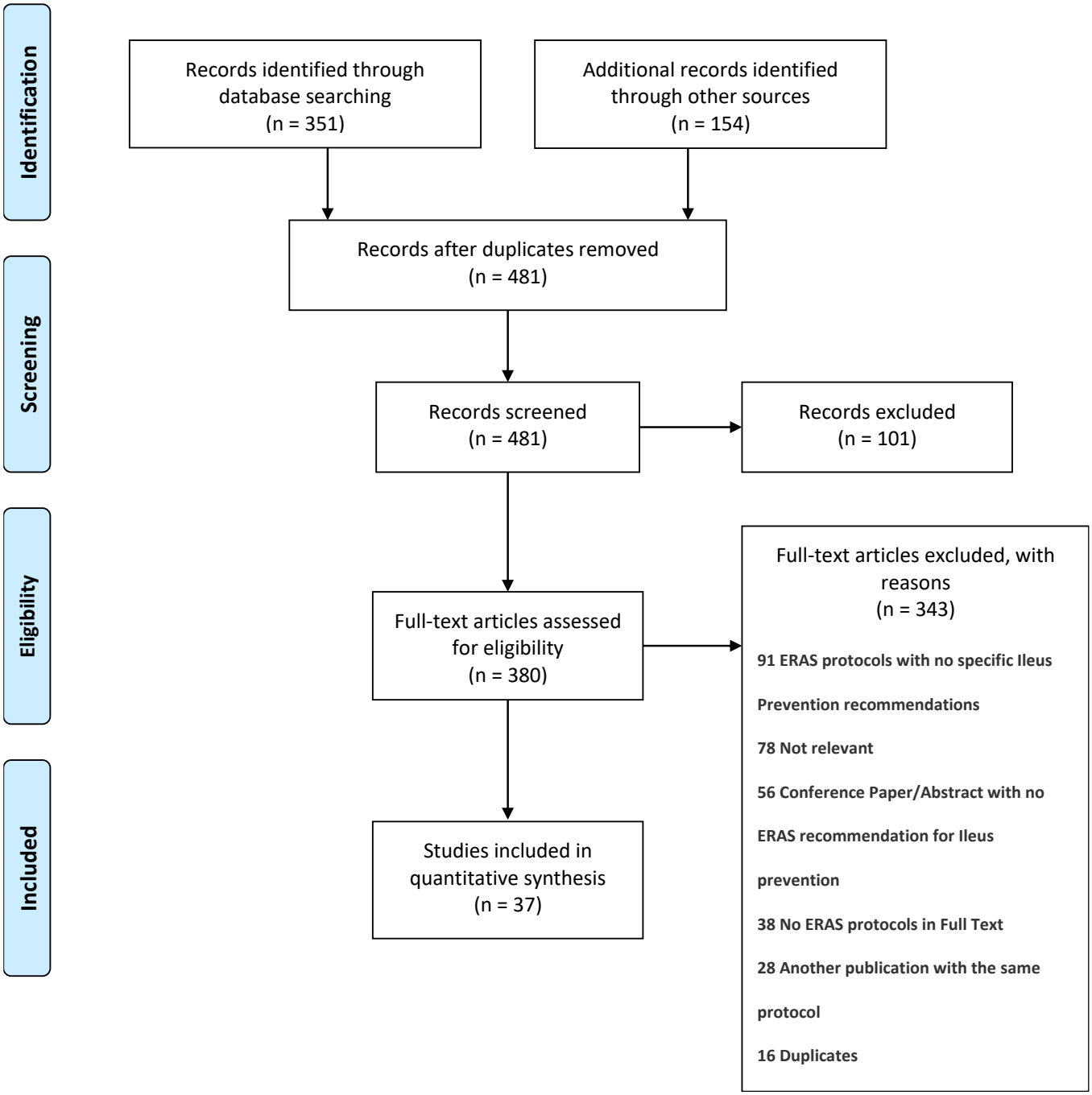

Fig. 2 PRISMA flow chart diagram for Systematic Scoping Review

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal. pmed1000097. For more information, visit www.prisma-statement.org.

First Author	Country of origin	Year	Study design	Recommended Intervention	Route of administration	Dosage	Frequency	From post-operative day	To post-operative day	Grade of recommendation based on Evidence in Guidelines
Alfonsi et al.[193]	France	2014	Guidelines	Chewing gum (C)	Oral	NA (Not available)	NA	NA	NA	(C) - Grade 2+
Bakker et al.[169]	The Netherlands	2015	Prospective Cohort	Magnesium (Mg)	Oral	1.5 gm	Once daily (OD)	Day 1	NA	
Basse et al.[170]	Denmark	2004	Prospective Cohort	Magnesia	Oral	1 gm	BD (Twice daily)	Day 0	NA	
Bray et al.[171]	USA	2017	Retrospective Cohort	Alvimopan	Oral	1 tab	BD	Day 0 1 day prior (One dose)	Till bowel opening (BO)	
Carmichael et al.[194]	USA	2017	Guidelines	Chewing gum (C) Alvimopan (A)	Oral	C - 1 stick A - 6-12mg	C – TDS [a] to QID [b] A - BD	NA	NA	(C) – Grade 1B (A) – Grade 1B
Cruz et al.[172]	USA	2017	Retrospective Cohort (Abstract)	Alvimopan	NA	NA	NA	NA	NA	
Ehrlich et al.[173]	Finland	2014	Prospective cohort	Milk of Magnesia	Oral	NA	NA	NA	NA	
Esteban et al.[187]	Spain	2013	Historically controlled study	Lactulose (Mg based)	Oral	1 Sachet	BD	Day 1	NA	
Forsmo et	Norway	2016	RCT	Chewing gum	Oral	NA	NA	Day 1	NA	

al.[39]				Alvimopan Magnesium						
Garulli et al.[197]	Italy	2017	RCT	Chewing gum	Oral	NA	NA	Day 0	NA	
Gignoux et al.[201]	France	2015	Case series	Chewing gum + Mg Supplements	Oral	NA	TDS [a]	NA	NA	
Gillissen et al.[188]	The Netherlands	2013	Historically controlled study	Magnesium Oxide (MgO)	Oral	1 gm	NA	Day 1	NA	
Gustafsson et al.[155]	New Zealand/ The Netherlands/ Sweden/ Switzerland/ UK/ USA	2018	Guidelines	Alvimopan (A) Bisacodyl (B) Chewing gum (C) Coffee (Co) Daikenchuto (D) MgO (Mg)	Oral	NA	NA	NA	NA	Grade 2 for all.
Haverkamp et al.[174]	The Netherlands	2012	Retrospective cohort	MgO	Oral	NA	NA	Day 1	NA	
Kehlet et al.[175]	Denmark	1999	Prospective cohort	Magnesium	Oral	1 gm	BD	Day 0	Post discharge -Not specified	
Keller et al.[202]	USA	2013	Narrative review	Alvimopan (A) Bisacodyl (B) Chewing gum (C)	Oral	A -12 mg B -10 mg C - 1 piece	A - BD B - BD C - NA	NA	A - Till discharge (Lap)/ 7 days (Open) B - NA C - NA	

Kennedy et al.[200]	UK	2012	RCT Protocol	Lactulose or Mg based preparation	Oral	NA	NA	NA	NA	
Khoo et al.[198]	UK	2007	RCT	Magnesium Hydroxide (MgOH)	Oral	NA	NA	NA	NA	
King et al.[189]	UK	2006	Historically controlled study	Lactulose	Oral	15 ml	BD	NA	NA	
Kisialeuski et al.[176]	Poland	2015	Prospective Cohort	Lactulose (L) Liquid Paraffin (P)	(L) – Oral (P) - Oral	NA	NA	NA	NA	
Liu et al.[154]	USA	2017	Historically controlled study	Chewing gum	Oral	NA	NA	NA	NA	
McLeod et al.[195]	Canada	2015	Guidelines	Chewing gum (C)	Oral	NA	NA	NA	NA	(C) – Grade 1B
Mohn et al.[177]	Norway	2009	Prospective cohort	MgO	Oral	1 gm	BD	Day 0	7 days	
Nygren et al.[178]	Sweden	2009	Prospective cohort	MgO	Oral	1 gm	BD	Day 0	Till discharge	
Nygren et al.[196]	Sweden/USA/Canada/Norway/UK/ New Zealand /Spain	2013	Guidelines	MgOH (Mg) Bisacodyl (B) Chewing gum (C)	Oral	NA	NA	NA	NA	(C) – Grade 1 (Mg), (B) – Grade 2
Oh et al.[179]	South Korea	2016	Retrospective Cohort	Laxative	Oral	NA	NA	NA	NA	
Okrainec et al.[180]	Canada	2017	Prospective cohort	Chewing gum	Oral	1 stick	TDS [a]	Day 1	NA	

Ota et al.[181]	Japan	2017	Prospective Cohort	Chewing gum Laxative	Oral	NA	NA	NA	NA	
Polle et al.[190]	The Netherlands	2007	Historically controlled study	MgO	Oral	1 gm	BD	Day 1	NA	
Ren et al.[199]	China	2012	RCT	Chinese herbal medicine with acupuncture Infusion of raw rhubarb (R) + neostigmine at Zusanli acupoint (N)	Infusion	R -10 gm N -0.5 mg	R - 5 times a day N - OD	Day 0	NA	
Romain et al.[182]	Switzerland	2016	Retrospective Cohort	Not specified (As per guidelines)[43,45]	NA	NA	NA	NA	NA	
Roulin et al.[183]	Switzerland	2017	Prospective Cohort	MgOH	Oral	NA	NA	NA	NA	
Schwenk et al.[184]	Germany	2008	Prospective Cohort	MgO	Oral	300 mg	TDS [a]	Day 0	Till first BO	
Shavit et al.[191]	USA	2015	Historically controlled study (Abstract)	Chewing Gum	Oral	NA	NA	Day 0	Day 1	
Shida et al.[185]	Japan	2017	Retrospective Cohort	MgO	Oral	NA	NA	NA	NA	
Slieker et al.[192]	Switzerland	2018	Historically controlled study	MgOH	Oral	450 mg	BD	NA	NA	
Wichmann et al.[186]	Germany	2007	Prospective Cohort	Neostigmine	SC[c]	0.5 mg	OD - Day 0 TDS [a] – Day 1	Day 0	Day 1	

Table 3 Summary characteristics of included studies

[a] TDS – three times a day

[b] QID – four times a day

[c] SC – subcutaneous

3.3.2 Intervention types

The interventions used varied throughout the protocols as shown in Table 4. Simple laxatives constituted the largest category of medications recommended in 24 of 37 studies (64.5%). The single most commonly used intervention for stimulation of bowel motility was a magnesium (Mg) based laxative (18 of 37, 48.6%) such as magnesium oxide (MgO) and magnesium hydroxide (MgOH). The second most common intervention used was chewing gum (13 of 37, 35.1%). Other less commonly recommended interventions were Alvimopan (6 of 37, 16.2%), lactulose (4 of 37, 10.8%), neostigmine (2 of 37, 5.4%) and Bisacodyl (2 of 37, 5.4%). Liquid paraffin, coffee, daikenchuto and Chinese herbal medicine with acupuncture infusion of raw rhubarb were only mentioned in one protocol each (2.7%).

Laxatives
Magnesium based laxatives • Magnesium • Magnesia • Magnesium based lactulose • Magnesium oxide (MgO) • Magnesium hydroxide (MgOH) **Lactulose** **Bisacodyl** **Liquid paraffin**
Sham feeding
Chewing gum
Mu antagonist
Alvimopan
Cholinesterase inhibitor
Neostigmine
Herbal medicine
Infusion of raw rhubarb at Zusanli acupoint **Daikenchuto**
Misc
Coffee

Table 4 Interventions recommended for targeting POI and return of GI function.

3.3.3 Medication doses

The dosage and frequency of the commonest medication used in the protocols (magnesium-based laxatives) ranged from 300 to 1500 mg given once daily to three times daily, whereas recommendation of usage of chewing gum ranged from one to three times daily. Alvimopan (6–12 mg) was recommended once to twice daily. Dosage and frequency of the medications were not mentioned in 19 of 37 protocols (51.4%).

3.3.4 Evidence quality reported

As per the evidence strength assessment reported in the included studies, the evidence for oral laxatives, including magnesium-based laxatives was reported to be weak for all outcome measures. The evidence for chewing gum in achieving the return of GI function changed from moderate/strong in earlier papers to weak in later papers because of available newer evidence.[157] Alvimopan was reported to have moderate to strong evidence for improving return of GI function, reduction in the incidence of ileus, and reduced day stay, especially in patients undergoing laparotomy.[155]

3.4 Discussion

We have conducted a systematic review of ERPs specifically looking at recommended interventions to reduce the duration of POI and/or improve return of GI function after colorectal surgery. We found 37 individual ERPs published from 41 centres with these interventions included. There was significant variation in recommended interventions, with simple laxatives, particularly magnesium-based laxatives, being most commonly recommended, followed by chewing gum, oral Alvimopan and a smaller number of other interventions.

It is interesting to note that even though laxatives such as magnesium oxide or hydroxide formed the most common recommendation in this context, there is only scant evidence

supporting its use as referenced in the guidelines. A small RCT conducted by Andersen et al.[203] with 49 patients failed to show any significant effect of oral magnesium on time to first flatus or bowel movement (18 versus 14 h and 42 versus 50 h, respectively; each P > 0.15). There was also no effect on early intake of fluids, protein drinks, solid food, nausea and vomiting, mobilization, or length of stay (LOS) within a well-established ERP. A scintigraphic study demonstrating the assessment of GI transit after surgery conducted by Basse et al.[204] showed a shorter time to post-operative defecation with MgOH but this study was limited by a very small sample size (n = 12), comparison with normal healthy volunteers in the control group, and potential confounding of the findings by relative contribution of epidural analgesia with morphine and cisapride (prokinetic). There has only been one other RCT investigating laxatives, published by Zingg et al.[205] with 169 patients undergoing colorectal surgery. The study group received oral bisacodyl (10 mg, twice a day) from the day before surgery to the third post-operative day. This study demonstrated significantly shorter time to GI-3 (mean time to first flatus passed, first defecation and first solid food tolerated) in the bisacodyl group (3.0 versus 3.7 days, P = 0.007) with a 1-day difference in time to defecation (3.0 versus 4.0 days, P = 0.001). Although this study demonstrated an improvement in post-operative intestinal function, there was no effect of bisacodyl on tolerance to solid food or LOS in hospital.

Chewing gum after elective colorectal resection was first proposed as a mechanism for sham feeding and gastric stimulation in 2002.[206] Sham feeding acts via the parasympathetic nervous system, stimulating bowel motility. A recent Cochrane review,[207] based on 81 studies with 9072 patients, showed that chewing gum reduced the time to first flatus by 10.6 h, the time to first bowel movement by 12.7 h and LOS by 0.7 days. The evidence, however, was considered to be of low quality and limited external validity, owing to small sample sizes (with the average number of patients per trial ranging from 20 to 50),

the absence of a perioperative ERPs setting and the limited diversity of surgical procedures. The results of this review have also since been refuted by a recent large multicentre RCT by de Leede et al.[157] which found that the addition of chewing gum to an institutionalized ERP following elective abdominal surgery did not decrease the LOS, time to first flatus or time to first defecation. This is considered by the authors to be the definitive study on this topic due to its high-quality design and large number of patients (2000 patients included).

Alvimopan is a competitive μ-opioid receptor antagonist, which blocks GI μ-opioid receptors without altering the central analgesic effects of opiates. Several RCTs and pooled post hoc analyses have demonstrated accelerated time to recovery of GI function and significantly shorter LOS with Alvimopan 6 and 12 mg doses compared with placebo for patients undergoing colorectal surgery.[158, 208-212] Early data which suggested that Alvimopan may have no added benefit in patients undergoing minimally invasive colorectal surgery within an ERPs setting[159, 213] has also now been refuted with the recent publication of large studies within established ERPs (2010–2014), showing significant patient benefits in terms of GI recovery and LOS.[214, 215] Some long-term benefits have also been reported, with less post-discharge ileus and a lower re-admission rate out to 90 days.[214]

In summary, ERP recommendations specific to interventions targeted at reducing the duration of POI and facilitating return of GI function are varied and inconsistent. There is good evidence reported to support the use of Alvimopan after elective colorectal surgery, and weaker evidence (from a single RCT) on the use of Bisacodyl. Despite the commonly recommended use of Mg-based laxatives, there is currently very little evidence available to support this practice. Moreover, there is no evidence available for the use. of inexpensive, off the shelf laxatives such as Coloxyl/Senna, polyethelene glycol or enemas after

colorectal surgery. With the advent of widespread adoption of early post-operative feeding, the role of chewing gum is questionable and is not supported by current evidence. The authors do not believe that further data on chewing gum is required and instead efforts should be directed towards generating data to support or refute the use of simple laxatives or other novel medical interventions.

This study has several limitations. ERPs use multimodal strategies to accelerate post-operative recovery and reduce morbidity. It is likely that the differences observed among different institutional protocols are due to both system-level and provider-specific factors. This also may explain the geographical differences in the interventions recommended (e.g., Alvimopan is currently not funded in Oceania). Another limitation of this study is that unpublished institution-specific ERPs could not be included, and there is a possibility that other laxatives are being actively used without prior publication. It should also be noted that this review constitutes a qualitative summary description of the interventions used in ERPs and did not capture effect sizes of these measures. Finally, this study focused on pharmacological agents aimed specifically at limiting the duration of ileus, but we do note the potential role of other measures such opioid minimization using multimodal analgesia, use of minimally invasive surgery, eliminating nasogastric tube placement and goal-directed fluid therapy.

3.5 Conclusion

ERP recommendations specific to interventions targeting POI and return of GI function are varied. While laxatives are the most commonly recommended intervention, there is only weak evidence reported to support this practice.

CHAPTER 4: SAFETY AND EFFICACY OF LAXATIVES AFTER MAJOR ABDOMINAL SURGERY- SYSTEMATIC REVIEW AND META-ANALYSIS

Statement of Authorship

Title of Paper	Safety and efficacy of laxatives after major abdominal surgery: systematic review and meta-analysis
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Dudi-Venkata NN, Seow W, Kroon HM, Bedrikovetski S, Moore JW, Thomas ML, Sammour T. Safety and efficacy of laxatives after major abdominal surgery: systematic review and meta-analysis. BJS Open. 2020 Aug;4(4):577-586. doi: 10.1002/bjs5.50301. Epub 2020 May 27. PMID: 32459069; PMCID: PMC7397346.

Principal Author

Name of Principal Author (Candidate)	Nagendra N. Dudi-Venkata		
Contribution to the Paper	Conception and design of the project Acquiring research data Analysis and interpretation of research data Drafting significant parts of the article and critically revising it		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	26/11/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Warren Seow		
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Signature		Date	26/11/2020

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Sergei Bedrikovetski		
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Signature		**Date**	26/11/2020

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Contribution to the paper	Conception and design of the project Analysis and interpretation of research data Drafting significant parts of the article and critically revising it		
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Signature		**Date**	26/11/2020

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Contribution to the paper	Conception and design of the project Analysis and interpretation of research data Drafting significant parts of the article and critically revising it		
Signature		**Date**	26/11/2020

4.1 Introduction

Recovery of gastrointestinal function is often delayed after major abdominal surgery, leading to post-operative ileus (POI).[1] For patients experiencing POI, it is a source of significant morbidity and discomfort, causing vomiting, abdominal distension and intolerance to diet, and often leading to invasive interventions such as insertion of a nasogastric tube.[2, 164] Post-operative complications such as POI can have a significant impact on patient outcome, in terms of short-term recovery, long-term survival, and quality of life.[3, 17, 216] Healthcare expenditure is almost twice as high when patients develop POI compared with that for patients who do not,[5, 43, 44] and there is evidence that 91 per cent of these increased costs relate directly to the patient's immediate postoperative stay.[5]

Since the implementation of enhanced recovery protocols (ERPs), the management of patients undergoing abdominal surgery has improved, with a reduction in the incidence of complications.[165-167, 217-220] However, despite the widespread adoption of ERPs, the incidence of POI remains high at around 10–30 per cent, with delayed return of gastrointestinal function continuing to be a common barrier to discharge from hospital.[3, 4, 6, 7] One possible reason for this could be because of a complex, intricate, and as yet incompletely defined relationship. between the neuroinflammatory, vagal and drug-induced processes underlying the pathophysiology of POI.[16, 221] Multimodal strategies have been employed to improve the return of gastrointestinal function after surgery, including the routine use of postoperative laxatives.[149, 155] The recommendations for laxative use are varied in different international ERP protocols, with only weak evidence quoted to support their efficacy.[156] In addition, published data on the safety of postoperative laxatives in this setting are limited, in particular with regard to anastomotic leak.

This systematic review aimed to assess the safety and efficacy of laxative use after major abdominal surgery.

4.2 Methods

The study protocol was registered prospectively with the PROSPERO database of systematic reviews (CRD42019126282). PRISMA guidelines[168] were used for conducting and reporting the results of this study.

4.2.1 Search strategy

Two independent reviewers performed a systematic search of the MEDLINE (1946 to 21 May 2019), Embase (1974 to 21 May 2019), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost) databases (1974 to 21 May 2019), and the Cochrane Database of Systematic Reviews, Cochrane Clinical Trials Register, and Database of Abstracts on Reviews and Effectiveness. All 'Primary Registries' listed in the WHO Registry Network (including ClinicalTrials.gov) were searched for ongoing (unpublished) RCTs (searched on 22 May 2019). The detailed search strategy is shown in Table 5. Medical subject headings (MeSH) and keyword search terms related to 'ERAS', 'recommendations', 'laxatives', 'abdominal', 'surgery', 'prevention', 'postoperative', 'ileus' and 'gastrointestinal 2' (GI-2) were used. Unpublished data were also sought from authors of trials listed in the registry. The search was limited to studies published in the English language. The last search update was on 22 May 2019.

4.2.2 Eligibility criteria

Studies were included if they were RCTs conducted in patients aged more than 16 years undergoing elective open or minimally invasive major abdominal surgery, and specifically assessed the effect of laxatives on the return of gastrointestinal function, defined by time to passage of stool or using a validated measure such as. GI-2 or GI-3. GI-2 is a

composite measure of tolerance to solid diet for 24 h (no vomiting) and passage of stool, whereas GI-3 is a composite measure of tolerance to solid diet for 24 h (no vomiting) and passage of flatus.[146] Eligible articles with a description of interventions directed towards stimulation of bowel motility, prevention of POI or reducing its duration, or facilitating the return of gastrointestinal function after surgery were included in the final analysis. All gastrointestinal (colorectal, gastric, small bowel, hepatic, pancreatic resection), urological (nephrectomy, cystectomy, prostatectomy) and gynaecological (uterus and ovary resection, pelvic floor reconstruction) operations, undertaken for any indication, were considered as major abdominal surgery. Studies with quasi randomized, prospective and retrospective design, and case–control studies were excluded.

Database: Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® < 1974 to 21st May 2019>, Embase <1974 to 21st May 2019>, CINAHL with full text (EBSCOhost) <1974 to 21st May 2019>, EBM Reviews – Cochrane Database of Systematic Reviews, Clinical Trials Register, Database of Abstracts on Reviews and Effectiveness <22nd May 2019>, World Health Organisation (WHO) Registry Network (including Clinical Trials.gov) and ANZCTR <22nd May 2019> [mp= ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, fx, dq, nm, kf, px, rx, an, ui, sy]	
ERAS	1. ERAS.mp 2. Fast track Protocols.mp 3. Multimodal pathway.mp 4. Multimodal rehabilitation.mp 5. Or/ 1-4
Recommendations	6. Recommendations.mp 7. Guidelines.mp 8. Protocols.mp 9. Or/ 6 - 8
Laxatives	10. Laxatives.mp 11. Aperients.mp 12. Cathartic.mp 13. Or/ 10 - 12
Abdominal	14. Abdominal.mp 15. Gastrointestinal.mp 16. Colon.mp 17. Rectum.mp 18. Or/ 14 - 17
Surgery	19. Abdominal surgery.mp 20. Digestive System Surgical Procedure.mp 21. Digestive surgery.mp 22. Colorectal surgery.mp 23. Colectomy.mp 24. General surgery.mp 25. Surgical oncology.mp 26. Gynaecologic surgery.mp 27. Laparoscopy.mp 28. Laparotomy.mp 29. Or/ 19 - 28
Prevention	30. Prevention.mp 31. Primary prevention.mp 32. Secondary prevention.mp 33. Or/ 30 - 32
Postoperative	34. Postoperative.mp 35. Postoperative period.mp 36. Postoperative care.mp 37. Post anaesthetic care.mp 38. Postoperative complications.mp 39. Or/ 34 - 38
Ileus	40. Ileus.mp

	41. Paralytic ileus.mp 42. Postoperative ileus.mp 43. Gastrointestinal motility.mp 44. Gastrointestinal tract function.mp 45. Bowel function.mp 46. Gastrointestinal recovery.mp 47. Digestive system recovery.mp 48. Intestinal pseudo-obstruction.mp 49. Colonic pseudo-obstruction.mp 50. Postoperative Complications.mp 51. Or/ 40 - 50
Gastrointestinal 2 (GI-2 is a composite measure of tolerance to solid diet for 24 hrs (no vomiting) AND passage of stool)	52. Gastrointestinal 2.mp 53. GI-2.mp 54. Time to tolerance of solid food.mp 55. Time taken tolerance of diet.mp 56. Time to passage of first stool.mp 57. Time to passage of stool.mp 58. Return of bowel function.mp 59. Return of gastrointestinal function.mp 60. Or/ 52 - 59
	61. AND/ 5, 9, 13, 18, 29, 33, 39, 51, 60

Table 5 Search strategy for systematic review

4.2.3 Study selection

All identified titles and abstracts were reviewed independently by two investigators. This was followed by a further review of the full texts of potentially relevant studies. Bibliographies of relevant articles also underwent a manual cross-reference search to identify any other studies that had been missed in the search. Any potential differences over study selection were resolved by consensus and, if needed, adjudication was undertaken by a third reviewer.

4.2.4 Data collection process

Data of all included studies were extracted independently by two reviewers using a standard data extraction form. Outcome measures data, including GI-2 or GI-3, time taken to passage of first stool, time taken to tolerance of solid food, time taken to first flatus,

length of hospital stay, postoperative complications, adverse drug effects and readmission to hospital, were extracted. In addition to the measured outcomes, other data related to general study characteristics, including author name, country of origin, year of study, study type, patient population, number of patients in control and intervention arm, site of surgery, type of intervention (laxatives) and route of administration, were also extracted. All the data were cross-checked at the end, and any discrepancies in the extraction of the data were resolved by the third reviewer.

4.2.5 Risk of bias in individual studies

The Cochrane Collaboration risk-of-bias tool[222] was used independently by two authors to assess the methodological quality of individual RCTs. A consensus was sought for any disagreements.

4.2.6 Assessment of quality of evidence

Quality of evidence and summary of findings were tabulated using the GRADEpro Guideline Development Tool (McMaster University, Hamilton, Ontario, Canada).

4.2.7 Statistical analysis

JBI SUMARI online software (https://www.jbisumari.org/) was used for quantitative analysis of aggregated data. An intention-to-treat methodology was adopted. Mean estimates were calculated by the method proposed by Wan et al.[223] Effect estimates are reported as odds ratios (ORs) and weighted mean differences (MDs) with 95 per cent c.i. for dichotomous and continuous outcomes, respectively. Considering the heterogeneity between the studies, pooled estimates of effect were calculated using a random-effects model. Statistical significance was set at $P<0{\cdot}050$ for the degree of heterogeneity, which was determined by the $\chi 2$ test. Heterogeneity measured by the I2 statistic was perceived as considerable when the I2 value was above 75 per cent.[224] To decrease potential bias

introduced by diverse indications and surgical methods, a planned subgroup analysis was performed on primary and secondary outcomes for patients who underwent colorectal surgery.

4.3 Results

The literature search identified 323 studies. After removal of 13 duplicates, a further 280 studies were excluded after screening by title and abstract. Four authors of unpublished studies from trial registries were contacted via e-mail to enquire about the progress of their study and the relevant results, if any. One author responded and confirmed that the trial was not yet completed. In addition, authors of all the RCTs included in the meta-analysis were contacted, requesting raw trial data to explore finer details of the trial further, but none responded. Thirty studies met the prespecified inclusion criteria and were evaluated by full-text analysis. This analysis initially yielded six RCTs for inclusion, but one[225] of these was excluded on further review as participants in this study received baseline laxative (docusate sodium) in both intervention and control groups. Hence, five RCTs[203, 205, 226-228] were finally selected for inclusion (Fig. 3).

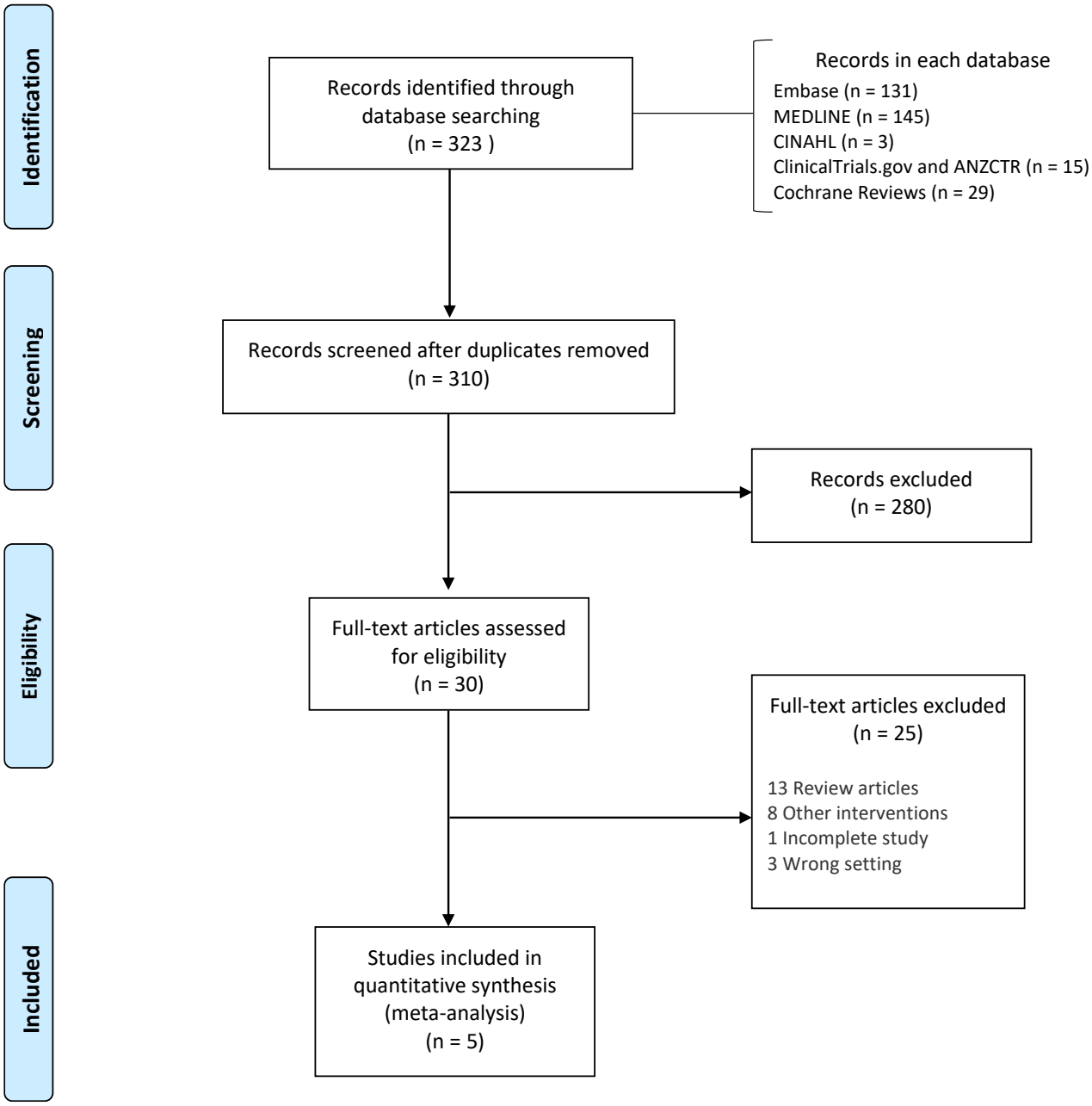

Fig. 3 PRISMA diagram for the Systematic review and Meta-analysis

CINAHL, Cumulative Index to Nursing and Allied Health Literature; ANZCTR, Australian New Zealand Clinical Trials Registry.

4.3.1 Characteristics of included studies

The five included RCTs[203, 205, 226-228] were published between 2007 and 2011 and included 416 patients (209 (range 10–100) in the laxative group and 207 (10–100) in the placebo group). Study characteristics, interventions and outcomes are summarized in Tables 6 and 7. The studies were conducted in six countries. Three RCTs[203, 205, 228] involved patients with colorectal disease, and the other two were in patients undergoing hysterectomy[226] and hepatic resection.[227]

Reference	Country	Year	Patient population	No. of patients			Intervention	Route of administration
				Intervention	Control	Total		
Andersen *et al*.[203]	Denmark	2011	Colorectal	31	31	62	Magnesium oxide	Oral
Hansen *et al*.[226]	Denmark	2007	Hysterectomy	34	32	66	Magnesium oxide Disodium phosphate	Oral
Hendry *et al*.[227]	UK Netherlands	2010	Hepatic resection	34	34	68	Magnesium oxide	Oral
Wiriyakosol *et al*.[228]	Thailand	2007	Colorectal	10	10	20	Bisacodyl	Rectal
Zingg *et al*.[205]	Switzerland	2008	Colorectal	100	100	200	Bisacodyl	Oral

Table 6 Characteristics of the included studies

Reference	Intervention	Control	Outcomes	
			Primary	Secondary
Andersen *et al*.[203]	Magnesium oxide 1 g orally, twice daily D0 at 18.00 hours D1–7 twice daily	Placebo	Time to first defaecation (h) Time to passage of flatus (h) Cumulative median no. of orally consumed drinks, supplementary protein drinks and solid foods on D0, D2–3	LOS (days)
Hansen *et al*.[226]	Magnesium oxide 1 g Disodium phosphate: 15 ml D0 6 h after surgery D1 twice daily	Placebo	Time to first defaecation (h) Pain score	
Hendry *et al*.[227]	Magnesium oxide 1 g twice daily D0 to day of discharge	No placebo Standard of care	Time to first defaecation (days) Time to passage of flatus (days)	Oral nutritional intake D1–3 LOS (days)
Wiriyakosol *et al*.[228]	Bisacodyl suppositories 10 mg once daily to twice daily D3 If no defaecation after first dose, second dose administered 12 h later	Placebo	Time to first defaecation (days)	Time to passage of flatus (days) Time to tolerance of diet (days) LOS (days)
Zingg *et al*.[205]	Bisacodyl 10 mg orally, twice daily D −1 to D3	Placebo	Time to first defaecation (days) Time to passage of flatus (days) Time to tolerance of solid diet (days)	LOS (days)

LOS, length of hospital stay; D0, day of surgery; D1, day 1 after surgery; D −1, 1 day before surgery.

Table 7 Characteristics of study Interventions and outcomes

4.3.2 Cochrane Collaboration risk-of-bias assessment

All seven components were assessed as low risk for three RCTs,[205, 227, 228] but there was a high risk of attrition bias for two trials[203, 226] owing to incomplete outcome data. Only a small number of trials were included in this study, so a funnel plot for potential publication bias was not generated as this would not have enough data points to be meaningful. Summary graphs for risk of bias are shown in Figs 4 and 5.

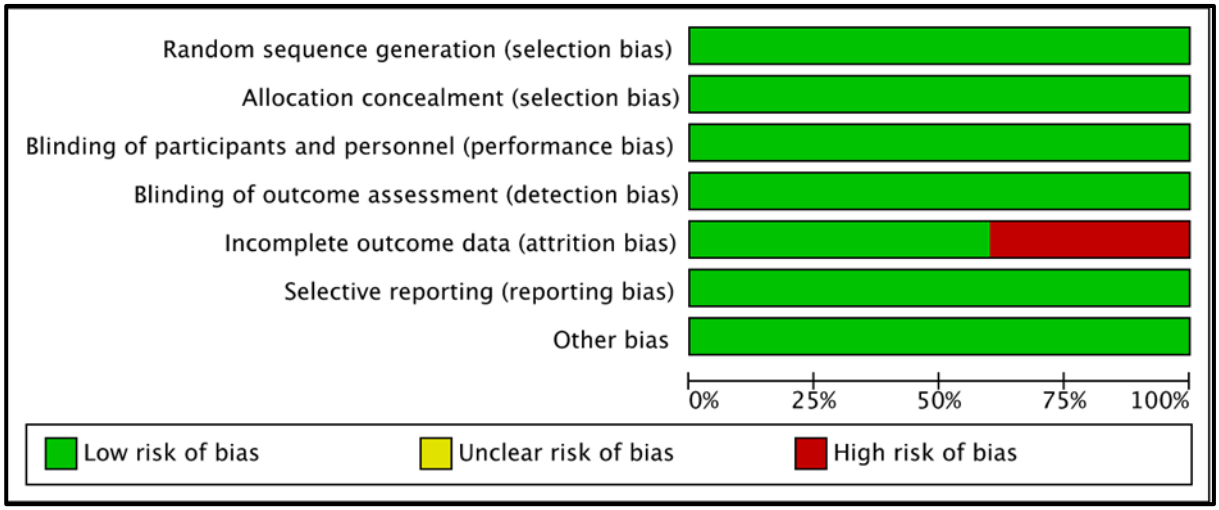

Fig. 4 Overall risk-of bias assessment for the included RCTs

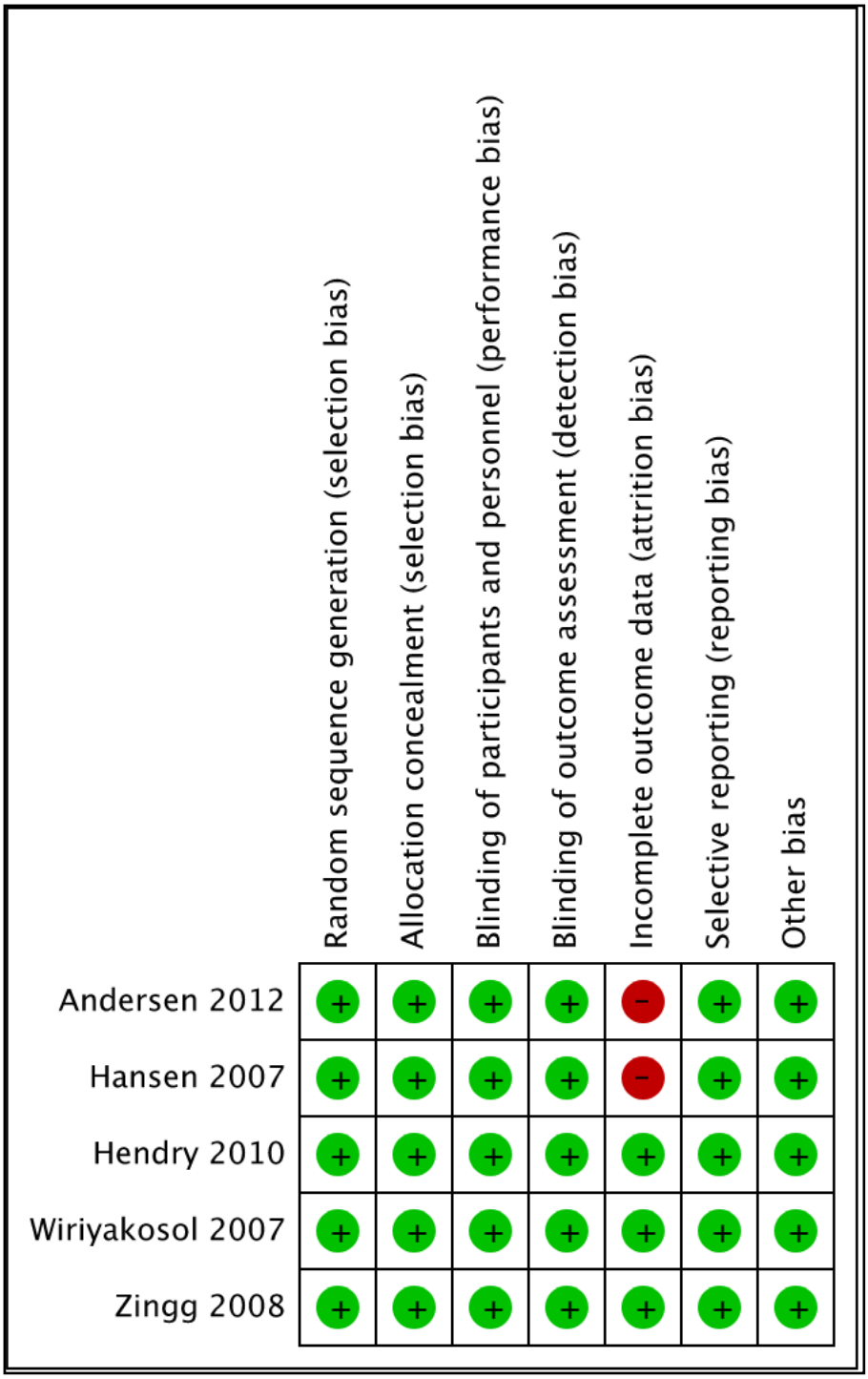

Fig. 5 Risk-of-bias assessment for the individual studies

4.3.3 Study interventions

The most tested laxatives were magnesium oxide and bisacodyl. Oral magnesium oxide was the intervention used in two studies,[203, 227] bisacodyl in two studies (one per rectum[228] and one orally[205]), and disodium phosphate along with magnesium oxide in one study[226]

(Table 6). Laxative regimens differed in terms of the day of starting the first dose and the total duration. Three studies[203, 226, 227] administered the laxatives from the day of surgery (D0), one[205] from the day before surgery (D-1), and one[228] from day three after surgery (D3) (Table 7). Four studies[203, 205, 226, 228] were double-blinded with placebo used as the control, whereas one study[227] was open-labelled to the interventions used because of lack of a feasible placebo and used standard of care in the control arm (no placebo).

4.3.4 Quantitative analysis

Return of gastrointestinal function None of the studies reported GI-2. One study[205] reported significantly shorter time to GI-3 in the laxative versus control group (median 3 (range 1–12·3) versus 3·7 (1·7–10·7) days respectively; P=0·007). Time to the passage of stool was reported by all five studies;[203, 205, 226-228] there was a statistically significant difference for laxatives compared with control (MD -0·83 (95 per cent c.i. -1·39 to -0·26) days; P=0·004), although there was significant heterogeneity between the studies for this outcome (I2 =94 per cent; P<0·001) (Fig. 6).

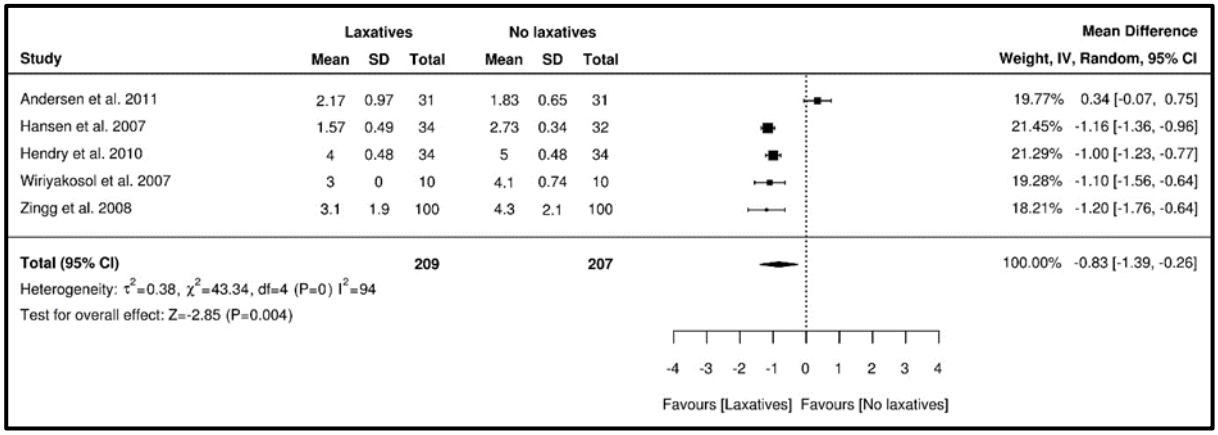

Fig. 6 Time taken to passage of stool in all studies.

4.3.5 Time to passage of flatus

Time to passage of flatus was reported by three studies;[203, 205, 227] there was no statistically significant difference between laxatives and control (MD -0·17 (95 per cent c.i. -0·59 to 0·25) days; P=0·432). There was significant heterogeneity between the studies for this outcome (I2 =87 per cent; P<0·001) (Fig. 7).

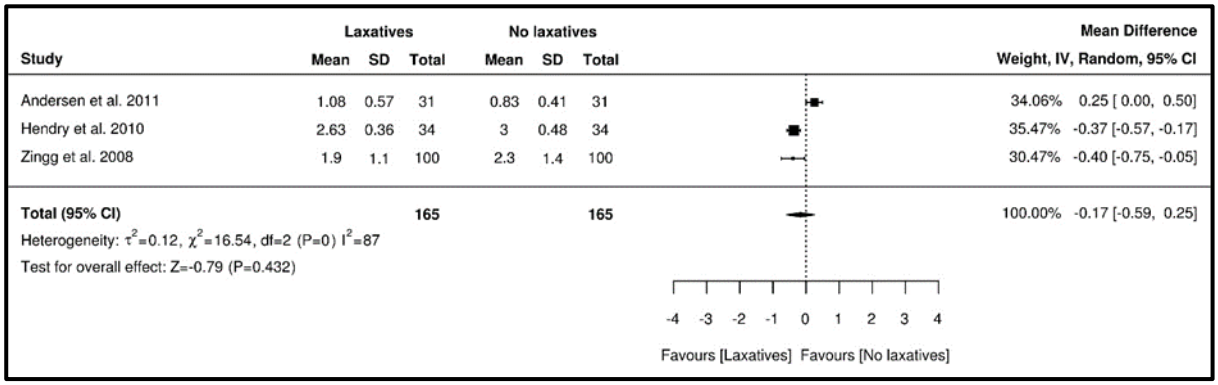

Fig. 7 Time taken to passage of flatus in all studies

4.3.6 Time to a tolerance of diet

Three studies[205, 227, 228] reported time to a tolerance of diet; there was no significant difference between the laxatives. and control group (MD -0·01 (95 per cent c.i. -0·12 to 0·10) days; P=0·865). There was no significant heterogeneity between the studies for this outcome (I2 =0per cent; P=0·677) (Fig. 8).

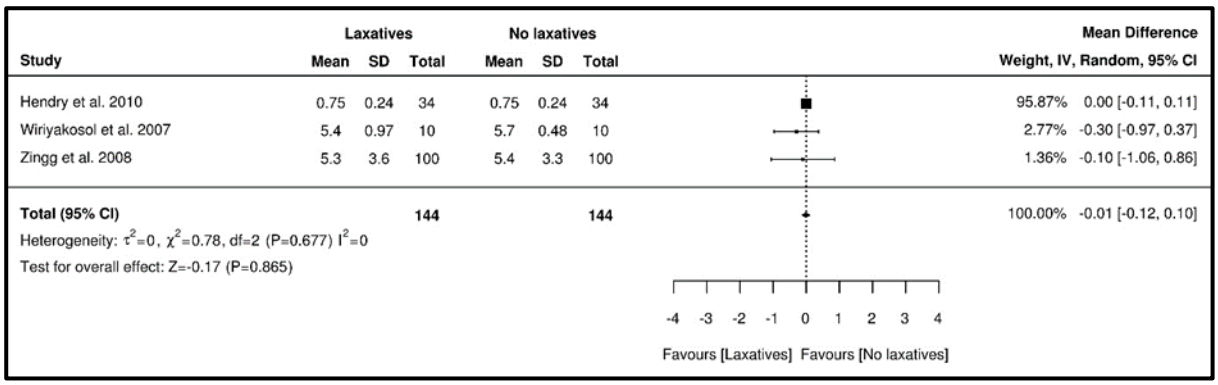

Fig. 8 Time to tolerate diet

4.3.7 Length of hospital stay

Length of hospital stay was reported by all studies;[203, 205, 226-228] there was no significant difference between the laxatives and control group (MD 0·01 (95 per cent c.i. -1·36 to 1·38) days; P=0·992). There was significant heterogeneity between the studies for this outcome (I2 =92 per cent; P<0·001) (Fig. 9).

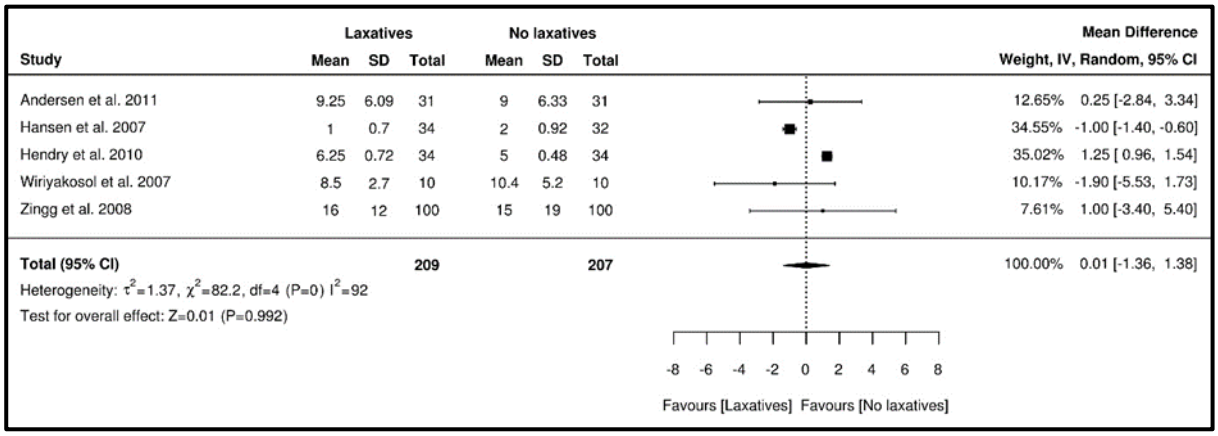

Fig. 9 Length of stay in hospital in all studies

4.3.8 Postoperative complications

Pooled analysis was not done on these outcomes as the data available in the included studies were limited. Superficial surgical-site infections were reported in two (20 per cent)

of ten patients in the control group in one study,[228] whereas another[203] reported one death (3 per cent) of 31 patients in the laxative group from cardiac arrest on the second postoperative day; however, the complication profile was similar in both groups in other reports.[226, 227] No significant difference in surgical complications (anastomotic leak, surgical-site infection, abdominal fascia dehiscence, postoperative bleeding) or non-surgical morbidity (pneumonia, cardiac failure, pulmonary embolism, renal failure, urinary tract infection) was reported in another RCT;[205] overall surgical morbidity in this study was 23·1 per cent, whereas non-surgical complications occurred in 13 per cent of all patients.

4.3.9 Subgroup analysis

In the three studies[203, 205, 228] with only colorectal patients, no significant difference was found in time to passage of stool between the laxatives and control group (MD -0·64 (95 per cent c.i. -1·63 to 0·34) days; P=0·201). Heterogeneity was significant for this outcome (I2 =92 per cent; P<0·001) (Fig. 10).

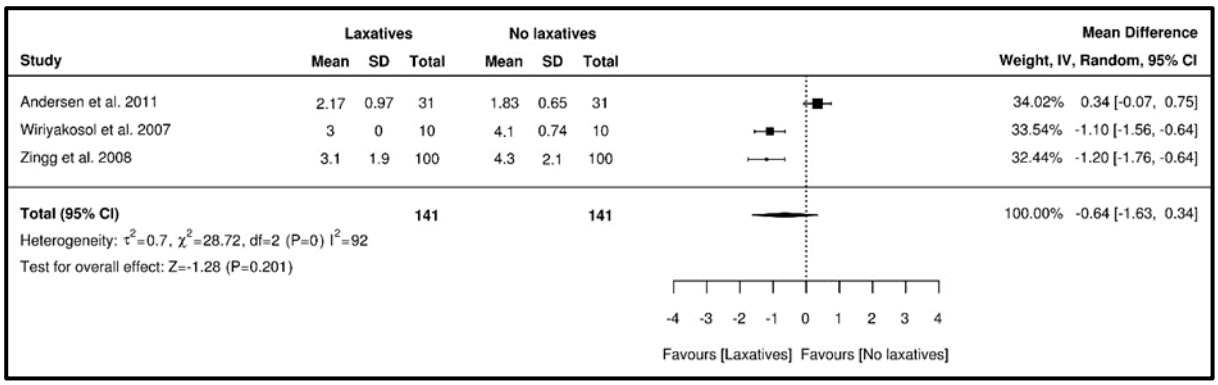

Fig. 10 Time to passage of stool in colorectal patients

Length of hospital stay in the laxatives and control group showed no significant difference (MD -0·29 (-2·36 to 1·79) days; P=0·787). There was no heterogeneity between studies for this outcome (I2 =0 per cent; P=0·548) (Fig. 11).

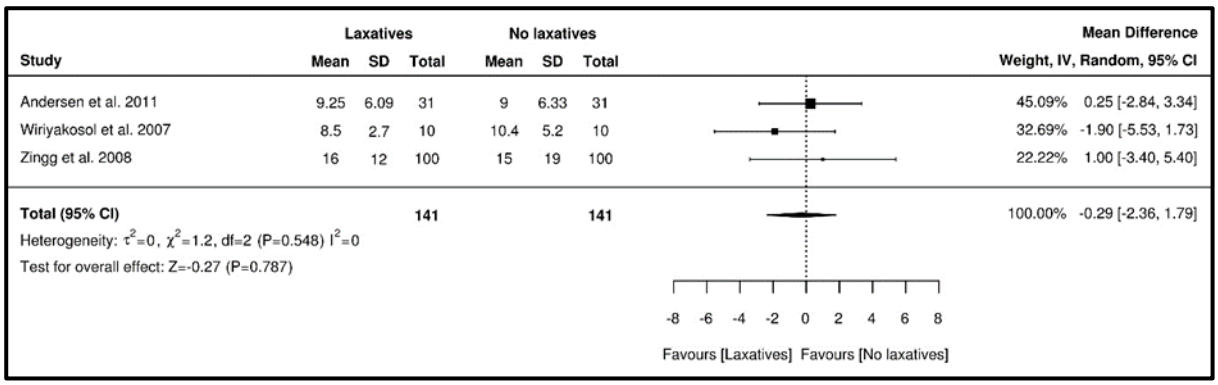

Fig. 11 Length of stay in hospital in colorectal patients

Anastomotic leak rates for these studies ranged between 0 per cent in both groups,[228] 8·3 versus 6·3 per cent (P>0·99),[203] and 8·4 versus 4·7 per cent (P=0·365)[205] in the laxative versus control group respectively.

4.3.10 GRADE assessment for quality of evidence

Using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria, the overall quality of evidence for time taken to defaecation and to tolerate diet was low, whereas it was very low for time taken to pass flatus and length of hospital stay (Table 8).

Certainty assessment								Summary of findings	
Outcomes	**No. of participants (Studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Certainty of the evidence (GRADE)**	**Anticipated absolute effects**	
								Risk with placebo	**Risk difference with laxatives**
Time taken to pass stool (TTS) assessed with: Number of days Scale: 0 to 8 (days)	416 (5 RCTs)	not serious	very serious [a]	not serious	not serious	none	⨁⨁◯◯ LOW	Mean TTS **1.57-3.1 (days)**	MD **0.83 lower** (1.39 lower to 0.26 lower)
Time taken to pass flatus (TTF) assessed with: Number of days Scale: 0 to 8 (days)	330 (3 RCTs)	not serious	very serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	Mean TTF **1.08-2.63 (days)**	MD **0.17 lower** (0.59 lower to 0.25 higher)
Time taken to tolerate diet (TTD) assessed with: Number of days Scale: 0 to 8 (days)	288 (3 RCTs)	not serious	not serious	not serious	very serious [c]	none	⨁⨁◯◯ LOW	Mean TTD **0.75-5.4 (days)**	MD **0.01 lower** (0.12 lower to 0.1 higher)
Length of hospital stay (LOS) assessed with: Number of days Scale: 0 to 20 (days)	416 (5 RCTs)	not serious	serious [d]	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	Mean LOS **1-16 (days)**	MD **0.01 higher** (1.36 lower to 1.38 higher)

Table 8 GRADE quality-of-evidence assessment of studies comparing laxatives with placebo in patients undergoing abdominal surgery.

CI: Confidence interval; MD: Mean difference

Explanations: a - I2 is 94%; b - I2 is 87%; c - Confidence intervals included potential for no effect; d - I2 is 92%

4.4 Discussion

This meta-analysis of all available RCTs evaluating laxatives after major abdominal surgery demonstrates that time to passage of stool is shorter with laxative use. However, there was significant heterogeneity between studies for this outcome measure, and time to passage of flatus, time to tolerance of diet and length of stay in hospital were unaffected. There were insufficient data to draw conclusions on the safety profile of laxatives used in this setting. The effect of laxatives on bowel motility depends on the type and mechanism of action. Some laxatives (such. as sennosides) work by stimulating gut activity and others (such as polyethylene glycol) by osmotic distension of the bowel lumen. A distended colon is more likely to initiate colonic contractions leading to a bowel movement than a non-distended, empty colon.[123, 229] There is also evidence of a postoperative 'brake' system in or around the rectosigmoid colon that acts as a physiological sphincter by causing retrograde contractions and inhibiting normal passage of enteric contents.[230] It is plausible that giving laxatives per rectum could counteract this pathophysiological effect, initiating an antegrade bowel movement. Published evidence of the use of laxatives to improve gastrointestinal function after surgery dates back to the late 1990s.[231-234] ERP guidelines commonly recommend using laxatives to stimulate bowel motility after surgery; however, these recommendations are not uniform and vary geographically. Moreover, the evidence behind these recommendations is quoted to be weak in several guidelines.[156]

The data in this review suggest there may be a benefit of laxatives after abdominal surgery. However, although earlier passage of stool is typically associated with earlier. recovery of gastrointestinal function, interpretation is limited when measured in isolation. Most validated measures of gastrointestinal recovery are composite scores including other relevant parameters.[149] It is interesting that there was no difference in time to tolerance of diet or time to discharge in the present meta-analysis. This could mean that laxatives

result in a stimulated bowel movement, but not in improved recovery after surgery. Another potential explanation could be that, although well patients in the intervention arm passed stool earlier overall, there was no difference in rates of POI in the subset of patients, leading to a similar, longer, hospital stay overall in both groups. As rates of POI and validated outcome measures such as GI-2 were not recorded in most studies, it is not possible to assess this further. This review has several limitations, including the significant heterogeneity of the included studies, lack of validated outcome measures, small sample sizes, and variation in the types of operation performed and types of intervention used. In addition, data on complications were not adequate for meta-analysis. Given that most common laxatives are cheap medications with a favourable toxicity profile, their use deserves further exploration in the postoperative setting.[16] To this end, further higher-powered RCTs are required with a specific focus on validated measures of gastrointestinal recovery and accurate collection of complications data (such as anastomotic leak). It remains unclear whether laxatives should be used after surgery in selected patients after abdominal surgery, or as a routine in all postoperative patients. The type and dose of laxative also varied between the included studies, and there may be a role for using a combination of laxatives with different mechanisms of action (both direct activity of bowel function and osmotic distension), as this is common in other aspects of enhanced recovery protocols (for example, multimodal pre-emptive analgesia and antiemetics). The STIMULAX RCT (Australian New Zealand Clinical Trials Registry number ACTRN12618001261202), which is currently recruiting patients undergoing colorectal surgery, should address some of these questions.

4.5 Conclusion

Routine postoperative laxative use after major abdominal surgery may result in earlier passage of stool but does not influence other postoperative recovery parameters. Better data are required for postoperative complications and validated outcome measures.

CHAPTER 5: A GLOBAL SURVEY OF SURGEONS' PREFERENCES AND PRACTICE WITH REGARD TO LAXATIVE USE AFTER ELECTIVE COLORECTAL SURGERY

Statement of Authorship

Title of Paper	A global survey of surgeons' preferences and practice with regard to laxative use after elective colorectal surgery
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Dudi-Venkata NN, Kroon HM, Bedrikovetski S, Moore JW, Thomas ML, Sammour T. A global survey of surgeons' preferences and practice with regard to laxative use after elective colorectal surgery. Int J Colorectal Dis. 2020 Apr;35(4):759-763. doi: 10.1007/s00384-020-03521-1. Epub 2020 Jan 31. PMID: 32006137.

Principal Author

Name of Principal Author (Candidate)	Nagendra N. Dudi-Venkata
Contribution to the Paper	Conception and design of the project Acquiring research data Analysis and interpretation of research data Drafting significant parts of the article and critically revising it
Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 26/11/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Hidde M Kroon
Contribution to the Paper	Conception and design of the project Analysis and interpretation of research data Drafting significant parts of the article and critically revising it
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Name of Co-Author	James W Moore		
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Signature		**Date**	26/11/2020

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Contribution to the paper	Conception and design of the project Analysis and interpretation of research data Drafting significant parts of the article and critically revising it		
Signature		**Date**	26/11/2020

5.1 Introduction

Delayed return of gastrointestinal (GI) function and prolonged postoperative ileus (PPOI) are common complications after abdominal colorectal surgery. They are associated with serious morbidity including pneumonia, delayed enteral nutrition and wound failure. They also prolong hospital stay and cause significant patient discomfort due to distention, nausea and the requirement for nasogastric tube insertion.[2, 3] PPOI places a substantial economic burden on the healthcare system to the extent of approximately $1.5 billion annually in the USA.[5]

Several and varied multimodal strategies have been employed as part of enhanced recovery protocols (ERPs) to improve the return of GI function after colorectal surgery. These include opioid avoidance, regional anaesthesia, early feeding, and mobilization. Routine use of laxatives postoperatively is often also recommended in ERPs; however, evidence for their benefit is limited and recommendations are heterogenous as shown in a recent systematic review.[155, 156] There appears to be a major knowledge gap and significant variability in the use of readily available, “off the shelf” medications to expedite GI recovery after surgery. More specifically, there is little data on current clinical preferences and practice patterns of colorectal surgeons in terms of postoperative laxative use.

The aim of this global survey was to gauge surgeons’ preferences and practice regarding laxative use after elective colorectal surgery.

5.2 Methods

A short de-identified web-based survey questionnaire was designed using the Research Electronic Data Capture application (REDCap).[235] The study received the local Research Ethics Committee approval (HREC/18/CALHN/662).

The survey was written in English and Chinese (Mandarin) and included six questions focused on the surgeons' preferences on laxative use after colorectal surgery. The survey can be viewed at http://j.mp/2RSJC3F. The online link was sent to 22 specialist colorectal societies worldwide with a request to send it to their member surgeons via email and newsletters (Table 9). A reminder email was sent to all members of the society where possible. The survey was also widely distributed via several social media channels (Twitter, Facebook, WeChat®, LinkedIn®) utilizing relevant society and colorectal "hashtags" to identify further potential responders. The survey remained open from November 2018 to September 2019.

Participation in the survey was voluntary, without any incentive (financial or otherwise) for surgeons to complete it. Upon clicking on the link, participants were provided with. brief background information before conducting the survey. Responding members were not mutually exclusive to one society and their affiliation to multiple specialist societies were considered, although only one response per individual was requested. All responses to the survey were kept anonymous.

Data were collected using REDCap tools hosted at the University of Adelaide, Australia.[235] Data were analysed using descriptive statistics.

Specialist Surgical Society	Contacted	Responded	Sent to members
American Society of Colon and Rectal Surgeons (ASCRS)	Yes	Yes	Yes
Asia-Pacific Federation of Coloproctology (APFCP)	Yes	No	No
Asociacion Espanola de Coloproctolgia (AECP)	No	NA	NA
Association of Colon and Rectal Surgeons of India (ACRSI)	Yes	Yes	No
Association of Coloproctology Great Britain and Ireland (ACPGBI)	Yes	Yes	No
Brazilian Society of Coloproctology (BSCP)	No	NA	NA
Canadian Society of Colon and Rectal Surgeons (CSCRS)	Yes	Yes	Yes
Chinese associations grouped together	Yes	Yes	Yes
Colorectal Surgical Society of Australia & New Zealand (CSSANZ)	Yes	Yes	Yes
Dutch Society of Gastrointestinal Surgery (NVGIC)	Yes	Yes	Yes
Dutch Society of Surgical Oncology (NVCO)	Yes	Yes	Yes
European Crohn's and Colitis Organisation (ECCO)	No	NA	NA
European Society of Coloproctology (ESCP)	Yes	Yes	Yes
European Society of Surgical Oncology (ESSO)	Yes	Yes	Yes
Intl Society of University of Colon & Rectal Surgeons (ISUCRS)	No	NA	NA
Iranian Coloproctology Society (IRCPS)	Yes	No	No
Japan Society of Coloproctology (JSCP)	No	NA	NA
Korean Society of Coloproctology (KSCP)	Yes	No	No
Malaysia Society of Colorectal Surgeons (MSCRS)	Yes	Yes	No
Mediterranean Society of Coloproctology (MSCP)	Yes	Yes	Yes
Mexican Society of Colon and Rectal Surgeons (SMCRC)	No	NA	NA
Palestinian Society of Coloproctology	No	NA	NA
Philippine Society of Colon and Rectal Surgeons (PSCRS)	Yes	Yes	Yes
RACS Colon and Rectal Surgery Section (RACS CRS)	Yes	Yes	No
Royal Society of Medicine Coloproctology Sections (RSM – CPS)	No	NA	NA
Russian Society of Coloproctology	No	NA	NA
Saudi Society of Colon & Rectal Surgery (SSCRS)	Yes	No	No
Societa Italiana di Chirurgia Colo-Rettale (SICCR)	Yes	Yes	Yes
Society of Colorectal Surgeons Singapore (SCRSS)	Yes	Yes	Yes
South African Colorectal Society (SACRS)	Yes	Yes	Yes
Turkish Society of Colon and Rectal Surgery (TKRCD)	Yes	No	No

Table 9 Specialist societies and their responses to survey request

5.3 Results

A total of 852 surgeons completed the survey, representing 1219 affiliated memberships to 28 specialist societies (Table 10). Six hundred eighty-three (80%) of responders were colorectal surgeons and 169 (20%) were general surgeons with colorectal interest. Seventy-one percent of the respondents had an ERP in their hospital, but only 27% routinely prescribed laxatives after elective colorectal surgery.

Specialist Surgical Society	n
American Society of Colon and Rectal Surgeons (ASCRS)	336
European Society of Coloproctology (ESCP)	139
Colorectal Surgical Society of Australia and New Zealand (CSSANZ)	126
RACS Colon and Rectal Surgery Section (RACS CRS)	100
Societa Italiana di Chirurgia Colo-Rettale (SICCR)	88
Chinese associations grouped together	73
Association of Coloproctology Great Britain and Ireland (ACPGBI)	72
European Society of Surgical Oncology (ESSO)	60
Dutch Society of Surgical Oncology (NVCO)	52
Dutch Society of Gastrointestinal Surgery (NVGIC)	44
Canadian Society of Colon and Rectal Surgeons (CSCRS)	22
Association of Colon and Rectal Surgeons of India (ACRSI)	15
Royal Society of Medicine Coloproctology Sections (RSM – CPS)	15
South African Colorectal Society (SACRS)	11
Asia-Pacific Federation of Coloproctology (APFCP)	11
Philippine Society of Colon and Rectal Surgeons (PSCRS)	10
International Society of University of Colon & Rectal Surgeons (ISUCRS)	7
Mediterranean Society of Coloproctology (MSCP)	6
Saudi Society of Colon & Rectal Surgery (SSCRS)	6
Turkish Society of Colon and Rectal Surgery (TKRCD)	6
Brazilian Society of Coloproctology (BSCP)	6
Society of Colorectal Surgeons Singapore (SCRSS)	4
Asociacion Espanola de Coloproctolgia (AECP)	3

European Crohn's and Colitis Organisation (ECCO)	2
Russian Society of Coloproctology	2
Japan Society of Coloproctology (JSCP)	1
Mexican Society of Colon and Rectal Surgeons (SMCRC)	1
Palestinian Society of Coloproctology	1

Table 10 Specialist societies and number of their responding members

There was a wide variation in laxative choice, with magnesium-based laxatives (42%), macrogol (Movicol, 36%) and lactulose (Duphalac, 22%) being the most used (Fig. 13). There was geographical variation with magnesium-based laxatives preferred by surgeons in North America (38%) and Europe (54%), macrogol (49%) preferred by surgeons from Oceania, Coloxyl Senna (23%) preferred by surgeons in Asia and lactulose was preferred by surgeons in South America (80%) and Africa (75%) (Table 11). The reasons for the 73% (n = 896) of surgeons not routinely using laxatives after elective colorectal surgery were the following: no evidence for benefit (48%), potential adverse events (24%), more than one reason (no evidence of benefit, potential adverse events and costs or combination of these, 21%) and other (7%). Only three surgeons listed costs as the reason for not using laxatives. Most non-users (93%) stated they would consider prescribing laxatives if better evidence for its efficacy was available (Fig. 12).

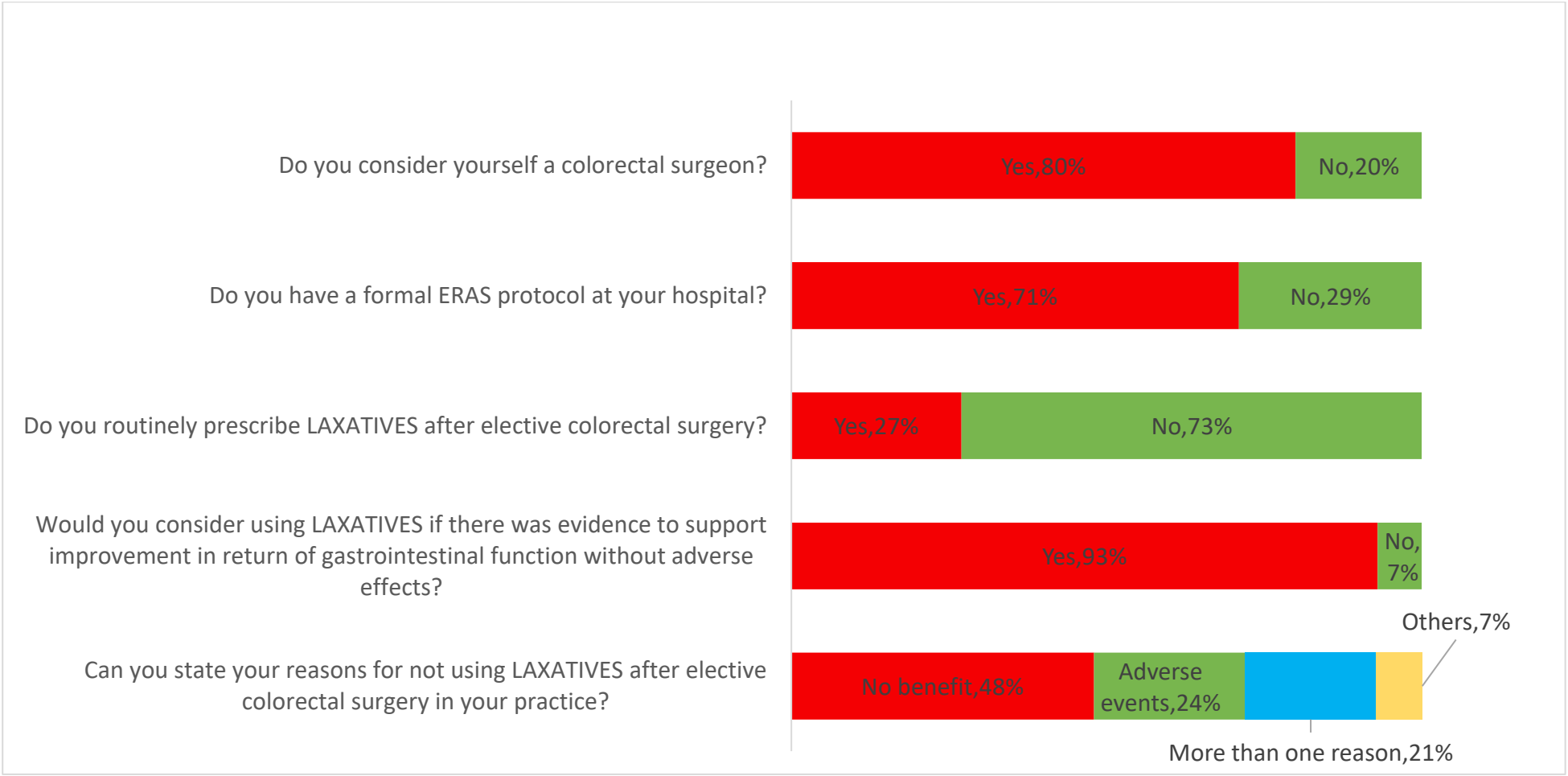

Fig. 12 Survey questionnaire responses

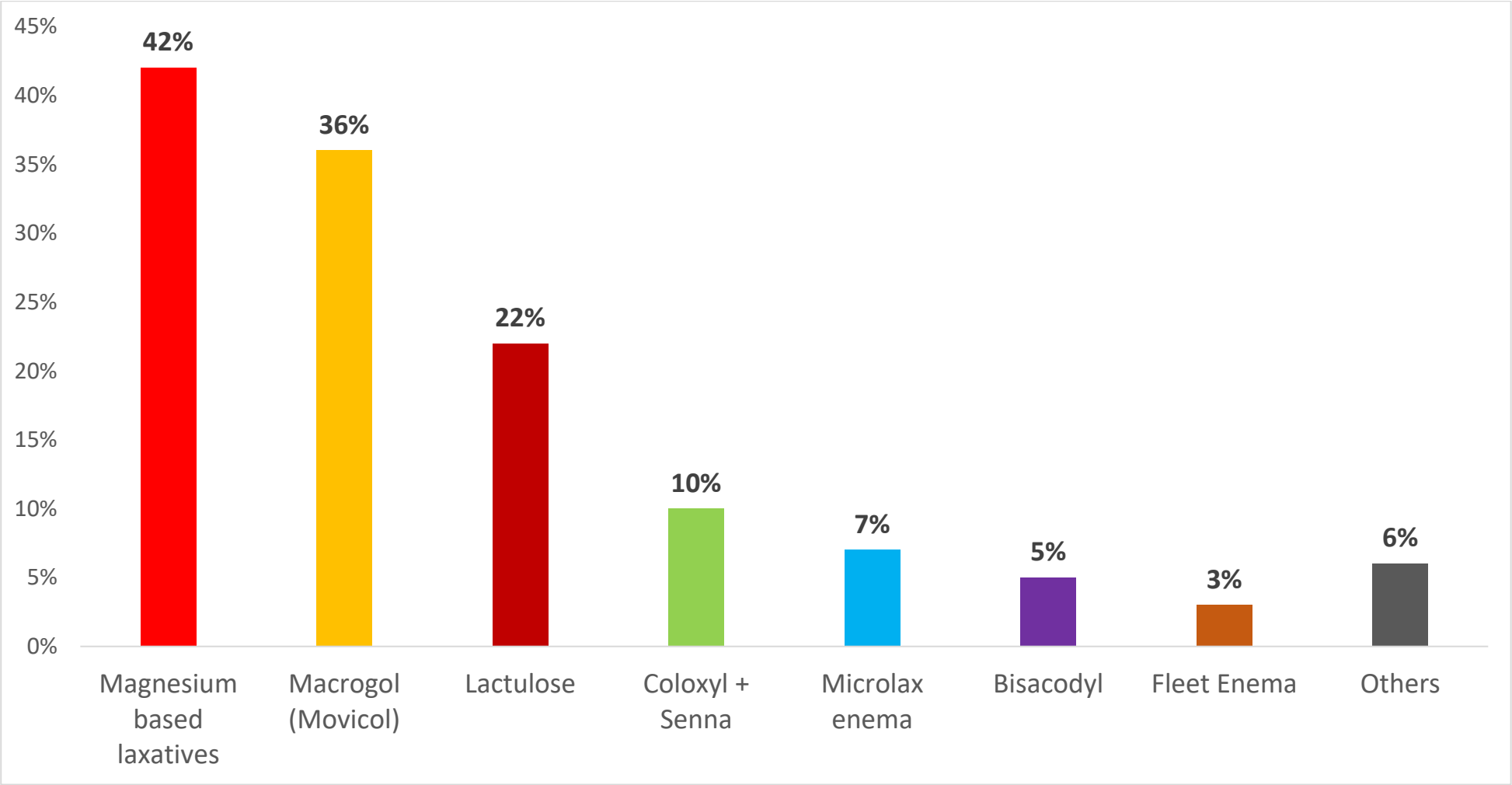

Fig. 13 Type of laxatives prescribed by surgeons

Continent	Surgical Society	No. of members responded	No. of members prescribing laxatives	Magnesium based laxatives	Macrogol (Movicol)	Lactulose	Coloxyl + Senna	Bisacodyl	Microlax enema	Fleet enema	Others
North America	ASCRS	336	48	17	12	8	4	10	0	1	1 Ayurvedic
	CSCRS	22	8	4	3	3	2	0	1	1	0
South America	BSCP	6	3	0	1	3	0	0	0	0	0
	SMCRC	1	1	0	0	0	0	0	0	0	1 Mosapride
	ISUCRS	7	1	0	1	1	0	0	0	0	0
Europe	ESCP	139	51	31	21	8	0	2	2	1	1 Docusate 1 Paraffin oil 1 Vaseline
	AECP	3	0	0	0	0	0	0	0	0	0
	NVGIC	44	32	26	13	3	2	0	4	0	0
	NVCO	52	34	28	11	4	2	0	3	0	0

	ESSO	60	24	11	7	8	3	1	3	0	0
	RSM-CPS	15	3	0	2	1	0	0	0	0	1Docusate
	ACPGBI	72	15	0	6	5	0	0	0	0	1Benefiber 3Docusate
	SICCR	88	23	2	13	7	1	0	0	0	1Paraffin oil 1Benefiber 1Pro-prebiotics
	ECCO	2	0	0	0	0	0	0	0	0	0
Oceania	CSSANZ	126	22	3	13	5	6	0	3	1	1Benefiber
	RACS CRS	100	23	3	9	6	8	1	4	2	1Benefiber
Asia	ACRSI	15	5	1	0	2	0	0	0	1	1Paraffin oil 1Ayurvedic
	APFCP	11	4	2	0	0	0	0	0	1	0
	PSCRS	10	0	0	0	0	0	0	0	0	0

	JSCP	1	1	1	0	0	0	0	0	0	0
	TKRCD	6	1	1	0	0	0	0	0	0	0
	SSCRS	6	1	1	0	0	0	0	0	0	0
	RSCP	2	1	0	0	1	0	0	0	0	0
	SCRSS	4	0	0	0	0	0	0	0	0	0
	MSCP	6	2	0	2	1	0	0	0	0	0
	PaSCP	1	0	0	0	0	0	0	0	0	0
	Chinese Society	73	16	1	1	3	4	2	2	0	1Paraffin oil 1Chinese med
Africa	SACRS	11	4	2	0	3	1	0	0	0	0
Total		1219*	323 (26.5%)	134 (41.5%)	115 (35.6%)	72 (22.3%)	33 (10.2%)	16 (5%)	22 (6.8%)	8 (2.5%)	19 (5.8%)

Table 11 Geographical pattern of surgeon preferences of prescribing laxatives after elective colorectal surgery

5.4 Discussion

We conducted a global survey of surgeons to gauge preferences and practice regarding laxative use after elective colorectal surgery. This survey found that most surgeons do not routinely use laxatives after elective colorectal surgery despite ERP recommendations, largely due to lack of evidence of benefit. Amongst those surgeons who do use them, there is wide variability in the type of laxatives used, with a correlation between geographical location and laxative choice. Most respondents indicated they would be amenable to routine laxative use if better evidence was available.

Only 27% of surgeons routinely used laxatives in patients after colorectal surgery. This is an interesting finding as it is at odds with the recommendations of most current enhanced recovery protocols (ERPs) which typically recommend laxative use after colorectal surgery, albeit based on low quality evidence.[156] Most respondents indicated that they had an established ERP at their institution, suggesting that their protocols either did not include laxatives or that laxatives were omitted in real world practice.

Lack of evidence supporting efficacy of routine laxatives after colorectal surgery was stated as the most common reason for not using laxatives. Indeed, there is a dearth of evidence on laxative use in colorectal surgery in the surgical literature. The largest randomised controlled trial (RCT) published by Zingg et al. included 169 patients undergoing colorectal surgery.[205] The intervention group received oral bisacodyl (10 mg, twice a day) from the day before surgery to the third postoperative day. This study demonstrated a significantly shorter time to GI-3 (mean time to first flatus passed, first defecation and first solid food tolerated) in the bisacodyl group (3.0 versus 3.7 days, P= 0.007) with a 1-day difference in time to defecation (3.0 versus 4.0 days, P= 0.001). There was no effect of bisacodyl on tolerance to solid food or length of hospital stay. A smaller

RCT conducted by Andersen et al. with 49 patients failed to show any significant effect of oral magnesium oxide on time to first flatus or bowel movement within a well-established ERP (18 vs 14 h and 42 vs 50 h, respectively, each P>0.15).[203]

Despite this limited evidence, most ERPs still recommend laxative use as part of a multimodal package of care, although the type and dosing are variable.[155] In addition to ERPs, the use of laxatives is also likely to have been driven by individual surgeons' preferences, which, while backed by knowledge and experience, is also influenced by risk perception and personal risk tolerance making the whole decision process complex.[236-238] A less common reason stated by responding surgeons in this survey for omitting laxatives was the fear of adverse events such as anastomotic leaks.[203-205] The study by Zingg et al. as mentioned above demonstrated an increased anastomotic leak in the laxative group (8.4%) vs. non-laxative group (4.7%), but this was not statistically significant (P= 0.36).[205] A recently conducted retrospective cohort study by our group noted the opposite, with quite a large difference in the anastomotic leak rate between groups, but in favour of laxatives. This again was not statistically significant (0 vs. 7.1%, P= 0.24).[239]

Surgical practice could change if there is good evidence available as demonstrated in this survey, in which 93% of the surgeons were happy to consider using laxatives if evidence supported it. Delayed return of GI function and postoperative ileus has been identified as a research priority in colorectal surgery and further investigation to identify clinically effective, patient-focused management strategies is warranted. Common laxatives are inexpensive and widely accessible in most countries; if safety and efficacy can be demonstrated, this could potentially make a difference to patient care and translate to significant cost savings for the health system. In view of this, the currently recruiting

STIMULAX randomised controlled trial should provide more insight (ACTRN 12618001261202).

To our knowledge, this is the first survey conducted on laxative use after colorectal surgery and the only colorectal survey with representation from surgeons working in every continent. Still, there are some limitations to note. Using electronic web-based and social media tools could potentially bias the responses towards surgeons familiar with this technology. The wide variation in laxative use could also be a reflection of the availability and cost of different medications in different geographic regions rather than surgeon's choice per se; however, the survey could not identify this.[156] Due to the wide distribution of the survey to multiple societies and on social media, it was not possible to calculate a response rate as the denominator was not known.

5.5 Conclusion

Most surgeons do not routinely prescribe laxatives after elective colorectal surgery due to lack of evidence. Amongst those surgeons who do use them, there is wide variability in the type of laxatives used. Further high-quality data on the risk benefit of laxative use after elective colorectal surgery are needed.

CHAPTER 6: THE IMPACT OF LAXATIVES ON RETURN OF GASTROINTESTINAL FUNCTION AFTER ELECTIVE COLORECTAL SURGERY - A PROPENSITY SCORE-MATCHED ANALYSIS

Statement of Authorship

Title of Paper	The Impact of Laxatives on the Return of Gastrointestinal Function After Elective Colorectal Surgery : A Propensity Score-Matched Analysis
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i. the candidate's stated contribution to the publication is accurate (as detailed above);

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6.1 Introduction

Postoperative ileus (POI) and delayed return of gastrointestinal (GI) function are major complications after colorectal surgery. They are a source of significant morbidity and discomfort for patients, delaying enteral nutrition, predisposing to wound failure and pneumonia, and delaying hospital discharge.[2, 3] The estimated annual cost of POI as a single complication is approximately $1.5 billion annually in the United States.[164]

Several multimodal strategies have been employed to improve the return of GI function after abdominal surgery, including the routine use of postoperative laxatives.[155] These strategies form part of Enhanced Recovery Protocols (ERP), the implementation of which has undoubtedly decreased the overall complications of colorectal patients worldwide in the last decade.[165-167, 240] However, despite widespread adaptation of ERPs, the incidence of POI remains high at around 10-30%, with delayed return of GI function continuing to be a barrier for discharge.[3, 4, 7, 44] Recently, we conducted a systematic review of ERPs looking at recommendations aimed at improving the return of GI function after colorectal surgery. We found that laxatives are commonly but variably recommended in different international protocols, with only weak evidence quoted to support their efficacy.[156] Published data on the safety of postoperative laxatives in this setting are limited, in particular with regards to anastomotic leak.

The Colorectal Unit at the Royal Adelaide Hospital (RAH) uses an ERP in which laxative use is optional depending upon surgeon preferences, and thus some patients receive laxatives as part of their postoperative management of POI while others do not.[241] The aim of this study was to assess the safety and efficacy of laxative use after elective colorectal surgery.

6.2 Material and Methods

This paper is reported using the Strengthening the Reporting of Observational Studies in Epidemiology guideline (STROBE guidelines).[242]

6.2.1 Study design

This is a single-centre retrospective cohort study conducted at the Colorectal Unit at the RAH, Adelaide, South Australia, Australia. The study was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC Reference number: HREC/18/CALHN/214, CALHN Reference number: R20180410).

6.2.2 Setting

The RAH is an 800-bed public teaching hospital located in South Australia with a tertiary colorectal surgical unit, performing approximately 300 major colorectal surgical procedures per annum. Consecutive patients who underwent elective surgery in the Colorectal Unit, between June 2017 and August 2018 were identified using the Operating Room Management Information System (ORMIS) and the elective colorectal operating lists. Both databases were searched and cross-referenced to identify missing patients. All operations were performed using the same oncologic and clinical principles by either consultant colorectal surgeons or under the direct supervision of a consultant colorectal surgeon. A total of 6 colorectal surgeons were involved in the study; all of them were trained in advanced colorectal surgery and are accredited members of Colorectal Surgical Society of Australia and New Zealand (CSSANZ).

6.2.3 Participants

All adult patients (18 years and above) who underwent large bowel resections (including colon and rectum), stoma reversals (colostomy/ileostomy) or formation of stoma

procedures, for any indication, were included. Patients younger than 18 years, patients who underwent emergency procedures and trans-anal operations were excluded.

All the patients were managed postoperatively according to a colorectal care pathway that included oral bowel prep for left sided resections with anticipated need for defunctioning loop ileostomy, and a Fleet enema only for all other cases, preoperative counselling, minimal oral restriction preoperatively, restrictive fluids, subcutaneous thromboprophylaxis, stepwise analgesia progression, avoidance of nasogastric tube and early postoperative feeding. This multimodal approach to postoperative care formed part of the institutional enhanced recovery protocol (ERP) pathway at RAH.[241]

Two of the surgeons in the colorectal unit routinely prescribed laxatives for all their postoperative patients. Most commonly these patients started laxatives on day 1 and were given: Coloxyl + Senna (one tablet twice a day), macrogol (Movicol, one sachet twice a day), and a Microlax enema (once daily) to patients who had right-sided resections. These patients were compared with patients who did not receive laxatives. The Laxative group received these medications postoperatively only while in hospital. Raw data analysis comparing both groups was conducted, followed by a propensity score matched analysis as described below.[4, 7, 243]

6.2.4 Variables

A database was created using Microsoft Excel 2010 (Seattle, WA, USA) including the following patient characteristics: age, sex, smoking status, body mass index (BMI), previous abdominal surgery, pre-existing stoma, ischemic heart disease, peripheral arterial disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, American Society of Anaesthesiologists (ASA) score, underlying pathology (malignancy, inflammatory bowel disease, diverticulosis, other benign disease), date of surgery, primary

operation, new stoma creation and its type, operative approach (open, laparoscopic/laparoscopic-assisted, robotic), conversion to open, operating time, type of intervention (Coloxyl + Senna (Coloxyl with Senna, Aspen, Australia), Movicol (Movicol, Norgine, Australia), or Microlax enema (Microlax, Johnson & Johnsons, Pacific), red cell transfusion and postoperative adjunct analgesia. used. Postoperative data on complications, re-interventions, length of hospital stay, readmissions and 30-day mortality were also collected.

The primary outcome measure was GI-2, a validated measure of GI recovery which is a composite measure of time (in whole days) to tolerance of solid diet AND passage of stool.[1, 146] Secondary outcome measures were days to first passage of stool, days to tolerance of solid diet, incidence of vomiting, incidence of nasogastric tube insertion, incidence of prolonged postoperative ileus (PPOI defined according to published definition),[1] anastomotic leak (defined according to published definition),[244] pneumonia, intra-abdominal collection, length of hospital stay, 30-day complication rate by highest Clavien-Dindo grade,[245] 30-day re-admission rate, return to theatre and reported adverse events. Readmissions were defined as admission to any of metropolitan or regional hospital within 30 days of discharge. Costing data was collected from the Department of Data and Analytics, Central Adelaide Local Health Network, SA Health, South Australia, Australia for all enrolled patients, including total cost of stay, as well as departmental costs including ward medical and nursing, allied health, imaging, laboratory services, and pharmacy costs.

6.2.5 Data sources

Data was recorded from electronic and paper medical records, the Operating Room Management Information System (ORMIS) database for operating notes and operating

time and a prospectively maintained departmental database for readmissions, adverse events, and morbidity data.

6.2.6 Statistical analysis

The number of colorectal procedures performed during the study period determined the study size. To overcome biases owing to the different distribution of co-variables among patients between the two groups, propensity score matching was carried out to obtain a one-to-one match by the optimal matching method. Known confounders including age, sex, BMI, previous abdominal surgery, type of operation, and operative approach were used for matching as they have been consistently shown to be independently predict POI in colorectal surgery.[4, 7, 242, 243] After matching, all covariates were found to have a standardized mean difference (d, as an absolute number) value of < 0.1 between the two groups suggesting the groups were adequately matched.[246]

Categorical data were analysed using the Fisher's exact and Chi-squared tests whereas continuous data were analysed with Student's t and Mann–Whitney U tests depending on whether the data were normally distributed or not. Descriptive statistics are reported as Mean (SD) or Median (range). Statistical analysis was performed using GraphPad Quick Calcs (GraphPad Software, San Diego, CA, USA). A P-value of <0.05 was considered statistically significant.

6.3 Results

6.3.1 Patient demographics and operative characteristics

A total of 173 patients were identified, 67 (38.7%) had routine laxatives prescribed, and 106 (61.3%) did not. Baseline demographic, clinical and operative characteristics were compared between the groups as shown in Table 12.

	Unmatched data			Matched data		
	Laxatives Group (n=67) *	***Non-laxatives Group (n=106) ****	***p value***	***Laxatives Group (n=48) ****	***Non-laxatives Group (n=48) ****	***p value***
Age **Mean (SD), years**	65.2 (14.6)	61.8 (16.5)	0.249	64.6 (15.1)	65.1 (13.5)	0.859
< 60 years ≥ 60 years	22 (32.8) 45 (67.2)	46 (43.4) 60 (56.6)	0.166	17 (35.4) 31 (64.6)	15 (31.3) 33 (68.6)	0.665
Gender						
Male	42 (62.7)	56 (52.8)	0.203	30 (62.5)	30 (62.5)	1.000
Female	25 (37.3)	50 (47.2)		18 (37.5)	18 (37.5)	
Smoking status	7 (10.5)	17 (16)	0.300	3 (6.3)	9 (18.8)	0.120
BMI						
≤30 kg/m^2	51 (76.1)	71 (67)	0.199	34 (70.8)	34 (70.8)	1.000
>30 kg/m^2	16 (23.9)	35 (33)		14 (29.2)	14 (29.2)	
ASA physical status						
1-2	33 (49.2)	58 (54.7)	0.483	23 (47.9)	20 (41.7)	0.538
3-4	34 (50.8)	48 (45.3)		25 (52.1)	28 (58.3)	
Previous abdominal surgery	38 (56.7)	65 (61.3)	0.548	25 (52.1)	25 (52.1)	1.000
Pre-existing stoma						
Ileostomy	10 (14.9)	14 (13.2)	0.750	5 (10.4)	6 (12.5)	0.749
Colostomy	3 (4.5)	9 (8.5)	0.373	1 (2.1)	0 (0)	1.000
Underlying pathology						
Carcinoma / Polyp	49 (73.1)	65 (61.3)	0.110	37 (77.1)	36 (75)	0.811
IBD	4 (6)	17 (16)	**0.057**	4 (8.3)	4 (8.3)	1.000
Diverticulosis	3 (4.5)	4 (3.8)	1.000	3 (6.3)	4 (8.3)	1.000
Other benign	3 (4.5)	8 (7.6)	0.533	N/A	N/A	N/A
For RLI	8 (11.9)	5 (4.7)	0.079	4 (8.3)	4 (8.3)	1.000
For ROH	0 (0)	7 (6.6)	**0.044**	N/A	N/A	N/A
Comorbidities						
IHD	12 (17.9)	15 (14.2)	0.506	8 (16.7)	10 (20.8)	0.601
DM	13 (19.4)	19 (17.9)	0.807	9 (18.8)	9 (18.8)	1.000
COPD	8 (11.9)	17 (16)	0.455	7 (14.6)	11 (22.9)	0.296
PAD	2 (3)	4 (3.8)	1.000	1 (2.1)	1 (2.1)	1.000
Operation type						
Open	31 (46.3)	46 (43.4)	0.711	17 (35.4)	17 (35.4)	1.000
Lap/Lap-assisted	33 (49.3)	56 (52.8)	0.647	28 (58.3)	29 (60.4)	0.835
Robotic	3 (4.5)	4 (3.8)	1.000	3 (6.3)	2 (4.2)	1.000
Primary operation						
Reversal of Loop Ileostomy	8 (11.9)	6 (5.7)	0.140	4 (8.3)	4 (8.3)	1.000
Rt Colectomy [1]	23 (34.3)	44 (41.5)	0.345	20 (41.7)	20 (41.7)	1.000
AR [2]	14 (20.9)	14 (13.2)	0.181	12 (25)	12 (25)	1.000

ULAR/LAR	5 (7.5)	14 (13.2)	0.239	5 (10.4)	5 (10.4)	1.000
TC [3]	3 (4.5)	5 (4.7)	1.000	3 (6.3)	3 (6.3)	1.000
APR/Hartmann's	7 (10.5)	7 (6.6)	0.367	2 (4.2)	2 (4.2)	1.000
Exenteration	7 (10.5)	2 (1.9)	**0.029**	2 (4.2)	2 (4.2)	1.000
ROH	0 (0)	6 (5.7)	0.083	N/A	N/A	N/A
Proctocolectomy [4]	1 (1.5)	7 (6.6)	0.153	1 (2.1)	1 (2.1)	1.000
Other	2 (3)	3 (2.8)	1.000	1 (2.1)	1 (2.1)	1.000
New stoma						
Ileostomy	10 (14.9)	22 (20.8)	0.336	8 (16.7)	5 (10.4)	0.371
Colostomy	10 (14.9)	4 (3.8)	**0.019**	3 (6.3)	1 (2.1)	0.617
Conversion	1 (2.8)	5 (8.3)	0.405	1 (3.3)	2 (6.5)	1.000
Total operating time Mean (SD), min	280.3 (148.1)	240.4 (91.4)	0.175	257.8 (100.5)	243.5 (100)	0.487
< 180 min	15 (22.4)	26 (24.5)	0.747	8 (16.7)	11 (22.9)	0.442
≥ 180 min	52 (77.6)	80 (75.5)		40 (83.3)	37 (77.1)	
Perioperative transfusion	12 (17.9)	11 (10.4)	0.155	4 (8.3)	4 (10.4)	1.000
Postop adjunct analgesia						
Epidural	10 (14.9)	6 (5.7)	**0.041**	5 (10.4)	3 (6.3)	0.715
Spinal	0 (0)	1 (0.9)	1.000	0 (0)	1 (2.1)	1.000
IV PCA	28 (41.8)	59 (55.7)	0.076	17 (35.4)	23 (47.9)	0.214
Wound catheter	4 (6)	9 (8.5)	0.768	4 (8.3)	4 (8.3)	1.000

Table 12 Patient demographics and operative characteristics

* Data are number of patients (%) unless otherwise indicated, SD – standard deviation; RLI – Reversal of loop ileostomy, ROH – Reversal of Hartmann's, IBD – Inflammatory bowel disease, IHD – Ischemic heart disease, DM – Diabetes mellitus, COPD – Chronic obstructive pulmonary disease, PAD – Peripheral arterial disease, APR – Abdominoperineal resection, IV PCA – Intravenous patient controlled analgesia

[1] Rt colectomy includes – Right hemicolectomy, Extended Right hemicolectomy, Transverse colectomy, Ileocolic resection

[2] AR – Anterior resection includes Left hemicolectomy, HAR

[3] TC – Total colectomy includes Subtotal Colectomy

[4] Proctocolectomy – Proctocolectomy includes Pan-proctocolectomy, Complete colectomy, Pouch, Completion proctectomy + End Ileostomy

In the unmatched analysis, there were fewer patients in the Laxative group with inflammatory bowel disease (6% vs 16%, P 0.057). The two groups also differed at baseline in terms of operation type with fewer reversal of Hartmann's (0% vs 6.6%, P 0.044) and more pelvic exenterations (10.5% vs 1.9%, P 0.029) in the Laxative versus No-laxative groups. There were more colostomies formed in the Laxative group (14.9% vs 3.8%, P 0.019), and epidurals were more commonly used (14.9% vs 5.7%, P 0.041).

Propensity matching resulted in 48 well-matched patients in each group with no significant differences in baseline characteristics.

6.3.2 Perioperative outcomes

In the unmatched analysis, patients in the Laxative group had significantly fewer anastomotic leaks (0 vs. 10.7%, P 0.013), and this trend remained the same even after matching, but was not statistically significant (0 vs. 7.1%, P 0.241) as shown in Table 13.

	Unmatched data			*Matched data*		
	Laxatives Group (n=67) *	***Non-laxatives Group (n=106) ****	***p value***	***Laxatives Group (n=48) ****	***Non-laxatives Group (n=48) ****	***p value***
Primary outcome# (GI2)[18-19] in days, median (range)	3 (1-15)	3 (1-98)	0.622	3 (1-10)	4 (1-13)	0.412
Secondary outcomes						
Incidence of PPOI	21 (31.3)	32 (30.2)	0.873	15 (31.3)	15 (31.3)	1.000
Time to first passage of stool#	2 (1-9)	3 (1-11)	0.107	2.5 (1-9)	3 (1-11)	0.348
Time to tolerance of solid diet#	1 (0-7)	1 (0-8)	0.067	1 (1-6)	1 (1-7)	0.503
Incidence of vomiting	32 (47.8)	42 (39.6)	0.292	21 (43.8)	16 (33.3)	0.294
Incidence of NGT insertion post- op	28 (41.8)	38 (35.9)	0.433	17 (35.4)	14 (29.2)	0.513
Length of hospital stay#	7 (2-57)	7 (1-114)	0.791	6 (2-49)	6 (3-43)	0.923
30-day postoperative Clavien-Dindo grade[21]						
1-2	44 (65.7)	57 (54.3)	0.196	31 (64.6)	25 (52.1)	0.406
3	3 (4.5)	6 (5.7)		1 (2.1)	1 (2.1)	
4	2 (3)	7 (6.6)		1 (2.1)	3 (6.3)	
5	2 (3)	0 (0)		2 (4.2)	0 (0)	
Complications						
Anastomotic leaks**	0 (0)	9 (10.7)	**0.013**	0 (0)	3 (7.1)	0.241
Pneumonia	8 (11.9)	12 (11.3)	0.901	4 (8.3)	6 (12.5)	0.740
Readmissions	8 (11.9)	13 (12.3)	0.949	5 (10.4)	8 (16.7)	0.371

Table 13 Perioperative outcomes

PPOI – Prolonged postoperative ileus

* Data are number of patients (%) unless otherwise indicated

** Anastomotic leaks were calculated including only patients with an anastomosis in the denominator

Data are median number of days (range)

There was no difference in any of the other outcome measures in the unmatched analysis between both groups. However, after propensity matching, there was a trend towards a shorter GI-2 and days to passage of stools of almost 1 day in favour of Laxative group, however this difference was not statistically significant. There were two deaths reported in the Laxative group, one of whom died of malnutrition related metabolic and respiratory decompensation and the other of a myocardial infarction on day 18 after being discharged home (with a known significant cardiac history).

6.3.3 Cost analysis

Table 14 demonstrates the cost differences between the two groups. Before and after matching, the total median costs were very similar in both groups.

	Unmatched data			***Matched data***		
Healthcare costs	***Laxatives Group (n=67) ****	***Non-laxatives Group (n=106) ****	**p-value**	***Laxatives Group (n=48) ****	***Non-laxatives Group (n=48) ****	**p-value**
Total cost of inpatient stay	$29,589 ($23,637-$43,914)	$28,994 ($21,900-$38,986)	0.358	$28,278 ($22,814-$37,541)	$28,552 ($20,871-$34,931)	0.387
Ward medical costs	$1,585 ($1,130-$2,721)	$1,579 ($1,097-$2,307)	0.516	$1,354 ($1,126-$2,270)	$1,197 ($948-$2,153)	0.429
Ward/Nursing costs	$4,224 ($2,999-$7,143)	$4,338 ($3,082-$6,018)	0.838	$3,735 ($2,948-$5,551)	$3,646 ($2,880-$5,449)	0.869
Allied health costs	$90 ($23-$541)	$96 ($24-$423)	0.812	$56 ($22-$401)	$64 ($22-$322)	0.852
Radiology costs	$69 ($2- $485)	$37 ($2-$663)	0.639	$67 ($2-$228)	$3 ($2-$213)	0.422
Pathology costs	$721 ($111-$1,292)	$837 ($530-$1,322)	0.082	$623 ($80-$1,297)	$868 ($581-$1,300)	0.080
Medications costs	$255.00 ($105-$608)	$252 ($118-$526)	0.884	$215 ($98-$358)	$179 ($85-$404)	0.744

Table 14 Summary of costs of inpatient stay

* Data are shown in Australian dollars. Mann-Whitney U test was used for non-parametric data. Data are displayed as median, (IQR).

6.4 Discussion

This study was aimed at assessing the safety and efficacy of laxative use after elective colorectal surgery. We found no statistically significant improvement in the return of gastrointestinal function with laxative use. However, laxative use in this setting appears to be safe with no increase in anastomotic leaks or other complications. In fact, there were no leaks in the Laxative group which was a surprising finding.

The effect of laxatives on bowel motility depends on the type and mechanism of action. Some laxatives (such as Sennosides) work by stimulating gut activity and others (such as Polyethylene Glycol) by osmotic distention of the bowel lumen. A distended colon is more likely to initiate colonic contractions leading to a bowel movement than a non-distended empty colon.[123, 229] There is also evidence of a postoperative “brake” system in/around the rectosigmoid colon which acts as a physiological sphincter by causing retrograde contractions and inhibiting normal passage of enteric contents.[230] It is suggested that giving laxatives per rectum could counteract this pathophysiological effect initiating an ante-grade bowel movement.

We used GI-2 as the primary outcome measure, as currently it is the most well validated published measurement and is considered a representative assessment of return of GI function after surgery.[146] There was a notable trend towards a reduction in the duration of GI2 in the Laxative group by one day, but this difference was not statistically significant. This could be because the propensity matched analysis could only include 48 patients in each arm and was therefore underpowered for this outcome. A reduction in the duration of recovery of gastrointestinal function by one day would still be clinically relevant,[5] and

therefore, these results need to be further validated by a larger prospective study. In view of this, we eagerly await the results of the STIMULAX randomized controlled trial which is currently actively recruiting patients (Registration number - ACTRN 12618001261202).

The use of laxatives within ERP's is likely to been driven by surgeon preference, which, while informed by knowledge and experience, is also influenced by risk perception and tolerance. making the whole decision process complex.[236-238] A recent global survey of colorectal surgeons showed that among 852 surgeons, only 27% used laxatives routinely after surgery. Around 24% stated that they did not use postoperative laxatives in fear of potential adverse events, including anastomotic leak.[247] Zingg et al. published an RCT in 2008 in which patients received oral bisacodyl (10mg, twice a day) from the day before surgery to the third postoperative day.[205] Their study demonstrated an increased anastomotic leak in the laxative group 8.4% vs. non laxative group 4.7%, but this was not statistically significant (P 0.365). As mentioned above, in the present study we noted the opposite, with quite a large difference in the anastomotic leak rate between groups in favour of laxatives, although not statistically significant (0 vs. 7.1%, P 0.241). Two possible theoretical explanations for these decreased rates could be: decreased pressure and tension at the anastomosis because of a reduction in faecal loading downstream and b) altered microbiota milieu reducing rates of collagenase producing bacteria. Both these hypotheses need to be explored further.[248]

There were two deaths in the Laxative group, however, these were not thought to be related to laxative use. One of the patients had a delayed presentation with three synchronous colorectal tumours and died of malnutrition related metabolic and respiratory decompensation several weeks after a total colectomy and ileorectal anastomosis. During the prolonged course of hospital stay, he underwent a CT scan and a subsequent relook

laparotomy for presumed sepsis both of which confirmed no surgical or anastomotic complication. The other patient had a known significant cardiac history and subsequently had a myocardial infarction on day 18 after being discharged home.

This study has limitations due to its retrospective nature leading to selection bias. Although propensity score matching was used to mitigate this, we could only ensure balance in measured confounders, but not in unmeasured ones. The data is also from a single institution with a relatively small number of included patients. The results could also have been influenced by differences in the technique used by individual surgeons, however all the participating surgeons were trained in advanced colorectal surgery under the uniform standards required of Colorectal Surgical Society of Australia and New Zealand (CSSANZ) members. To further confirm the conclusions of this study, a prospective multi-centre cohort study including a higher number of patients or an adequately powered randomised controlled trial will be required.

6.5 Conclusion

Postoperative laxative use following colorectal surgery appears safe. Efficacy requires further investigation in an adequately powered prospective study.

CHAPTER 7: THE STIMULAX

RANDOMIZED CONTROLLED TRIAL

Statement of Authorship

Title of Paper	Impact of STIMUlant and osmotic LAXatives (STIMULAX trial) on gastrointestinal recovery after colorectal surgery: randomized clinical trial
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Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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7.1 Introduction

Delayed recovery of gastrointestinal (GI) function, or postoperative ileus (POI), is a common complication after colorectal surgery.[1] It causes significant morbidity and patient discomfort, with vomiting, abdominal distension, and intolerance to diet, often leading to insertion of a nasogastric tube (NGT).[2, 164] POI as a single complication is also associated with doubling of direct healthcare expenditure in the immediate postoperative phase.[43, 44]

Implementation of enhanced recovery protocols (ERPs) has improved the management of patients undergoing abdominal surgery and reduced complication rates.[165-167] However, the incidence of POI remains high at around 10-30 per cent, with delayed return of GI function continuing to be a common barrier to hospital discharge.[3, 4, 6, 7] Multimodal strategies, including the routine use of postoperative laxatives, aim to promote recovery of GI function.[149, 155] Recommendations about laxative use vary in different international ERPs, with only weak evidence quoted to support their efficacy and limited data on their safety in this setting.[156, 249] Novel therapeutic medications such as Alvimopan may prevent POI, but these medications are costly and not licensed in all countries.[163, 250]

There has been heterogeneity in definitions of POI, and GI-2, a composite measure of time to tolerance of solid intake for 24 h without vomiting and passage of stool, is the only validated outcome measure currently available.[9, 146, 221] Three previous RCTs looking at the role of single-modality laxatives in colorectal surgery have not used a validated composite measure such as GI-2, limiting the interpretation of their results.[203, 205, 228] This pragmatic open-label RCT aimed to determine whether the addition of multimodal laxatives to an ERP reduces GI-2 and improves recovery of GI function in patients undergoing major abdominal colorectal surgery.

7.2 Methods

7.2.1 Study design and settings

STIMULAX (STIMUlant and osmotic LAXatives) is an investigator-initiated, open-label, pragmatic RCT of laxatives in patients undergoing elective colorectal surgery at the Royal Adelaide Hospital (RAH), Adelaide, South Australia, Australia. The RAH is an 800-bed public teaching hospital with a tertiary colorectal surgical unit. This study was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC/18/CALHN/250/R20180420) and was registered with anzctr.org.au (ACTRN12618001261202). The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and the principles of Good Clinical Practice (ICH-GCP E6).[251]

7.2.2 Eligibility

All adults (aged at least 18 years) undergoing elective open, laparoscopic, or robotic colorectal resections for any indication, or having formation or reversal of stoma (colostomy/ileostomy) at the RAH between August 2018 and May 2020 were screened for inclusion. Exclusion criteria were: age less than 18 years; pregnant, and lactating women; allergy to Coloxyl® with Senna (Aspen, St Leonards, New South Wales, Australia), macrogol (Movicol®; Norgine, Frenchs Forest, New South Wales, Australia) or sodium phosphate (Fleet®; Prestige Consumer Healthcare Inc., Lynchburg, Virginia, USA) enema; hyperphosphatemia (over1.5 mmol/l); ASA fitness grade IV and higher; active inflammatory bowel disease; colonic motility disorder; moderate-severe congestive cardiac failure (New York Heart Association class III or IV); established ileus as suggested by the need to place a NGT for decompression, vomiting, and inability to tolerate food; intestinal obstruction or perforation; abdominal pain of unknown cause; moderate to severe renal impairment (estimated glomerular filtration rate below 45 ml/min/1.75m^2); severe hepatic

impairment (Child-Pugh grade C); use of calcium channel blockers or diuretics, with significant electrolyte abnormalities; and inability to give consent or participate in postoperative assessments owing to dementia, cognitive impairment or language barrier.

7.2.3. Interventions

All patients underwent surgery by, or under the supervision of, one of six specialist colorectal surgeons at RAH. Perioperative management of all patients was standardized using an established evidence-based ERP program as described in Table 15. Preoperative bowel preparation was consistent with current standard practice in Australia and New Zealand; patients undergoing left-sided resections received oral bowel preparation without antibiotics (2 x sodium picosulfate + magnesium citrate) starting the day before surgery, and those having right-sided resections received a Fleet® enema only (dibasic sodium phosphate and monobasic sodium phosphate) on the day of the surgery.

Trial participants were randomized into two groups: STIMULAX (Intervention) and control. The control group received routine standard-of-care treatment (no placebo) in accordance with the current ERP, which does not include postoperative stimulants or laxatives. The STIMULAX group received identical care, but with the addition of multimodal laxatives. These included a stimulant laxative, oral Coloxyl® with Senna (1 tablet twice a day), and an osmotic laxative, oral macrogol (1 sachet Movicol® twice per day), both starting 6 h after surgery. Additionally, patients undergoing right-sided procedures received a sodium phosphate enema (Fleet®) daily at midday from day 1 after surgery. All study interventions were given until the participant achieved the primary outcome of GI-2 or was discharged from hospital, whichever occurred earlier. The surgical team could prescribe off-study stimulants or laxatives if patients did not achieve the primary outcome by postoperative

day 5. This was not considered a deviation from the protocol, as it was standard practice before the study started.

Preoperative	
Preadmission clinic	Detailed counselling regarding perioperative management and expected postoperative progress, reinforcing the expectation of early oral intake, early ambulation and self-care.
	Smoking cessation advice. A minimum four-week abstinence from smoking is required to decrease pulmonary and wound complications.
	Discharge planning (Discharge goals and post-discharge support)
Bowel Preparation	Picolax x 2 for L sided cases, Fleet enema for Rt sided cases
Preoperative fasting	Fast from solids for 6h, from clear fluid from 2h
Carbohydrate drink (200ml Preop by Nutricia)	2 loading drinks the night prior and 1 loading drink morning of surgery (0600), except if any reason for delayed gastric emptying, and cautiously in diabetic patients.
Immuno-nutrition	3 daily drinks of Immuno-nutrition (Impact Advanced Recovery) to be given for 5 days preop to patients with colorectal cancer
Intraoperative	
Intravenous fluids	Aim for euvolemia
Antibiotic prophylaxis	Cefazolin + Gentamicin + Metronidazole (Or Vancomycin instead of Cefazolin if Penicillin / Cefazolin allergy)
Antiemetic	IV dexamethasone/ondansetron/Droperidol
Analgesia	1g IV paracetamol, parecoxib, IV tramadol and titrated

	fentanyl (Maximising opioid sparing techniques)
Regional blocks	0.2% Ropivacaine TAP block under direct vision AND wound or rectus sheath catheter continuous infusion to start at end of operation (2*0.2% prefilled ropivacaine at 10ml/hr.). Attached epidural filter to this. Lignocaine intra-operative infusion can also be considered Mid-thoracic epidural (T6-T10) if medical indication in open cases only
Oxygenation	80% oxygen intraoperatively and in recovery via non-rebreather masks.
Hypothermia prevention	Under bodywarmer, warm air blanket if temp < 36 degrees Body temp monitoring catheter Bladder IDC optional for right hemicolectomy.
VTE prophylaxis	TEDS and SCD (remove SCD at end of operation) Heparin 5000U SC heparin if no increased bleeding risk
Vasopressor	Titrated metaraminol or ephedrine for hypotension.
Surgery	Minimally invasive if possible. Consider intra-op orogastric tube to be removed at the end of the operation No routine peritoneal drains. No routine post-operative nasogastric tube. If IDC inserted for right hemicolectomy, consider removal at the end of the case
Postoperative Day 0	
Warming blanket to continue in recovery if temp < 36 degrees	

Oxygen supplementation as required to maintain SpO2 > 95%	
Hourly deep breathing and coughing	
Pantoprazole 40 mg IV OD regular	
If surgery in the morning and patient returns to the ward prior to 1800 → sit out of bed	
Multimodal analgesia	Paracetamol (1g 6 hourly) oral regular Pregabalin 75mg PO BD (50mg if > 70yrs): Do not use if eGFR < 60. Tramadol 50mg PO 4hourly regular: Do not use if on SSRI or eGFR < 60 Celecoxib 200mg PO BD regular (100mg if >70yrs): Do not use if eGFR < 80 or had intraop NSAID (Start on Day1) PCA as last resort
Oral intake	Free oral fluids from 4hrs after surgery→ Limit to 1000ml in first 12 hrs. Protein supplemental drink from 4hrs following surgery Light diet for dinner if fluids tolerated and no nausea Stop drinking if nausea or vomiting or hiccupping Early NG insertion if clinical suspicion of ileus (do not wait for vomiting)
Antiemetic	Ondansetron 8mg IV Q8hr regular Maxolon 10mg IV Q8h regular: Do not use in patients > 75yo
IV therapy	4% dextrose / 0.18% NaCl +20KCl running at 50ml/hr Stop IV fluids completely if patient tolerating oral intake Urine output $\geq$ 20ml/h averaged over 4hr is acceptable, avoid bolusing

Postoperative Day 1 until discharge	
Continue SC heparin 5000 U BD until discharge **Continue TEDs until discharge**	
If IDC in, consider removal after medical review.	
Hourly deep breathing and coughing	
Pantoprazole 40 mg IV OD regular	
Sit out of bed for meals 4 hours in chair during the day. May be split up	
60-meter walk x 2, then increased walking as tolerated from post-operative day 2 **No bed pans or urinals.**	
Multimodal analgesia	Paracetamol (1g 6 hourly) oral regular Pregabalin 75mg PO BD (50mg if > 70yrs): Do not use if eGFR < 60. Tramadol 50mg PO 4hourly regular: Do not use if on SSRI or eGFR < 60 Celecoxib 200mg PO BD regular (100mg if >70yrs): Do not use if eGFR < 80 or had intraop NSAID (Start on Day1) PCA as last resort
Oral intake	General diet as tolerated Protein supplemental drink BD Light diet for dinner if fluids tolerated and no nausea Stop drinking if nausea or vomiting or hiccoughing Early NG insertion if clinical suspicion of ileus (do not wait for vomiting)
Antiemetic	Ondansetron 8mg IV Q8hr regular Maxolon 10mg IV Q8h regular: Do not use in patients > 75yo

Table 15. Royal Adelaide Hospital Enhanced Recovery Protocol (ERP)

7.2.4 Outcomes

The primary outcome was GI-2, a validated composite measure of GI recovery defined as the interval from surgery until first passage of stool and tolerance of a solid intake for 24 hrs (in whole days) in the absence of vomiting.[146] Secondary outcomes were: time to first passage of flatus and stool, and tolerance of solid diet; incidence of prolonged POI (defined by GI-2 not being achieved on or after day 4);[146] incidence of vomiting; NGT insertion; duration of hospital stay; readmission; 30-day postoperative complications graded according to the Clavien-Dindo classification;[245] return to theatre; comprehensive complication index (CCI®) score [252] and direct hospital cost per patient as assessed by data linkage to patient costing database in euros. Patient reported outcome were recorded using the Surgical Recovery Score (SRS) at baseline, discharge and at 30days.[29] Perioperative analgesic consumption was recorded, including the morphine equivalent daily dose.[253]

To determine GI-2, participants were reviewed daily for 10 days after surgery by one of the study investigators. If a patient was discharged, daily review was conducted by telephone until GI-2 was achieved. Discharge criteria were based on prespecified criteria in accordance with the ERP. Total duration of hospital stay (for index admission plus readmission) was recorded. Readmission was defined as return to hospital within 30 days of surgery, requiring a hospital stay of at least 24 hours. All participants were invited to attend a follow-up appointment at 30 days and those unable to attend were followed up by telephone.

7.2.5 Randomization

Randomization was conducted using random numbers obtained from a computer-based random number generator. Once the operation had been completed, an investigator extracted the random numbers that were retained in sealed envelopes containing allocated interventions to assign patients randomly to either the STIMULAX or control group.

7.2.6 Statistical analysis

A power calculation was carried out a priori using G*Power 3.1© (Franz Faul, Universitat Kiel, Germany) and data from the ALCCaS (Australian Laparoscopic Colon Cancer Surgical) trial, which showed a mean duration (s.d.) interval of 4.65 (2.15) days before the first bowel motion after elective colorectal surgery in both groups.[254] Using this as a surrogate marker for GI-2, it was estimated that, if therapeutically active, stimulant and osmotic laxatives may reduce this by 1 day to 3.65 days, representing a clinically significant change. To detect this 22 per cent difference with an allocation ratio of 1:1, an α error of 0.05, β error of 0.2, and power of 0.8, a minimum of 64 patients would be required in each arm. To account for possible attrition, withdrawals, and protocol violations, a recruitment target of 85 patients in each arm was set.

Statistical analyses was conducted by an investigator who was masked to the group allocation. Normality was determined using the Shapiro-Wilk test. Normally distributed data were expressed as mean (s.d.) and skewed data as median (i.q.r). Univariate analysis was carried out using the $\chi 2$ test for categorical variables, and Mann-Whitney U test and Student's t-test for continuous variables with a non- normal and normal distribution, respectively. Kaplan-Meier curves were constructed for primary outcome. $P < 0.050$ was

considered statistically significant. The analysis was performed on an intention-to-treat basis using SPSS® for Windows® Version 26 (IBM, Armonk, New York, USA)

7.3 Results

7.3.1 Participant Recruitment and Flow

Patient recruitment is summarized in the CONSORT diagram for the trial (Fig. 14).[255] Between August 2018 and May 2020, 278 patients were screened for inclusion. Of these, 170 patients were randomized equally between the STIMULAX (85) and Control (85) groups. In the STIMULAX group, two patients (2 per cent) received additional laxatives out of protocol. In the Control group, 15 patients received laxatives, six (7per cent) before postoperative day 5; this was regarded as a protocol violation. All patients completed the study with no loss to follow up. Baseline characteristics were similar in the two groups (Table 16).

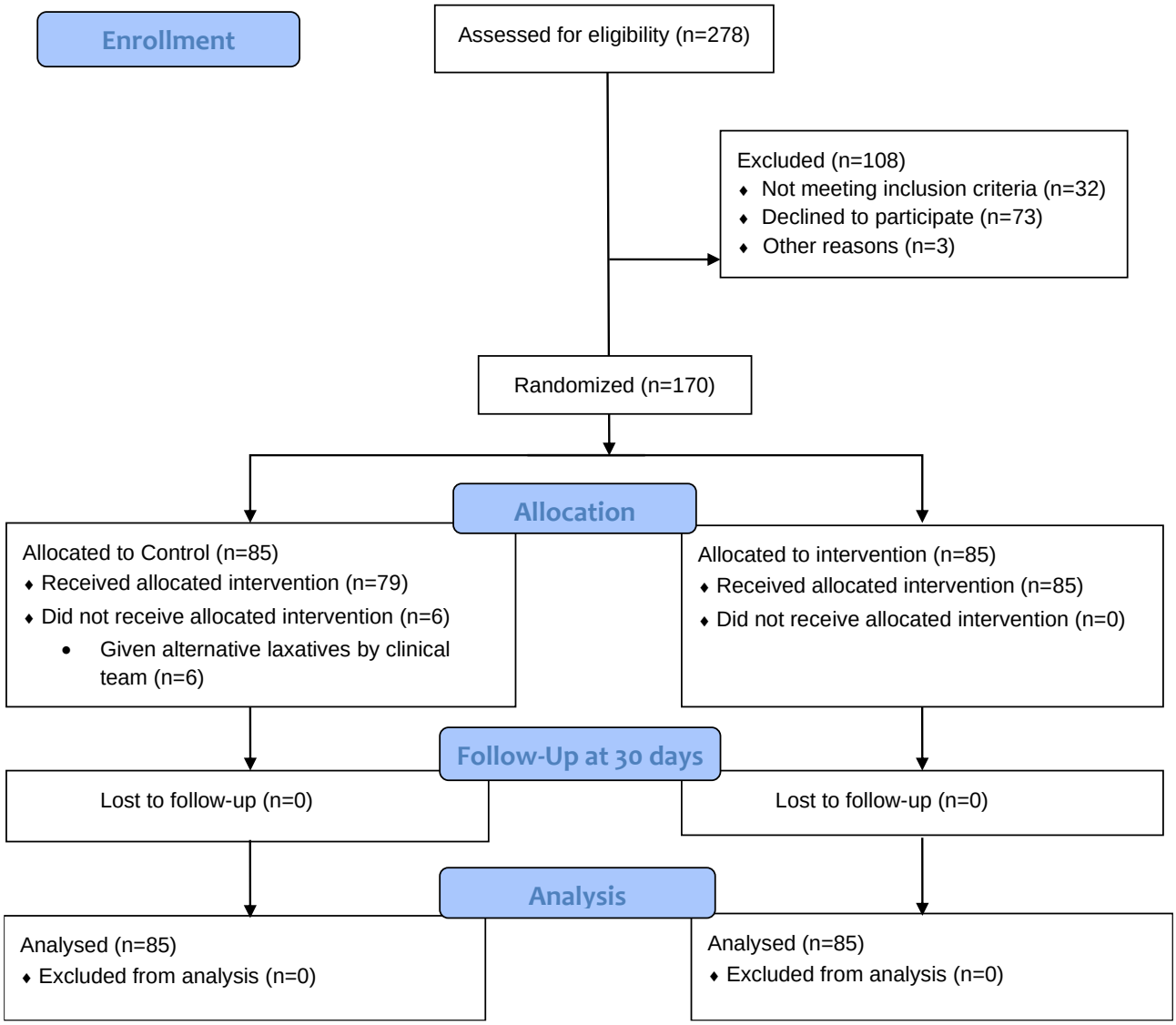

Fig. 14 CONSORT diagram

	STIMULAX (n=85) [a]	Control (n=85) [a]
Age (years) *	65 (57-74)	64 (55-73)
Sex ratio (M : F)	45:40	56:29
Smoker	20 (24)	16 (19)
BMI (kg/m^2) *	27.1 (23.5-31.9)	27.3 (24.1-32.0)
ASA fitness grade		
I	3 (4)	2 (2)
II	51 (60)	51 (60)
III	31 (36)	32 (38)
Modified Frailty Index Score		
0	39 (46)	39 (46)
1	26 (31)	30 (35)
2	18 (21)	15 (18)
3	2 (2)	1 (1)
Previous abdominal surgery	47 (55)	44 (52)
Pre-existing stoma		
Ileostomy	12 (14)	13 (15)
Colostomy	9 (11)	9 (11)
No stoma	64 (75)	63 (74)
Indications for operation		
Neoplasia/polyp	55 (65)	55 (65)
Diverticulosis	6 (7)	4 (5)
Other benign	24 (28)	26 (30)
Bowel Preparation		
Sodium picosulphate +Magnesium citrate	18 (21)	24 (28)
Fleet® enema	36 (42)	34 (40)
No preparation	31 (37)	27 (32)
Operation type		
Open	40 (47)	40 (47)
Laparoscopic/laparoscopically assisted	42 (49)	41 (48)
Robotic	3 (4)	4 (5)
Conversion to open surgery		
Yes	9 (20)	5 (11)
No	36 (80)	40 (89)
Primary operation		
Right Colectomy [†]	28 (33)	22 (26)
Anterior Resection [‡]	22 (26)	32 (38)
Total Colectomy [§]	6 (7)	4 (5)
APR/Hartmann's	5 (6)	3 (4)
Proctocolectomy [¶]	1 (1)	2 (2)
Exenteration	3 (4)	1 (1)
Reversal of Loop Ileostomy	6 (7)	11 (13)
Reversal of Hartmann's	8 (9)	7 (8)
Formation of stoma	4 (5)	2 (2)

Other	2 (2)	1 (1)
Side of operations		
Right sided [#]	35 (41)	34 (40)
Left sided [**]	50 (59)	51 (60)
New stoma		
Ileostomy	8 (9)	14 (17)
Colostomy	12 (14)	7 (8)
No stoma	65 (77)	64 (75)
Prokinetics (metoclopramide)	59 (69)	63 (74)
Total duration of operation (min) *	201 (149-247)	205 (148-254)
Intraoperative complications		
Splenic capsular tear	1 (1)	1 (1)
Bleeding needing transfusion or conversion	1 (1)	1 (1)
Enterotomy small bowel	0 (0)	1 (1)
Repeat transection with anastomosis	1 (1)	0 (0)
None	82 (97)	82 (97)

Table 16 Baseline characteristics of the Intention-to-treat population.

Values in parenthesis are percentages unless indicated otherwise; [*] values are median (i.q.r.).

[†] Includes right hemicolectomy, extended right hemicolectomy, transverse colectomy, and ileocolic resection.

[‡] Includes left hemicolectomy and sigmoidectomy.

[§]includes subtotal colectomy

[¶] Includes pan-proctocolectomy and complete colectomy

[#] Includes right hemicolectomy, extended right hemicolectomy, transverse colectomy, ileocolic resection, reversal of loop ileostomy, total colectomy, subtotal colectomy, pan-proctocolectomy, and complete colectomy

[**] Includes abdominoperineal resection (APR), anterior resection, left hemicolectomy, sigmoidectomy, reversal of Hartmann's, and exenteration.

Fleet ® (Prestige Consumer Healthcare Inc., Lynchburg, Virginia, USA).

7.3.2 Primary outcome

7.3.2.1 Return of GI function (GI-2)

GI-2 was 1 day shorter in the STIMULAX group than in the control group: median 2 (i.q.r.1.5-4) versus 3 (2-5.5) days, 95 per cent c.i. -1 to 0 day, P = 0.029) (Fig. 15).

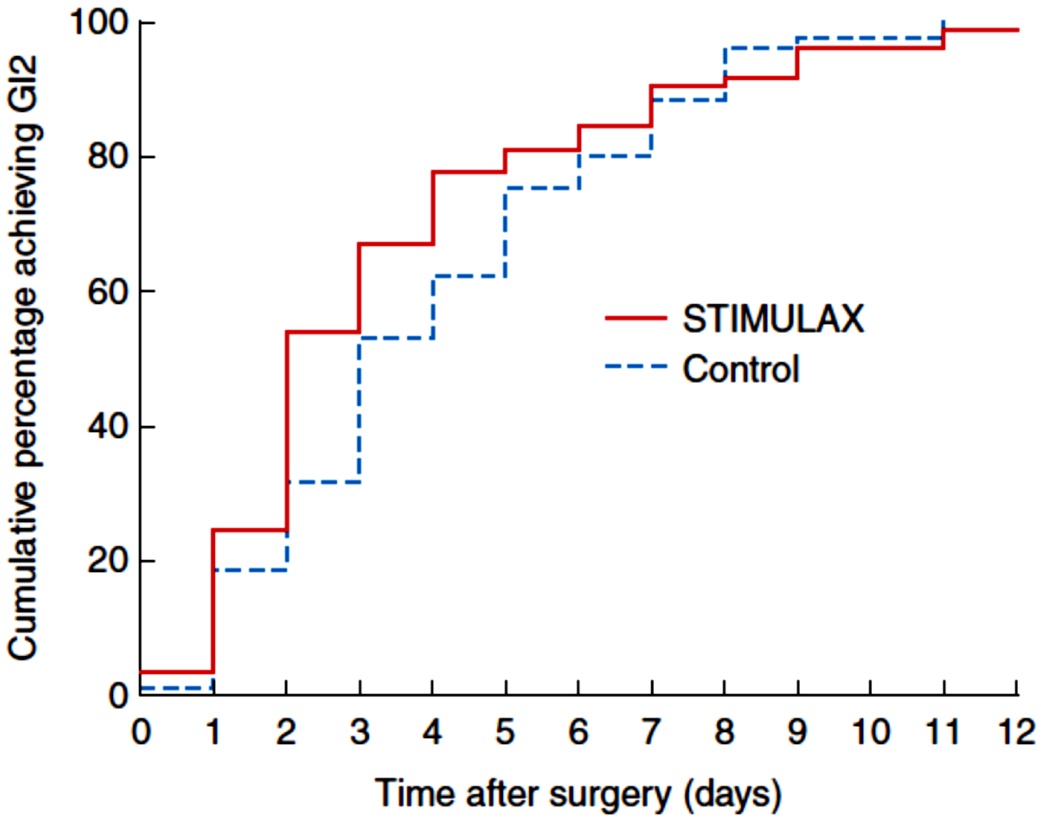

Fig. 15 Kaplan-Meier curves for time to achieve GI-2

7.3.3 Secondary outcomes

The secondary outcomes are presented in Table 17. The STIMULAX group had a shorter interval to first passage of stool after surgery, but there was no difference in time to flatus or to tolerance of solid diet. The STIMULAX group experienced a lower rate of prolonged POI. There was no difference between the groups in the incidence of vomiting, NGT insertion and median duration of NGT insertion (Table 17).

	STIMULAX (n=85)	Control (n=85)	P§
Primary outcome			
GI-2 (days)*	2 (1.5-4)	3 (2-5.5)	0.029¶
Secondary outcomes			
Prolonged POI	19 (22)	32 (38)	0.030
Time to passage of stool (days)*	2 (1-2)	3 (1-4)	<0.001¶
Time to passage of flatus (days)*	1 (1-2)	1 (1-2)	0.516¶
Time to tolerance of solid diet (days)*	1 (0-1)	1 (0-1)	0.575¶
Vomiting	41 (48)	38 (45)	0.645
NGT insertion after surgery	28 (33)	29 (34)	0.871
Timing of insertion after surgery (days)*	3 (2-4)	3 (2-3.5)	0.587¶
Duration of insertion (days)*	2 (1-4)	2 (2-3)	0.431¶
Duration of stay (days)*	5 (4-8)	6 (4-9)	0.171¶
Total duration of hospital stay (days)*†	5 (4-8)	6 (4-9)	0.270¶
Readmissions			1.000
Yes	6 (7)	6 (7)	
No	78 (93)	78 (93)	
Return to theatre	7 (8)	4 (5)	0.535
Direct Hospital Costs (€)*	22 199 (16 379-28 685)	22 154 (16 978-29 756)	0.805¶

Table 17 Perioperative outcomes in STIMULAX and control groups

Values in parentheses are percentages unless indicated otherwise.

* Values are median (i.q.r.).

† Includes length of stay during index admission and on readmission.

GI-2, validated composite measure defined as the interval from surgery until first passage of stool and tolerance of solid intake for 24 h in the absence of vomiting; POI, postoperative ileus; NGT , nasogastric tube.

§ χ^2 test, except ¶ Mann–Whitney U test.

There were no differences in 30-day postoperative complications or anastomotic leak rate between study groups (Table 18). The 30-day postoperative mortality rate was 1 per cent (1 death in the STIMULAX group, which was not related to the use of laxatives). The median CCI® was 8.7 (0-22.6) in the STIMULAX group compared with 20.9 (0-26.8) in the control group (P = 0.574). Full data on complications are available in Table 18. There were no differences in morphine equivalent dose between study groups as shown in Table 19.

	STIMULAX (n=85)	Control (n=85)	P Value
SRS Baseline (65), Mean (SD)	45 (12.7)	45 (12.7)	0.896
SRS at discharge (60), Mean (SD)	29.5 (11.9)	29.3 (11.0)	0.905
SRS at F/u (65), Mean (SD)	42.2 (13.8)	40.2 (12.4)	0.394
CCI			0.574
Coded *	8.7 (0-22.6)	20.9 (0-26.8)	
30-day total post-operative complications (Clavien-Dindo grade)			
1	34	32	0.478
2	46	62	0.096
3	6	3	0.250
4	7	5	0.458
5	1	0	0.480
30-day highest Clavien-Dindo grade per patient, n (%)			0.301
Nil	35 (41.2)	32 (37.6)	
1	14 (16.5)	10 (11.8)	
2	25 (29.4)	37 (43.5)	
3	4 (4.7)	1 (1.2)	
4	6 (7.1)	5 (5.9)	
5	1 (1.2)	0 (0.0)	
Surgical Complications			0.921
Anastomotic leak a	4 (5.6%)	5 (6.5%)	>0.99
Wound Infection	12	12	
Bleeding / transfusion	5	4	
Small Bowel Obstruction	1	2	
Urinary retention	4	7	
Other	2	1	
Non-Surgical Complications			0.228
Pneumonia	9	5	0.264
Other infection	6	6	
Diarrhoea/High Stoma output b	7	11	
Electrolyte Imbalance	14	13	
Cardiac	4	3	
Neurological	5	0	
Acute renal failure	1	3	
TPN needed	1	2	

Table 18. Postoperative outcomes in STIMULAX and control group

Values in parentheses are percentages unless indicated otherwise.

* Values are median (i.q.r.).

[a] Anastomotic leaks were calculated including only patients with an anastomosis in the denominator.

[b] Diarrhoea or high stoma output requiring needing electrolyte replacement.

SRS, Surgical Recovery Score; SD, Standard deviation; CCI, Comprehensive complication index; i.q.r., Interquartile range; TPN, Total parenteral nutrition

	STIMULAX (n=85)	Control (n=85)	P Value
Postoperative adjunct analgesics			
Epidural	4 (4.7)	10 (11.8)	0.161
IV PCA	23 (27.1)	17 (20.0)	0.278
Wound catheter / TAP blocks	42 (49.4)	36 (42.4)	0.356
None	29 (34.1)	33 (38.8)	0.524
MEDD usage*			
MEDD-Intraoperative	100 (69-120)	90 (56-119)	0.200
MEDD-Recovery	32.8 (16-53)	29.5 (10-50)	0.577
MEDD Day0	188 (125.1-244.3)	158 (120-229)	0.273
MEDD Day1-3	90 (22.3-241.8)	127.5 (30-246.3)	0.590
MEDD Total	323 (175-630.5)	325 (156.3-652.3)	0.993
NSAIDS (D1-10)	34 (40)	33 (38.8)	0.875

Table 19 Postoperative analgesics in STIMULAX and control group

Values in parentheses are percentages unless indicated otherwise.

* Values are median (i.q.r.), Interquartile range.

Duration of stay (5 (4-8) versus 6 (4-9) days; P = 0.171) and total hospital stay (5 (4-8) versus 6 (4-9) days; P = 0.270) were reduced by 1 day in the STIMULAX group compared with the control group. There were no differences between groups in readmission or

return-to-theatres rates, or direct hospital costs per patient (Table 17). Patient-reported functional recovery, as measured by the SRS, was also similar in both groups (Table 18).

7.4 Discussion

In this open-label RCT, laxatives reduced the duration of recovery of GI function (GI-2) by 1 day after major abdominal colorectal surgery. Laxatives also significantly reduced the incidence of prolonged POI. This did not appear to translate to a difference in duration of hospital stay, although the study was not powered to examine this. Laxative use in the postoperative setting appeared to be safe, with no increase in anastomotic leaks or overall complications.

Three previous RCTs have investigated the role of laxatives after colorectal surgery,[203, 205, 228] but only one of these was conducted within an ERP setting.[203] All three trials used single (rather than multimodal) interventions, and varying definitions for recovery of GI function as an outcome measure.[203, 205, 228] In the study by Zingg and colleagues, oral bisacodyl was compared with a placebo in 169 patients, and resulted in a significantly shorter time (3 versus 3.7 days; P = 0.007) to achieving the primary outcome of GI-3, a composite measure including time to first flatus passed, first defecation and first solid food tolerated. Interpretation of the results was limited owing to the inclusion of flatus, which is often considered an unreliable criterion for measurement.[146, 256] In contrast, a smaller RCT conducted by Andersen et al., with 49 patients and using oral magnesium oxide, failed to show a significant effect using the single outcome measure of time to passage of flatus or bowel movement (18 versus 14 h and 42 versus 50 h respectively; each P > 0.15).[203] In the third study by Wiriyakosol and co-workers, bisacodyl suppository commencing on postoperative day 3 was compared with a placebo suppository in 20 patients. All patients in this study who received bisacodyl suppository had a bowel movement on the day of

administration, whereas those receiving the placebo achieved this a day later (3 versus 4.1 days; $P < 0.001$).[228] The limitations identified in these RCTs were used to inform the design of the STIMULAX trial, namely pre-emptive use of multimodal laxatives within an established ERP, and use of currently recommended, validated, and reproducible definitions for recovery of GI function (GI-2).[146, 257]

The present trial showed no difference in complication rates between the STIMULAX and control groups. Laxatives did not appear to cause anastomotic leak. This is an important finding as the use of laxatives appears to be driven by individual surgeons' preferences and risk perception. A recent global survey of over 800 colorectal surgeons demonstrated that, despite ERP recommendations, a majority of surgeons were reluctant to use laxatives owing to lack of evidence and concern regarding adverse events such as anastomotic leak.[236, 237, 247]

Interestingly, even though there was a reduction in prolonged POI incidence in the STIMULAX group, this did not result in a decrease in duration of hospital stay or treatment cost for these patients. There are several factors that influenced the length of stay in this pragmatic trial. One of these was the rotating team of fellows and trainees involved in the postoperative care of patients, all of whom had different discharge tolerances. The second factor is the need for stoma education, and the ability to get beds at the rehabilitation centre for patients needing them. Finally, many of the patients in this study came from remote areas, and social factors such as arranging transport often delayed discharge.

There was no difference in incidence of vomiting or NGT insertion between groups despite a reduction in prolonged POI in the STIMULAX group. The reason for this may relate to the specific definitions used, which attempted to capture patients with true significant prolonged POI rather than simple postoperative nausea and vomiting or reflex NGT

insertion (during surgery or without ileus). Prolonged POI was precisely defined as GI-2 not being achieved on or after day 4. The incidence of vomiting in this study encompassed any vomiting episode at any time during the inpatient stay (for example, vomiting in recovery was recorded).

Using a combination of laxatives with different mechanisms of action sets this trial apart from previous studies. Although this makes it difficult to attribute the outcomes to one specific medication or combination, the design emulates the principles of prophylaxis used in other aspects of ERPs, such as multimodal pre-emptive analgesia and antiemetics.[123, 229] The use of a Fleet® enema for right sided procedures is also novel and warrants explanation. Although this may lead to confounding, the decision to include this intervention was based on recent evidence of a postoperative rectosigmoid 'brake' system which acts as a physiological sphincter by causing retrograde contractions and inhibiting normal passage of enteric contents, thus contributing to POI .[230] It is plausible that giving a Fleet® enema counteracts this pathophysiological effect, initiating an antegrade bowel movement, and releasing the brake. Although the bowel movement criterion was met, irrespective of whether it was a spontaneous action or after an enema with therapeutic effect, it is important to stress that the primary outcome in this trial was a composite outcome measure; all participants were required to have met all three criteria to be considered to have achieved the primary outcome.

This study has some limitations. It was undertaken in a single center study with a strict ERP in place, meaning the results may not be applicable to other settings. Nevertheless, the trial had broad inclusion criteria, with varied indications, operations, and patients with a stoma included, which makes the findings more widely applicable to general colorectal practice.[258] Blinding of participants and assessors was not considered feasible because of

the nature of the interventions (Fleet® enema in particular). However, the data analysis was done blinded to the group allocation. Although patient comfort was not assessed formally, anecdotally some patients could not tolerate high volumes of liquid given with macrogol (250ml a day), in addition to the usual encouragement of oral intake in the authors' ERP. Finally, this study was not powered for secondary outcomes including complications, and no subset analyses or adjustments were performed using these data.

7.5 Conclusion

Routine postoperative use of multimodal laxatives after elective colorectal surgery results in earlier recovery of gastrointestinal function and reduces the incidence of prolonged POI.

CHAPTER 8: PYRICO-PILOT – PYRIDOSTIGMINE TO REDUCE THE DURATION OF POSTOPERATIVE ILEUS AFTER COLORECTAL SURGERY – A PHASE II STUDY.

Statement of Authorship

Title of Paper	PyRICo-Pilot - Pyridostigmine to reduce the duration of postoperative ileus after colorectal surgery - a phase II study
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Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

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8.1 Introduction

Recovery after abdominal surgery requires patients to tolerate diet, mobilise independently and demonstrate evidence of return of gastro-intestinal (GI) function. Delayed recovery of GI function or postoperative ileus (POI) is a major impediment to post-operative recovery.[1, 259] Despite the advent of enhanced recovery protocols (ERPs) in the last decade, POI is still common and occurs in almost one in three patients after colorectal surgery.[3, 4, 6, 7] It is a source of major morbidity and discomfort for patients, delaying enteral nutrition, predisposing to wound failure and pneumonia and often requiring invasive interventions that significantly impact recovery after surgery.[2] POI as a complication has the largest overall effect on length of postoperative hospitalization and thus substantially increases the costs of surgical care.[3, 44, 260]

Multi-modal strategies have been employed to improve the return of GI function as part of ERPs. These include the routine use of postoperative laxatives, avoidance of opioids, early feeding, and mobilisation.[149, 155] However, these interventions have had a limited impact on the rate and severity of POI in general. This is attributed to the complex pathophysiology of POI, characterised by an intricate relationship between inflammatory, neurogenic, and vagal mechanisms.[16, 221]

Despite autonomic dysfunction playing a central role in the aetiology of POI, there appears to be a major knowledge gap in the use of agents that target the autonomic system in this setting, such as acetylcholinesterase inhibitors (ACIs).[261] ACIs such as pyridostigmine and neostigmine, increase GI motility by enhancing the availability of acetylcholine at neuromuscular synapses in the myenteric plexus.[262, 263] The release of acetylcholine also prevents macrophages from triggering the inflammatory phase of POI. This neuro-inflammatory channel is commonly known as “cholinergic anti-inflammatory pathway

(CAIP)".[264-267] ACIs have been used successfully in the treatment of chronic constipation,[268] pseudo-obstruction,[269] abdominal distention,[270] and dyspepsia.[271] ACIs have also been used safely after spinal surgery to improve GI motility and reduce the duration of POI.[10, 272] Though there have been some concerns regarding the use of neostigmine in the post-operative setting due to potential cardiac and respiratory side effects and a requirement for intensive monitoring, oral pyridostigmine is much safer in this regard and may be a good therapeutic option. In a randomised controlled trial (RCT) conducted by Maleknejad et al. in patients undergoing abdominal surgery,[273] the safety and efficacy data appeared promising, with a one day reduction in time to first passage of stool and flatus , and no obvious adverse effects. However, in this study, all patients underwent non-colorectal abdominal surgery, with a lower baseline risk of ileus and a lower risk of cardiorespiratory complications. There have not been any studies conducted in patients undergoing colorectal surgery, and safety in this setting has yet to be established.

We hypothesise that, within an optimised ERPs setting, giving oral pyridostigmine to patients postoperatively will result in a reduction in the duration of ileus. However, prior to conducting an adequately powered RCT to test efficacy, a Stage 2A/2B study is required as per the IDEAL framework for studies in development and exploratory phase.[274]

The purpose of this pilot study is to determine the safety of use of oral pyridostigmine in patients after elective colorectal surgery.

8.2 Methods

8.2.1 Study design, participants, and settings

PyRICo-Pilot is a prospective stage 2B (IDEAL framework)[275] study of oral pyridostigmine in patients undergoing elective colorectal surgery conducted at the Royal Adelaide Hospital (RAH), Adelaide, South Australia, Australia. This study was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (MyIP - 13049) and was registered with anzctr.org.au (ACTRN12620001262998). The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and the principles of Good Clinical Practice (ICH-GCP E6).[251]

All adult (≥ 18 years) patients undergoing elective open, laparoscopic, or robotic colorectal resections for any indication or having formation or reversal of stoma (colostomy / ileostomy) at the RAH between September 2020 and January 2021 were screened for inclusion. Exclusion criteria were: patients under 18 years of age, pregnant and lactating females, patients allergic to pyridostigmine, patients with ASA ≥ 4, active inflammatory bowel disease, prolonged QT syndrome (greater than 0.43sec for males, 0.45 for females), colonic motility disorder, asthma, ischemic heart disease or cardiac arrhythmias within the previous 12 months, epilepsy, Parkinson's, hyperthyroidism, peptic ulcer disease, pelvic disorders causing constipation, irritable bowel syndrome, faecal incontinence, history of bowel obstructions, strictures or any disease affecting bowel transit such as hypocalcaemia or hypothyroidism, moderate to severe renal impairment (eGFR < 45), patients already on anti-cholinergic medications and those with an inability to give consent or participate in postoperative assessments due to dementia, cognitive impairment or language barrier. The exclusion criteria include factors that may be confounders for the outcome parameter (GI2). In addition, precautions for the use of

pyridostigmine stated by the national therapeutics' goods regulatory body were also considered. All patients provided written informed consent prior to participation.

8.2.2 Interventions

All patients underwent surgery by, or under the supervision of, one of the six specialist colorectal surgeons at RAH, who are accredited members of the Colorectal Surgical Society of Australia and New Zealand (CSSANZ). Perioperative management (including details of bowel preparation) of all patients was standardized using an established evidence-based ERP program available at: http://www.tinyurl.com/raheras. In addition, all patients received 60 mg oral Pyridostigmine twice a day (Mestinon, iNova Pharmaceuticals, Australia), starting six hours after surgery. The study intervention was given until the patients opened their bowels or were discharged from the hospital, whichever occurred earlier. Nursing and medical staff were made aware of the presence of the study protocol via formal interactive ward-based teaching sessions and one-on-one reminders to involved personnel. In addition, a one-page summary of the protocol including the list of commonly seen adverse effects of pyridostigmine was placed in the clinical notes folder of participants upon recruitment. Pyridostigmine can have muscarinic effects such as nausea, vomiting, diarrhoea, abdominal cramps, increased peristalsis, salivation, and bronchial secretions, miosis and diaphoresis. Nicotinic effects are usually muscle cramps, fasciculation, and weakness. Bradycardia and hypotension may also occur.

8.2.3 Outcomes

The primary outcomes were: 30-day postoperative complications graded using the Clavien-Dindo (CD) classification system (minor, grades 1–2; major, grades 3–5),[245] adverse events, and GI-2. GI-2 is a validated composite measure of GI recovery defined

as the interval from surgery until first passage of stool and tolerance of a solid intake for 24 hrs (in whole days) in the absence of vomiting.[146] Secondary outcomes were time to first passage of flatus, stool and tolerance of solid diet, incidence of prolonged POI (PPOI, defined as GI-2 not achieved on or after day 4),[146, 276] incidence of vomiting, nasogastric tube (NGT) insertion, length of hospital stay, readmission, return to theatre, comprehensive complication index score (CCI®).[252] Patient-reported outcomes were also recorded using the Surgical Recovery Score (SRS) at baseline, discharge and 30days.[29]

To determine GI-2, participants were reviewed daily for ten days following surgery by one of the investigators in the study team. Stool and diet charts were maintained by the nursing staff and checked daily. If a patient was discharged earlier, a daily review was conducted by telephone until GI-2 was achieved. Discharge criteria were pre-specified as per ERP. Total hospital stays (length of hospital stay on index admission plus hospital stay on readmission) was derived and recorded. Readmission was defined as returning to the hospital within 30 days of surgery, requiring a hospital stay of > 24 hours.

Data related to patient age, gender, smoking status, body mass index, previous abdominal surgery, pre-existing stoma, modified frailty index (mFI-5),[277] American Society of Anaesthesiologists (ASA) score, underlying pathology (malignancy, diverticulosis, other benign diseases), date of surgery, primary operation, new stoma creation and its type, operative approach (open, laparoscopic/laparoscopic-assisted, robotic), conversion to open, operating time, red cell transfusion and postoperative analgesia used were also collected.

8.2.4 Sample size and statistical analysis

Sample size calculation was not possible due to the pilot study design, and participant recruitment was based on convenience sample methodology. Statistical analyses of the

data were conducted using SPSS for Windows (Version 26; SPSS, Chicago, IL). Continuous data was assumed to be non-parametric considering the sample size was small and are presented as median ± interquartile range (IQR). Categorical data are presented as frequency (percentage).

8.3 Results

Fifteen patients were included in the study. All patients completed the study with no loss to follow up. Median age was 58 (50-82) years, and seven (47%) were men. Most participants had an ASA grade ≥ II (53%), and the median BMI was 27 (24-35). Benign conditions such as reversal of stoma and diverticulosis were the most common indication for surgery (n=8, 53%), and 53% of procedures were minimally invasive. (Table 20)

Patient characteristics	Number (%) [a]
Age, Median (IQR)	58 (50-82)
Sex	
Male	7 (47)
Female	8 (53)
Smoking	6 (40)
BMI, kg/m^2, Median (IQR)	27 (24-35)
ASA	
1	1 (7)
2	8 (53)
3	6 (40)
mFI	
0	8 (53)
1	3 (20)
2	4 (27)
Previous abdominal surgery	12 (89)
Pre-existing stoma	
Ileostomy	4 (26)
Colostomy	2 (14)
No stoma	9 (60)
Indications for operation	
Neoplasia/polyp	7 (47)
Diverticulosis/Other benign	8 (53)
Bowel Prep	
Picolax/Colonlytely	5 (33)
Fleet enema	2 (14)
No prep	8 (53)
Operation type	
Open	7 (47)
Lap/Lap-assisted	8 (53)
Conversion to open [b]	
Yes	3 (37.5)
No	5 (62.5)
Primary operation	
Right Colectomy [c]	4(26)
Anterior Resection	3 (20)
Left Colectomy	1 (7)
APR	1 (7)
Reversal of Loop Ileostomy (RLI)	3 (20)
Reversal of Hartmann's (ROH)	3 (20)
New stoma	
Ileostomy	2 (14)
Colostomy	1 (7)
No stoma	12 (89)
Total operating time, Median (IQR), min	212 (101-283)

Table 20 Baseline characteristics of the PyRICo-P patients

[a] Data are number of patients (%) unless otherwise indicated.

[b] Remaining data are nor applicable.

[c] Rt colectomy includes – Right hemicolectomy, Extended Right hemicolectomy

IQR, Interquartile range; BMI, Body mass index; ASA, American Society of Anaesthesiologist; mFI, Modified Frailty Index; APR, Abdominoperineal resection.

There were 13 post-operative complications: seven were CD 1, five CD 2, and one CD 3 complications. Electrolyte derangement was the most common complication. One patient had atrial bigeminy, which was managed conservatively without any medication, and after consulting cardiology, this was thought to be an undiagnosed baseline state unrelated to pyridostigmine administration. All the patients were hemodynamically stable after administering pyridostigmine and none reported symptoms of excessive parasympathetic activity, such as increased sweating or abdominal cramping. Three patients had a transient episode of diarrhoea between day two and four which settled without any intervention. There was no 30-day postoperative mortality. Median CCI was 8.7 (0-22.6). (Table 21).

Median GI-2 was two days (1-4) with the median time to first passage of flatus, stool, and tolerating solid diet without vomiting for 24 hrs being one day, two days, and one day, respectively. The rate of PPOI in this cohort was 20% (n=3). (Table 21) The median length of index stay was 4 days (3-6) and total hospital stay was 6 days (3-6). Three patients were readmitted for reasons unrelated to the study drug, and there were no returns to theatre. Patient-reported functional recovery, as measured by the SRS, was 47 at baseline, 24 at discharge and 42 on follow up at 30 days. (Table 21).

Participant No.	Age (years)	Gender	Operation	No. of doses given	Drugs ceased d/t side effects	Possible Side effects	Highest CD grade	Time to passage of stool (days)	Time to GI2 (days)	Length of hospital stay (days)
1	68	M	Reversal of loop ileostomy	4	No	Nil	2	2	2	3
2	55	M	Reversal of hartmann's	2	No	Diarrhea On Day 2	-	1	1	3
3	77	F	Right hemicolectomy	8	No	Diarrhea on Day 4	-	4	4	5
4	48	M	High anterior resection	2	No	Nil	2	1	1	5
5	50	M	Reversal of hartmann's	3	No	Nil	-	2	2	3
6	57	F	Extended right hemicolectomy	4	No	Atrial bigeminy	2	2	2	3
7	58	M	Reversal of hartmann's + loop ileostomy + Cholecystectomy	4	No	Nil	1	1	4	7
8	68	F	Left hemicolectomy	3	No	Nil	1	2	2	4
9	68	F	Right hemicolectomy	2	No	Nil	1	5	5	6
10	82	M	Right hemicolectomy	4	No	Nil	1	2	2	3
11	49	F	High anterior resection	3	No	Nil	3	1	1	4
12	50	F	Reversal of loop ileostomy	2	No	Nil	1	4	5	6
13	72	F	Ultra-low anterior resection + loop ileostomy	3	No	Nil	1	0	1	6
14	82	F	Abdomino-perineal resection	1	No	Nil	2	3	5	9

15	19	M	Reversal of loop ileostomy	2	No	Diarrhea On Day 2	-	1	2	2

Table 21 Perioperative outcomes in PyRICo-P participants

GI2 - a validated composite measure of GI recovery defined as the interval from surgery until first passage of stool and tolerance of a solid intake for 24 hrs (in whole days) in the absence of vomiting.

CD – Clavien-Dindo (CD) classification system

8.4 Discussion

This pilot Stage 2B study demonstrated that the use of oral pyridostigmine in patients after colorectal surgery appeared to be safe with no obvious increase in serious complications or treatment-related adverse events. While we did not design the study to investigate efficacy, we did note fairly rapid return of GI function (two days) and a low incidence of PPOI (20%) compared with a historical comparison group.[276] Our findings suggest that the use of pyridostigmine to improve recovery of GI function after colorectal surgery should be further investigated using a larger, adequately powered randomised controlled trial with efficacy as the primary outcome.

Currently, most of the published literature on the role of ACIs in GI motility disorders is in the field of colonic pseudo-obstruction.[278-281] ACIs treat pseudo-obstruction by reversing or regulating the deranged autonomic balance between sympathetic and parasympathetic activity in the colon.[280] This therapeutic action of ACIs has not been widely explored in the prevention and treatment of post-operative ileus despite a known partial causal role of the autonomic nervous system in this process.[262, 282] Postoperative ileus is characterized by general hypomotility of the gastrointestinal tract. This hypomotility results from inflammation in the intestinal muscularis layer due to the activation of resident macrophages triggered by bowel manipulation.[46, 50] While perioperative stimulation of the vagus nerve may ameliorate this, the effectiveness of this stimulation depends on the cholinergic inhibition of macrophage activation, through the “cholinergic anti-inflammatory pathway”.[265-267, 283] Administration of acetylcholinesterase inhibitor agents like pyridostigmine, results in an increase of acetylcholine at neuromuscular synapses in the myenteric plexus, thereby achieving the same effect and stimulating GI motility.[265-267]

In a study of 40 patients conducted by Maleknejad et al., pyridostigmine administered through a nasogastric tube after abdominal surgery resulted in significantly shorter time to passage of stool (4.9 vs 36.2 hours, P = 0.001), and passage of flatus (5.4 vs 32.4 hours, P= 0.001) when compared with a placebo.[273] This study also found that the treatment response to pyridostigmine occurred within 24 hrs for 95% (n=19) of patients compared to only 50% (n=10) in the placebo group. No significant side effects were observed. Interpretation of this studies results is limited as all patients underwent non-colorectal abdominal surgery (50% caesarean section, 25% cholecystectomy, 15% antrectomy, 10% other), with a lower baseline risk of ileus, and low risk of cardiorespiratory complications. Another limitation was in the assessment of recovery of GI function which was done by a single outcome measure (passage of a bowel movement) rather than a validated composite measure such as GI2.[146] There are two other studies which have successfully used ACIs in adult patients after spinal and vascular surgery to reduce the duration of ileus without increasing the risk of postoperative complications. Though these studies outlined some concerns due to increased cholinergic symptoms such as arrhythmia, excessive sweating, and abdominal cramps, this was likely due to the use of intravenous or epidural neostigmine rather than oral pyridostigmine, which is a much safer and better tolerated option.[10, 272, 279, 280, 284] In the current study, postoperative complications were mostly minor (12 out of 13) defined as CD grade ≤2, and there was no treatment-related adverse event to report. All the seven CD grades 1 were electrolyte derangement, five CD grade 2 included surgical site infections (2), Ileus (1), intra-op blood transfusion (1), and antibiotics given for suspicious clostridium difficle infection (1). There was only one CD grade 3 complication which was a surgical site infection needing wound debridement in the ward.

The limitations of this study included the small number of patients enrolled, and the lack of a control group. However, this study was designed from the outset as a phase II study,

with a plan for a larger randomised controlled trial to follow if appropriate. Patients in this study were given laxatives routinely as part of the ERP, along with pyridostigmine, and it is therefore difficult to attribute the outcomes to one specific medication or to a combination. The question of whether adding oral pyridostigmine to the ERP in addition to the prescribed multimodal laxatives has an incremental effect on the recovery of GI function needs to be examined further in a future randomised controlled trial.

8.5 Conclusion

Oral pyridostigmine appears to be safe to use in after elective colorectal surgery in a select group of patients. However, considering this is a pilot study with a small sample size, larger controlled studies are needed to confirm this finding and establish efficacy for POI prevention.

THESIS SYNOPSIS

This thesis was ultimately aimed at answering the following five questions:

1. What are the recommendations for preventing POI or reducing the duration of GI recovery after colorectal surgery in Enhanced recovery protocols?
2. Is there any level 1 evidence for using routine laxatives to improve GI function recovery after abdominal surgery?
3. What are the preferences and practice by surgeons regarding laxative use following elective colorectal surgery?
4. Is there any benefit in adding multimodal laxatives to an ERP to improve GI function return in patients undergoing colorectal surgery?
5. Is it safe and effective to use oral pyridostigmine after elective colorectal surgery?

In a brief overview presented in the introduction, the aetiology of postoperative ileus was described, focusing on its impact on patient outcomes and healthcare services, and challenges to the management of ileus and research in this field. Delayed recovery of GI function after surgery results from inflammatory cell activation, autonomic dysfunction with a sympathetic shift, disruption of enteric continuity, activation of gut opioid-receptors and, gastrointestinal neuropeptide disturbances. Owing to complicated multifactorial pathophysiology and a lack of uniform recommendations for managing this condition in enhanced recovery protocols, ileus rates have remained recalcitrant, particularly following major colorectal surgery. Heterogeneity in definitions and outcome measures of POI also has led to a poor understanding of its incidence, risk factors, and has compromised the external validity of clinical trials appraising interventions to shorten its duration.

The first study was a systematic scoping review undertaken to summarize management recommendations targeting postoperative ileus and delayed recovery of GI function available from published ERPs. A comprehensive systematic review of the literature was

performed through the Ovid MEDLINE, Embase, Cochrane Library and PubMed databases for all publication types, including conference papers and abstracts, from January 1990 to May 2018 using keywords and database-specific indexed subject headings. Of 481 manuscripts screened, 37 individual ERPs were published in 37 studies, including 41 centres. There were 18 cohort studies, seven historically controlled studies, five guidelines, four randomized controlled trials (RCTs), one RCT protocol, one case series and one narrative review. The interventions used varied throughout the protocols. Simple laxatives constituted the largest category of medications recommended in 24 of 37 studies (64.5%). The single most used intervention for stimulation of bowel motility was a magnesium (Mg) based laxative (18 of 37, 48.6%) such as magnesium oxide (MgO) and magnesium hydroxide (MgOH). The second most common intervention used was chewing gum (13 of 37, 35.1%). Other less commonly recommended interventions were Alvimopan (6 of 37, 16.2%), lactulose (4 of 37, 10.8%), neostigmine (2 of 37, 5.4%) and Bisacodyl (2 of 37, 5.4%). Liquid paraffin, coffee, daikenchuto and Chinese herbal medicine with acupuncture infusion of raw rhubarb were only mentioned in one protocol each (2.7%). As per the evidence strength assessment reported in the included studies, the evidence for oral laxatives, and chewing gum was weak for all outcome measures. Alvimopan was reported to have moderate to strong evidence for improving return of GI function, reduction in the incidence of ileus, and reduced day stay, especially in patients undergoing laparotomy.

The second study was a systematic review and meta-analysis conducted to map out the current level 1 evidence available in the literature to assess the safety and efficacy of laxative use for improving recovery of gastrointestinal function after major abdominal surgery. A systematic search of the MEDLINE (1946 to 21 May 2019), Embase (1974 to 21 May 2019), Cumulative Index to Nursing and Allied Health Literature (CINAHL)

(EBSCOhost) databases (1974 to 21 May 2019), and the Cochrane Database of Systematic Reviews, Cochrane Clinical Trials Register, and Database of Abstracts on Reviews and Effectiveness was done. All ‘Primary Registries’ listed in the WHO Registry Network (including ClinicalTrials.gov) were also searched for ongoing (unpublished) RCTs on 22 May 2019. Medical subject headings (MeSH) and keyword search terms related to ‘ERAS’, ‘recommendations’, ‘laxatives’, ‘abdominal’, ‘surgery’, ‘prevention’, ‘postoperative’, ‘ileus’ and ‘gastrointestinal 2’ (GI-2) were used. Unpublished data were also sought from authors of trials listed in the registry. A total of 323 studies were initially identified with data finally extracted from five RCTs for 416 patients after criteria-led exclusion of other studies. Laxatives reduced the time to passage of stool (mean difference (MD) −0·83 (95 per cent c.i. −1·39 to −0·26) days; P=0·004), but there was significant heterogeneity between studies for this outcome measure. There was no difference in time to passage of flatus (MD −0·17 (−0·59 to 0·25) days; P=0·432), time to tolerance of diet (MD −0·01 (−0·12 to 0·10) days; P=0·865) or length of hospital stay (MD 0·01(−1·36 to 1·38) days; P=0·992). There were insufficient data available on postoperative complications for meta-analysis. This study highlighted the knowledge gap in using the laxatives in studies with validated outcome measures for GI recovery to provide better evidence.

Considering the laxatives’ role after elective colorectal surgery was unclear, resulting in heterogenous guidelines and variability in clinical practice, the third study aimed to gauge surgeons’ preferences and practice regarding laxative use following elective colorectal surgery. A short one-minute anonymous web-based questionnaire using the Research Electronic Data Capture application (REDCap) was distributed to member surgeons of every identifiable international colorectal specialist society via email communication, physical newsletters and social media channels. Data on the frequency of laxative use after elective colorectal surgery, type of laxative used, and, if not used, the reasons for not

using laxatives were collected. A total of 852 surgeons, representing 28 surgical societies completed the survey: 80% were colorectal surgeons, and 20% were general surgeons with colorectal interest. Twenty-seven per cent of the respondents routinely prescribed laxatives after colorectal surgery. There was wide variation in the type of laxatives used, with magnesium-based laxatives (42%), macrogol (Movicol, 36%) and lactulose (Duphalac, 22%) being the most common. Geographical location was correlated with choice of laxative. Those not routinely using laxatives stated the reasons as being no evidence for a benefit (48%), the potential of adverse events (24%), more than one reason (21%) and other (7%). The majority (93%) non-users suggested that they would consider using laxatives if better evidence was available.

The fourth study was a retrospective cohort study conducted to gather evidence on safety and efficacy of laxative use in improving return of gastrointestinal (GI) function after elective colorectal surgery in the local setting at the Royal Adelaide Hospital. All adult patients (18 years and above) who underwent large bowel resections (including colon and rectum), stoma reversals (colostomy/ileostomy) or formation of stoma procedures, for any indication, from June 2017 to August 2018 were included. The primary outcome measure was GI-2, a validated measure of GI recovery, a composite measure of time (in whole days) to the tolerance of solid diet AND passage of stool. Secondary outcome measures were days to first passage of stool, days to the tolerance of solid diet, incidence of vomiting, incidence of nasogastric tube insertion, incidence of prolonged postoperative ileus, anastomotic leak, pneumonia, intra-abdominal collection, length of hospital stay, 30-day complication rate by highest Clavien-Dindo grade, 30-day readmission rate, return to theatre and reported adverse events. To overcome biases due to the different distribution of co-variables among patients between the two groups (Laxatives vs Non-laxatives), propensity score matching was carried out to obtain a one-to-one match by the optimal

matching method. Known confounders including age, sex, BMI, previous abdominal surgery, type of operation, and operative approach were used for matching.

Of 173 eligible patients, 67 (38.7%) had routine laxatives prescribed, and 106 (61.3%) did not. On raw analysis, the baseline characteristics differed in terms of operation type with fewer reversal of Hartmann's (0% vs 6.6%, P 0.044) and more pelvic exenterations (10.5% vs 1.9%, P 0.029) in the Laxative versus No-laxative groups. Also, there were significantly fewer anastomotic leaks in Laxative group (0 vs 10.7%, P 0.013), but otherwise, there were no differences in any other outcome measures. Forty-eight patients remained in each group after propensity score matching (PSM). Time to GI-2, anastomotic leak, and readmission rates showed a trend favouring the laxative group after PSM though none were statistically significant. This study showed that postoperative laxative use following CRS appeared safe; however, their efficacy required further investigation in an adequately powered randomised controlled trial.

The fifth study was the STIMULAX Trial – a pragmatic open-labelled randomised controlled trial of STIMUlant and osmotic LAXatives to improve recovery of gastrointestinal function after colorectal surgery. All adults (≥ 18 years) patients undergoing elective open, laparoscopic, or robotic colorectal resections for any indication or having formation or reversal of stoma (colostomy/ileostomy) at the Royal Adelaide Hospital (RAH) between August 2018 and May 2020 were screened for inclusion. Trial participants were randomized into two groups: Intervention (STIMULAX) and Control. The control group received routine standard of care treatment (no placebo) as per the current ERP, which does not include postoperative stimulants or laxatives. The STIMULAX group received identical care but with the addition of multimodal laxatives. These included a stimulant laxative: Oral Coloxyl with Senna, and an osmotic laxative: Oral Macrogol, both starting six

hours after surgery. Additionally, right-sided cases received a Sodium Phosphate Enema (one enema once a day) from day one after surgery at mid-day. The primary outcome was GI-2, a validated composite measure of GI recovery defined as the interval from surgery until first passage of stool and tolerance of a solid intake for 24 hrs (in whole days) in the absence of vomiting. All study interventions were given until the participant achieved the primary outcome of GI-2 or were discharged from the hospital, whichever occurred earlier. Secondary outcomes were time to first passage of flatus, stool and tolerance of solid diet, incidence of prolonged POI, incidence of vomiting, NGT insertion, length of hospital stay, readmission, 30-day postoperative complications, return to theatre, comprehensive complication index score (CCI®) and direct cost assessment. After screening for inclusion, 170 patients were randomized equally between the STIMULAX (n=85) and Control group (n=85). Baseline characteristics between both groups were similar. GI-2 was a day shorter in the STIMULAX group compared to the control group, and this was statistically significant (median [IQR] 2 days (1.5-4) vs 3 days (2-5.5), 95% CI -1 to 0 day, P = 0.029) The STIMULAX group had a significantly faster time to first passage of stool compared to the Control group (2 (1-2) vs 3 (1-4) days, 95% CI -1 to 0 day, P < 0.001). There was no difference in time to flatus (1 vs 1 day, P = 0.516) or time to tolerance of solid diet (1 vs 1 day, P = 0.575). The STIMULAX group had a significant lower rate of PPOI compared to the Control group (n=19 (22%) vs n= 32 (38%), P = 0.030). There were no significant differences in 30-day postoperative complications or the anastomotic leak rate (n=4 (5.6%) vs n=5 (6.5%), P >0.99). This study did show that routine postoperative use of multimodal laxatives after elective colorectal surgery results in earlier recovery of gastrointestinal function and reduces the incidence of PPOI.

Finally, the sixth study was a safety and feasibility study to investigate the effectiveness of oral pyridostigmine after elective colorectal surgery. This study was conducted as a phase

2 trial and aimed to determine the possibility of conducting a future randomised controlled trial using oral pyridostigmine to improve GI recovery after colorectal surgery. This is a single centre, open-label, prospective study. All consecutive patients undergoing elective abdominal colorectal resections for any indication or having formation or reversal of stoma at the Royal Adelaide Hospital (RAH) were included in the study. Patients received 60 mg of oral pyridostigmine tablet twice a day from the day of operation till they opened their bowels. The primary outcome was 30-day postoperative complication rate, adverse events, and GI-2, a validated composite measure of time to tolerance of solid intake for 24 hours without vomiting and passage of stool. Fifteen patients were included in the study. All patients tolerated the study drug with no complications or serious adverse events at 30 days. Median GI-2 was 2 days in all patients with prolonged postoperative Ileus occurring in three patients (20%).

CONCLUSION

Based on the research presented in this thesis, a few conclusions can be drawn.

Firstly, there is considerable heterogeneity in the interventions recommended by published enhanced recovery protocols for improving the recovery of gastrointestinal function in patients after surgery.

Secondly, there is a lack of consensus on laxatives use in the postoperative setting. Until now, the extremely limited supportive evidence has resulted in relatively low uptake of these medications in colorectal practice worldwide.

Thirdly, and perhaps most importantly, we have been able to demonstrate that routine use of postoperative multimodal laxatives after elective colorectal surgery results in earlier recovery of gastrointestinal function and a reduction in the incidence of prolonged postoperative ileus. However, laxatives do not seem to have any impact on other important postoperative recovery parameters. This raised a question about the potential effects of other mechanisms of POI, which are not affected by laxatives, such as autonomic dysfunction.

Finally, acetylcholinesterase inhibitors like oral pyridostigmine, appear to be safe to use in after elective colorectal surgery in a select group of patients. However larger randomised controlled studies are needed to explore the efficacy of these.

FUTURE RESEARCH DIRECTIONS

This thesis has outlined the current evidence for management of ileus and established the baseline rate that can be achieved with simple multimodal laxative use after elective colorectal surgery. While the data show that laxatives are affective at attenuating the duration of ileus, several areas have been identified for future investigation.

Considering the biggest hurdle in researching ileus has been the wide variation in definitions and reported outcome measures for its resolution, future initiatives need to further define this aspect. Creating a definitive core outcome set for gastrointestinal recovery will ensure that future research studies are clinically meaningful, replicable, and relevant to patients undergoing abdominal surgery. An international project addressing this is already well advanced and underway with input from our research lab.

The STIMULAX trial has undoubtedly shown that multimodal laxatives can help patients recover their gastrointestinal function earlier after surgery and reduce the incidence of prolonged postoperative ileus. However, the study stopped short of showing any significant improvements in other recovery parameters, including patients' length of hospital stay. One of the reasons could be that the study was not powered for these outcomes. A multicentre, double-blinded randomised controlled trial conducted with a factorial, pragmatic design could perhaps add power, as well as external validation of the results in other clinical settings.

Finally, the future lies in looking at novel therapies that target individual pathways in the pathogenesis of ileus, such as neural blockade, suppression of inflammation, mechanical reduction of oedema and gut neuropeptide manipulation. In particular, rebalancing of the autonomic pathway requires active investigation as a logical next step. A double blinded randomized controlled rial of pyridostigmine in this setting is currently planned.

APPENDIX – A: ONLINE GLOBAL SURVEY

Email Invitation

Subj: **ONE MINUTE SURVEY** – Laxatives after colorectal surgery

Dear Dr [Insert Name],

We are conducting a research survey of colorectal surgeons worldwide and would like you to please consider sending this to members of the [Insert Colorectal Society Name] and your friends by email or link in newsletters. We have designed the survey to be extremely short and efficient to undertake. This is a quick one-page survey which should take **less than one minute** to complete.

Please find a link attached for your review:

Link: http://j.mp/2RSJC3F

The issue of laxatives after surgery is very infrequently discussed and perhaps the most under-investigated aspect of most modern ERAS protocols. In addition, there is a wide geographic variation, which is precisely why we are keen to include your members' perspectives in this study. This survey aims to capture a snapshot of surgeon preferences on the use of laxatives after elective colorectal surgery. Participation is voluntary and anonymous.

For any queries about the survey please contact:

Dr. Nagendra Dudi-Venkata

Colorectal research fellow

Royal Adelaide Hospital Adelaide, South Australia – 5000

Email ID: drnags3@gmail.com

Mobile: +61 4 3075 9215

Survey Questionnaire

Survey: Laxatives after colorectal surgery

You are invited to take part in a very short survey on laxatives after elective colorectal surgery.

We anticipate this would take approximately one minute of your time.

Participation is entirely voluntary. We greatly appreciate your participation.

All responses are anonymous.

1. Do you consider yourself a Colorectal Surgeon or a General Surgeon?

a. Colorectal Surgeon

b. General Surgeon

c. Other (Specify).....

2. Are you a member of one of the organisations?

a. RACS Colon and Rectal Surgery Section

b. CSSANZ

c. ACPGBI

d. RSM Coloproctology Section

e. ESCP

f. APFCP

g. ESSO

h. NVCO

i. NVGIC

j. BSCP

k. ASCRS

l. SACRS

m. CSCRS

n. SSCRS

o. IRCPS

p. ACRSI

q. SICCR

r. Other (Specify).....

3. Do you have a formal Enhanced Recovery After Surgery (ERAS) protocol at your hospital?

a. Yes

b. No

4. Do you routinely prescribe LAXATIVES after elective colorectal surgery? (If yes - Q5, If no - Q6 + Q7)

a. Yes

b. No

5. Which type of laxatives do you use after elective colorectal surgery?

a. Coloxyl + Senna

b. Bisacodyl

c. Movicol

d. Lactulose

e. Fleet enema

f. Microlax enema

g. Magnesium oxide/ hydroxide / silicate (or any other Mg based laxative)

h. Other (Specify).....

6. Can you state your reasons for not using laxatives after elective colorectal surgery in your practice?

a. No evidence for benefit

b. Potential adverse events

c. Cost

d. Other (Specify).....

7. Would you consider using laxatives if there was evidence to support improvement in return of gastrointestinal function without adverse effects?

a. Yes

b. No

8. Do you have any other comments?

APPENDIX – B: STIMULAX TRIAL - PATIENT INFORMATION SHEET & CONSENT FORM

STIMULAX Study

Open label randomized controlled trial of combination of simple STIMUlant and osmotic LAXatives to reduce the duration of post-operative Ileus (POI) in patient's undergoing colorectal surgery

Participant Information Sheet/Consent Form

Interventional Study – *Adult providing own consent*

Version 02 30/05/2018

Royal Adelaide Hospital

Title	STIMULAX Study – Open label randomized controlled trial of combination of simple STIMUlant and osmotic LAXatives to reduce the duration of post-operative Ileus (POI) in patient's undergoing colorectal surgery.
Short Title	STIMULAX Study
HREC Approval Number	HREC/18/CALHN/250
Principal Investigator	Dr. Nagendra Dudi-Venkata MBBS Grad. Dip. Surg Ed.
Supervising / Co Investigators	Assoc. Prof. Tarik Sammour BHB MBChB FRACS PhD Mr. James Moore MBBS MD FRACS

Part 1 What does my participation involve?

Introduction

Dear Participant,

You are invited to participate in the research project described below.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read

• Consent to take part in the research project

• Consent to have the tests and treatments that are described

• Consent to the use of your personal and health information as described

What is the research about?

After bowel surgery, it usually takes time for the intestines to recover. This is called "postoperative ileus" (POI), or simply "ileus". It usually takes a few days before patients start to tolerate a normal diet, and to open their bowels after a major colorectal operation. This can be associated with unpleasant symptoms like nausea, vomiting and abdominal distension. Often, this necessitates us to have a small tube put in through your nose to decompress this distension and make you feel better, but this step is bereft with risks of aspirating leading to chest infections and pneumonia. POI is also found to be the commonest reason for the delay in discharge home of the patients like you.

We think it might be plausible that using stimulant and osmotic laxatives may help patients recover their normal bowel movements and this study is designed to investigate this. It usually depends on hospital practices and individual surgeon's preferences in giving patients these medications post operatively. This strategy has not been tested in a rigorous study to see whether it's truly effective in reducing the duration of postoperative ileus and hence leading to early discharge home.

We are conducting this research study to test the effectiveness of this known treatment strategy for postoperative ileus in bowel surgery, in addition to our usual standard postoperative care.

If stimulant and osmotic laxatives provide a significant reduction in postoperative ileus and lead to early recovery, then we will add this treatment to our standardised protocol for the management of people having bowel surgery.

Why am I being invited to participate?

You are undergoing major abdominal operation. This makes you an eligible candidate for the study, should you wish to participate. Patients like you at Royal Adelaide Hospital are eligible to take part.

As a person who will have major bowel surgery (bowel resection, or formation/reversal of stoma) you have received, or will receive, education on what the hospital, your doctors, and you, can do before and after surgery to make your operation and your recovery the best it can be. This study aims to assess if, in addition to our suite of standard postoperative care, prescribing stimulant and osmotic laxatives like Coloxyl-Senna, Movicol and Sodium Phosphate Enema after surgery can help patients recover their bowel motility and tolerate oral diet earlier, and further hasten the postoperative recovery leading to an earlier discharge from hospital. The theory is that duration of the Ileus may be able to be reduced by early interventions to support the bowels in their initial phase of paralysis after surgery.

Medication, drugs, and devices have to be approved for use by the Therapeutic Goods Administration (TGA). Coloxyl-Senna, Movicol and Sodium Phosphate Enema are

approved medications in Australia to treat constipation. We will assess how this use in this setting improves your recovery following bowel surgery.

If this preventive package of stimulant and osmotic laxatives provides a significant improvement to postoperative ileus and recovery, then we will add this treatment to our standardised protocol for the management of people having bowel surgery in the future.

What does participation in this research involve?

You will need to sign a consent form prior to any study assessments being performed. As part of your normal work-up for bowel surgery you will be asked a series of health-related questions and have blood tests. These will be used to determine if you are eligible to participate in the research project.

If eligible, you will be participating in an open label randomised controlled research project.

- Open label means that you, doctors conducting the research, team treating you and all peripheral staff will know which treatment you are receiving.
- Sometimes to find out if a treatment for a condition has any effect, we compare the treatment to a placebo or standard treatment (in this study). We put people into groups and give one group the treatment and the other group a standard postoperative care and compare the results between groups. To try to make sure the groups are equal, each participant is put into a group by chance (random), and we call the study randomised.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You will receive the standard care for a person having bowel surgery at the Royal Adelaide Hospital.

As part of your standard care, after your operation you will be provided regular pain relief. You would be fed from day one postoperatively and a note would be made of your bowel sounds, bowel movements, nausea and vomiting. You would have a tube draining your bladder postoperatively which will be taken out on day one postoperative.

In addition to that standard care, during your postoperative stay depending on your treatment allocation group, you may also receive standard doses of laxatives, specifically Coloxyl-Senna twice a day, one sachet of Movicol twice a day and one dose of Sodium phosphate enema from postoperative day one if you have had right side bowel operation.

The principal investigator will visit you daily while in hospital to note whether you have been going well and find out details about your first passed wind (flatus), first bowel movements and when you drank or ate first. These details are also collected routinely in all patients after these operations as standard of care irrespective of whether you participate in the study or not. We would ensure you are happy with your progress and if there are any concerns, they are attended to immediately.

As part of standard care, you will be discharged from hospital when:

1. you have had a bowel motion

2. you are able to tolerate oral diet without nausea or vomiting
3. you are able to mobilise safely
4. your pain medication requirement is for oral tablets only

Following discharge, you will have follow up appointment with your Colorectal Surgeon as per normal protocol. In addition, as part of this research project, you will be contacted by the principal investigator to check your well-being and making sure you have not had any adverse events like wound infections, chest infections and any re-admissions into any hospital for any concerning issue at day 30 after operation.

Other relevant information about the research project

154 people will be able to participate in this research project. Half of those participants will receive the stimulants / laxative medications and half would receive standard postoperative care.

This research project is limited to people receiving care at The Royal Adelaide Hospital.

Do I have to take part in this research project?

Participation in any research project is completely voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. You do not have to provide any explanation for your decision.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with The Royal Adelaide Hospital.

What are the alternatives to participation?

You do not have to take part in this research project. The alternative is standard management for your medical condition.

What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research, but it is possible that your bowels will work more quickly after surgery. In addition, the knowledge we gain from this study may help future patients undergoing similar surgery.

What are the possible risks and disadvantages of taking part?

Clinical safety of the medications used in any trial of this nature is always of paramount concern. Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate, or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

The proposed study medications have been used with minimal side effects for quite some time in surgical patients in different centres and they are generally well tolerated (commonly used for constipation). There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. You may feel mild discomfort because of postoperative enema use and can have potential diarrhoea with the laxatives. These symptoms will be mitigated by stopping the medications at the onset of a loose bowel movement or diarrhoea. However, sometimes side effects can be serious, long lasting, or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you at the time.

Potential side Effects

Coloxyl-Senna: Abdominal discomfort, diarrhoea.

Sodium phosphate enema: None reported.

Movicol: Allergic reactions such as skin rash, difficulty in breathing, itching, redness of skin, abdominal pain, diarrhea, abdominal distension, anal discomfort, flatulence, vomiting, nausea, headache, electrolyte disturbances. Movicol is contraindicated in prolonged postoperative ileus (PPOI) which is suggested by patients having abdominal distension, needing nasogastric tube for decompression, absence of flatus over last 24 hrs, unable to tolerate food > 24 hrs and nausea or vomiting.

Severe side effects reported for these medications are similar to those observed with similar other stimulants and laxatives. These may result from over dosage, delayed absorption or metabolism of the drug. They should not be confused with the normal effects of the drug.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any

counselling or support will be provided by qualified staffs who are not members of the research project team. This counselling will be provided free of charge.

What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

Can I have other treatments during this research project?

It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture, or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to collect your details and discontinue collection of other data relevant to you in the study.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the research team up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include:

• Unacceptable side effects

• The drug/treatment being shown not to be effective

• The drug/treatment being shown to work and not need further testing

What happens when the research project ends?

If this preventive package of stimulant and osmotic laxatives provides a significant improvement to postoperative ileus and recovery, then we will add this treatment to our standardised protocol for the management of people having bowel surgery in the future.

On request, participants will be forwarded a summary of results at the completion of this study. This will be towards the end of 2020.

Part 2: How is the research project being conducted?

What will happen to my information about me?

By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. This information will be stored in a hard copy and electronic file in the Research Office of the Colorectal Surgical Unit, Royal Adelaide Hospital which is subject to the normal confidentiality restraints of personal information within the hospital environment, such as a coded lock on the door and password protected electronic devices. Your information will only be used for the purpose of this research project, and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the institution relevant to this Participant Information Sheet at The Royal Adelaide Hospital as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Information about your participation in this research project will be recorded in your health records.

In accordance with relevant Australian and/or South Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

Complaints and compensation

If you have a concern or complaint regarding your treatment by a member of staff this should be directed to their manager or to the hospital patient advocate officer, contactable through the switchboard.

If you have questions or problems associated with the practical aspects of your participation in the project or wish to raise a concern or complaint about the project, then you should consult the Principal Investigator or to the hospital patient advocate officer, contactable through the switchboard.

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In the event of loss or injury, the parties involved in this research project have agreed to manage your claim in the same manner as any claim arising from treatment during admission under the Consultant Colorectal Surgeon.

Who is organising and funding the research?

This research project is being conducted by Dr Nagendra Dudi-Venkata, Research Fellow, Colorectal Surgical Unit, Royal Adelaide Hospital / PhD Candidate, University of Adelaide. No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

There are no commercial sponsors, external partners.

You will not benefit financially from your involvement in this research project. In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

Who has reviewed and approved the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of The Royal Adelaide Hospital.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor, Dr Nagendra Dudi-Venkata on mobile 0430759215, or your Colorectal Surgeon.

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Chair

Central Adelaide Local Health Network Human Research Ethics Committee (CALHN HREC)

CALHN Research Office

Phone: (08) 7117 2229 or 08 8222 6841

Email: Health.CALHNResearchEthics@sa.gov.au

Consent Form – Adult providing own consent

Title	STIMULAX Study – Open label randomized controlled trial of combination of simple STIMulant and osmotic LAXatives to reduce the duration of post-operative Ileus (POI) in patient's undergoing colorectal surgery.
Short Title	STIMULAX Study
HREC Approval Number	HREC/18/CALHN/250
Principal Investigator	Dr. Nagendra Dudi-Venkata MBBS Grad. Dip. Surg Ed.
Locations	Royal Adelaide Hospital

Declaration by Participant

I am 18 years of age or older.

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals, or laboratories outside this hospital to release information to the Royal Adelaide Hospital concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to discuss this information with a family member or friend.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I may not benefit from taking part in this study.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please _____

Signature _____ Date _____

Name of Witness* to Participant's

Signature (please print) _____

Signature _____ Date _____

_____ _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project; its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/ Co-

Investigator/Supervising

Investigator (please print) _____

Signature _____ Date _____

Note: All parties signing the consent section must date their own signature.

APPENDIX – C: STIMULAX TRIAL - DATA COLLECTION FORM

STIMULAX Study
Data Collection sheet

Government of South Australia
SA Health

Patient information

S. No. _____ Random No. _____ Group _____ Date of OT _____ Smoker: Y / N BMI: < 18.5 / 18.5-24.9 / 25-30 / > 30 Prev. Abd. Surgery: Y / N

Hospital Label:

ASA : 1 / 2 / 3 / 4 / 5 Current Stoma: No Stoma / Ileostomy / Colostomy Most recent preop Creatinine (umol/l) _____

Functional status: Independent (0) / Partially or Totally Dependent (1) CCF within last 30 d (Y - 1 / N - 0) COPD (Y - 1 / N - 0)

HTN on Rx : (Y – 1 / N – 0) DM: Y – 1 (On tablets or Insulin) / N - 0 mFI: _____

Op. Note

Diagnosis: Malignancy / IBD / Diverticular disease / other benign If Malignancy then site – Rt colon / Lt colon / Rectum / NA Epidural: Y / N

Bowel Prep: Picolax / Fleet Enema/NA Op. Approach: Open / Lap or Lap-assisted / Robotic Conversion: Y / No / NA New Stoma: N / Ileostomy / Colostomy

Start of Surgery: _____ End of Surgery: _____ Total duration in min (OT): _____ Intraop Complication: N / Y – Details _____

Primary Operation: Right Hemi / Extended Rt Hemi / Transverse Colectomy / Left Hemi / Sigmoidectomy / Pan-proctocolectomy / Completion colectomy / APR

Total Colectomy / Anterior Resection / Sub – total Colectomy / Ileocolic Resection / Stoma Closure / Other_____

GI FUNCTION

POD 0 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N

POD 1 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 2 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 3 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 4 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 5 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 6 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 7 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 8 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 9 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 10 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

STIMULAX Study
Data Collection sheet

Government of South Australia
SA Health

Patient information

Post Op Analgesics

POD 0 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 1 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 2 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 3 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 4 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 5 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 6 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 7 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 8 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 9 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 10 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 1- 10 → RBC Transfusions: Y / N **Prokinetic:** Y / N **Postop Adjunctive Analgesia:** Epidural / Spinal / IV PCA / Wound catheter / None

Postop Complication:

Complication 1: _____ CD Grade: _____

Complication 2: _____ CD Grade: _____

Complication 3: _____ CD Grade: _____

Complication 4: _____ CD Grade: _____

Complication 5: _____ CD Grade: _____

Complication 6: _____ CD Grade: _____

Complication 7: _____ CD Grade: _____

Return to Theatre: N / Y – Reasons → _____

CCI (0-100) : _____ LOS (days): _____ **TRD (days) :** _____

SRS at Baseline: _____ **@ Discharge:** _____ **@ 30 days:** _____

Readmit within 30 days: N / Y – Reasons → _____

Direct Hospital Costs: _____

APPENDIX – D: PYRICO-P TRIAL - PATIENT INFORMATION SHEET & CONSENT FORM

PyRICo-P Study

Pyridostigmine to **R**educe the duration of postoperative **I**leus after **Co**lorectal Surgery – a **P**hase II

Participant Information Sheet/Consent Form

Interventional Study – *Adult providing own consent*

Version 03 08/05/2020

Royal Adelaide Hospital

Title	**PyRICo-P** – **Py**ridostigmine to **R**educe the duration of postoperative **I**leus after **Co**lorectal Surgery – a **P**hase II study.
Short Title	PyRICo-P Study
HREC Approval Number	13049
Principal Investigator	Dr. Nagendra N Dudi-Venkata MBBS GDipSurgicalEd.
Supervising / Co Investigators	Assoc. Prof. Tarik Sammour BHB MBChB FRACS PhD Mr. James Moore MBBS MD FRACS
Locations	Royal Adelaide Hospital

Part 1 What does my participation involve?

Introduction

Dear Participant,

You are invited to participate in the research project described below.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read

• Consent to take part in the research project

• Consent to have the tests and treatments that are described

• Consent to the use of your personal and health information as described

What is the research about?

After bowel surgery, it usually takes time for the intestines to recover. This is called "postoperative ileus" (POI), or simply "ileus". It usually takes a few days before patients start to tolerate a normal diet, and to open their bowels after a major colorectal operation. This can be associated with unpleasant symptoms like nausea, vomiting and abdominal distension. Often, this necessitates us to have a small tube put in through your nose to decompress this distension and make you feel better, but this step has a risk of aspiration leading to chest infections and pneumonia. POI is also found to be the commonest reason for the delay in discharge home of the patients like you.

We think it might be plausible that using an acetylcholinesterase inhibitor (ACE) medication named pyridostigmine may help patients recover their normal bowel movements and this study is designed to investigate this. It usually depends on hospital practices and individual surgeon's preferences in giving patients these medications post operatively. This strategy has not been tested in a rigorous study to see whether it's truly effective and safe in reducing the duration of postoperative ileus and hence leading to

early discharge home. We are conducting this research study to test the safety and effectiveness of this treatment strategy for postoperative ileus in bowel surgery, in addition to our usual standard postoperative care.

If this medication provides a reduction in postoperative ileus safely without any concerns and adverse events, this will pave way to test them in a larger trial to test their effectiveness. If positive, this could potentially lead to early recovery of patients and will eventually be included as a treatment strategy to our standardised protocol for the management of people having bowel surgery.

Why am I being invited to participate?

You are undergoing major abdominal operation. This makes you an eligible candidate for the study, should you wish to participate.

As a person who will have major bowel surgery (bowel resection, or formation/reversal of stoma) you have received, or will receive, education on what the hospital, your doctors, and you, can do before and after surgery to make your operation and your recovery the best it can be. This study aims to assess if, in addition to our suite of standard postoperative care, prescribing oral pyridostigmine after surgery can help patients safely recover their bowel motility and tolerate oral diet earlier, and further hasten the postoperative recovery leading to an earlier discharge from hospital. The theory is that duration of the Ileus may be able to be reduced by early interventions to support the bowels in their initial phase of paralysis after surgery.

Medication, drugs and devices have to be approved for use by the Therapeutic Goods Administration (TGA). Pyridostigmine has been used successfully for the treatment of

chronic constipation, abdominal distention, and dyspepsia as documented in medical literature. [271, 285]ACIs have also been used successfully in adult patients, especially after spinal surgery in reducing the duration of ileus without increasing the risk of postoperative complicationsis. It has been approved as a medication for paralytic ileus in USA and UK but has not been approved for this condition in Australia at the moment. We will assess how this use in this setting improves your recovery following bowel surgery and possibly follow up with a larger trial to see its effectiveness to eventually make way for getting it approved for this medical condition.

If this preventive package of oral pyridostigmine provides a significant improvement to postoperative ileus and recovery, then we will add this treatment to our standardised protocol for the management of people having bowel surgery in the future.

What does participation in this research involve?

You will need to sign a consent form prior to any study assessments being performed. As part of your normal work-up for bowel surgery you will be asked a series of health-related questions and have blood tests. These will be used to determine if you are eligible to participate in the research project.

If eligible, you will be participating in this research project.

- Your doctors conducting the research, team treating you and all peripheral staff including yourself will know the treatment you are receiving.
- Sometimes to find out if a treatment for a condition has any effect, we compare the treatment to a standard treatment. Considering this is a pilot study, if chosen and eligible you would receive the above-said treatment and we would compare the results with the historical or between group of patients who have not received this

treatment. To try to make sure the groups are equal, each participant will be matched to a group similar in their baseline characteristics.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You will receive the standard care for a person having bowel surgery at the Royal Adelaide Hospital.

As part of your standard care, after your operation you will be provided regular pain relief. You would be fed from day one postoperatively and a note would be made of your bowel sounds, bowel movements, nausea and vomiting. You would have a tube draining your bladder postoperatively which will be taken out on day one postoperative.

In addition to that standard care, during your postoperative stay, you would also receive standard doses of oral pyridostigmine from postoperative day zero.

The principal investigator will visit you daily while in hospital to note whether you have been going well and find out details about your first passed wind (flatus), first bowel movements and when you drank or ate first. These details are also collected routinely in all patients after these operations as standard of care irrespective of whether you participate

in the study or not. We would ensure you are happy with your progress and if there are any concerns, they are attended to immediately.

As part of standard care, you will be discharged from hospital when:

5. you have had a bowel motion
6. you are able to tolerate oral diet without nausea or vomiting
7. you are able to mobilise safely
8. your pain medication requirement is for oral tablets only

Following discharge, you will have follow-up appointment with your Colorectal Surgeon as per normal protocol. In addition, as part of this research project, you will be contacted by the principal investigator to check your well-being and making sure you have not had any adverse events like wound infections, chest infections and any re-admissions into any hospital for any concerning issue at day 30 after operation.

Other relevant information about the research project

15 people will be able to participate in this research project.

This research project is limited to people receiving care at The Royal Adelaide Hospital.

Do I have to take part in this research project?

Participation in any research project is completely voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. You do not have to provide any explanation for your decision.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with The Royal Adelaide Hospital.

What are the alternatives to participation?

You do not have to take part in this research project. The alternative is standard management for your medical condition.

What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research, but it is possible that your bowels will work more quickly after surgery. In addition, the knowledge we gain from this study may help future patients undergoing similar surgery.

What are the possible risks and disadvantages of taking part?

Clinical safety of the medications used in any trial of this nature is always of paramount concern. Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate, or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

The proposed study medications have been used with minimal side effects for quite some time in different centres and they are generally well tolerated. There may be side effects

that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. You may feel mild discomfort because of postoperative medication use and can have potential diarrhoea. These symptoms will be mitigated by stopping the medications at the onset of a loose bowel movement or diarrhoea. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you at the time.

Potential side Effects

Pyridostigmine has a lower incidence of gastrointestinal stimulation and other muscarinic side effects seen with other anticholinesterases. However, nausea, vomiting, diarrhoea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, myosis and diaphoresis may occur. Atropine may be used to counter these effects but not without danger, due to the difficulties in distinguishing myasthenic and cholinergic crisis. Nicotinic effects are usually muscle cramps, fasciculation, and weakness. Bradycardia and hypotension may occur. Occasionally the bromine radical may induce a rash.

Severe side effects reported for these medications are similar to those observed with similar other medications. These may result from over dosage, delayed absorption, or metabolism of the drug. They should not be confused with the normal effects of the drug.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staffs who are not members of the research project team. This counselling will be provided free of charge.

What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

Can I have other treatments during this research project?

It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture, or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain you which treatments or medications need to be stopped for the time you are involved in the research project.

What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to collect your details and discontinue collection of other data relevant to you in the study.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the research team up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include:

• Unacceptable side effects

• The drug/treatment being shown not to be effective

• The drug/treatment being shown to work and not need further testing

What happens when the research project ends?

If this preventive package of ACE inhibitors provides a significant improvement to postoperative ileus and recovery safely, then we will embark onto doing a larger study to investigate its effectiveness and add this treatment to our standardised protocol for the management of people having bowel surgery in the future.

On request, participants will be forwarded a summary of results at the completion of this study. This will be towards the end of 2020.

Part 2: How is the research project being conducted?

What will happen to my information about me?

By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. This information will be stored in a hard copy and electronic file in the Research Office of the Colorectal Surgical Unit, Royal Adelaide Hospital which is subject to the normal confidentiality restraints of personal information within the hospital environment, such as a coded lock on the door and password protected electronic devices. Your information will only be used for the purpose of this research project, and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the institution relevant to this Participant Information Sheet at The Royal Adelaide Hospital as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Information about your participation in this research project will be recorded in your health records.

In accordance with relevant Australian and/or South Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

Complaints and compensation

If you have a concern or complaint regarding your treatment by a member of staff this should be directed to their manager or to the hospital patient advocate officer, contactable through the switchboard.

If you have questions or problems associated with the practical aspects of your participation in the project then you should consult the Principal Investigator (Ph. No. 0430759215) or to the hospital patient advocate officer, contactable through the switchboard.

If you wish to raise a concern or complaint about the project, you can contact the Chair of the Central Adelaide Local Health Network Human Research Ethics Committee, (CALHN HREC), Mr Ian Tindall on 08-7117-2215 or via email Health.CALHNResearchEthics@sa.gov.au. If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In the event of loss or injury, the parties involved in this research project have agreed to manage your claim in the same manner as any claim arising from treatment during admission under the Consultant Colorectal Surgeon.

Who is organising and funding the research?

This research project is being conducted by Dr Nagendra N Dudi-Venkata, Research Fellow, Colorectal Surgical Unit, Royal Adelaide Hospital / PhD Candidate, University of Adelaide.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

There are no commercial sponsors, external partners.

You will not benefit financially from your involvement in this research project. In addition, if knowledge acquired through this research leads to discoveries that are of commercial

value to the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

Who has reviewed and approved the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Central Adelaide Local Health Network HREC.
This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor, Dr Nagendra N Dudi-Venkata on mobile 0430759215, or your Colorectal Surgeon.

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Chair
Central Adelaide Local Health Network Human Research Ethics Committee (CALHN HREC)
CALHN Research Office
Phone: (08) 7117 2229 or 08 8222 6841

Email: Health.CALHNResearchEthics@sa.gov.au

Consent Form – Adult providing own consent

Title	**PyRICo-P** – **Py**ridostigmine to **R**educe the duration of postoperative **I**leus after **Co**lorectal Surgery – a **P**hase II study.
Short Title	PyRICo-P Study
HREC Approval Number	13049
Principal Investigator	Dr. Nagendra N Dudi-Venkata MBBS GDipSurgicalEd.
Locations	Royal Adelaide Hospital

Declaration by Participant

I am 18 years of age or older.

I have read the Participant Information Sheet, or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals, or laboratories outside this hospital to release information to the Royal Adelaide Hospital concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to discuss this information with a family member or friend.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I may not benefit from taking part in this study.

I understand that I will be given a signed copy of this document to keep.

I agree to an external provider being contacted regarding:

·My medical history if relevant to the study

·Treatment in the event of an emergency

I agree to my medical records (paper and electronic) being accessed for both the duration and follow up of the study; PyRICo-P – Pyridostigmine to Reduce the duration of postoperative Ileus after Colorectal Surgery – a Phase II study". □

Yes □ No

Name of Participant (please _____

Signature _____ Date _____

Name of Witness* to Participant's

Signature (please print) _____

Signature _____ Date _____

_____ _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project; its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/ Co-Investigator/Supervising Investigator (please print) _____
Signature _____ Date _____

Note: All parties signing the consent section must date their own signature.

APPENDIX – E: PYRICO-P TRIAL -DATA COLLECTION FORM

Data Collection Sheet 2

PyRICo-P Study
Data Collection sheet

Government of South Australia
SA Health

Patient information

S. No. _____ Random No. _____ Group _____ Date of OT _____ Smoker: Y / N BMI: < 18.5 / 18.5-24.9 / 25-30 / > 30 Prev. Abd. Surgery: Y / N

Hospital Label:

ASA : 1 / 2 / 3 / 4 / 5 Current Stoma: No Stoma / Ileostomy / Colostomy Most recent preop Creatinine (umol/l) _____

Functional status: Independent (0) / Partially or Totally Dependent (1) CCF within last 30 d (Y - 1 / N - 0) COPD (Y - 1 / N - 0)

HTN on Rx : (Y – 1 / N – 0) DM: Y – 1 (On tablets or Insulin) / N - 0 mFI: _____

Op. Note

Diagnosis: Malignancy / IBD / Diverticular disease / other benign If Malignancy then site – Rt colon / Lt colon / Rectum / NA Epidural: Y / N

Bowel Prep: Picolax / Fleet Enema/NA Op. Approach: Open / Lap or Lap-assisted / Robotic Conversion: Y / No / NA New Stoma: N / Ileostomy / Colostomy

Start of Surgery: _____ End of Surgery: _____ Total duration in min (OT): _____ Intraop Complication: N / Y – Details _____

Primary Operation: Right Hemi / Extended Rt Hemi / Transverse Colectomy / Left Hemi / Sigmoidectomy / Pan-proctocolectomy / Completion colectomy / APR

Total Colectomy / Anterior Resection / Sub – total Colectomy / Ileocolic Resection / Stoma Closure / Other_____

GI FUNCTION

POD 0 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N

POD 1 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 2 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 3 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 4 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 5 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 6 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 7 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 8 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 9 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

POD 10 Passage - flatus: Y / N - Stool: Y / N Vomiting: Y / N Oral Intake: N / Fluid / Solid NG tube drainage: Y / N Coloxyl/Senna: Y / N Movicol: Y / N Fleet enema: Y / N

Data Collection Sheet 2

PyRICo-P Study
Data Collection sheet

Government of South Australia
SA Health

Patient information

Post Op Analgesics

POD 0 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 1 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 2 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 3 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 4 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 5 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 6 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 7 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 8 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 9 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 10 Received NSAIDS: N / Y – Cox 2 Selective / Y – Other Received Opiods: N / Y – Strong / Y – Weak Opiod dosage/day: _____

POD 1- 10 →RBC Transfusions: Y / N **Prokinetic:** Y / N **Postop Adjunctive Analgesia:** Epidural / Spinal / IV PCA / Wound catheter / None

Postop Complication:

Complication 1: _____ CD Grade: _____

Complication 2: _____ CD Grade: _____

Complication 3: _____ CD Grade: _____

Complication 4: _____ CD Grade: _____

Complication 5: _____ CD Grade: _____

Complication 6: _____ CD Grade: _____

Complication 7: _____ CD Grade: _____

Return to Theatre: N / Y – Reasons → _____

CCI (0-100) : _____ LOS (days): _____ **TRD (days) :** _____

SRS at Baseline: _____ **@ Discharge:** _____ **@ 30 days:** _____

Readmit within 30 days: N / Y – Reasons →_____

Direct Hospital Costs: _____

APPENDIX – F: SURGICAL RECOVERY SCORE

Questionnaire – Surgical Recovery Score

Please think about the last two days and tick the box that applies best to you.

During the last 2 days….	Not at all	Almost never	Some of the time	Fairly often	Very Often	All of the time	Total score
I have been feeling energetic							
I have been feeling worn out							
I have been feeling vigorous							
I have done very little with the day							
I have been feeling fatigued							
Physically, I have felt tired							
I have had to restrict how much I try and do in a day							
I have been feeling lively							
I have been able to read a newspaper/book or watch TV							
I have been able to Dress							
I have been able to Visit or socialize with family and friends							
I have been able to engage in leisure or recreational activities							
Shop or do errands							

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