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An Improved Clinical and Pathophysiologic Characterisation of Post-Operative Ileus

Ryash Vather
INTRODUCTION Post-operative ileus is a major cause of morbidity globally. The objectives of this body of work are to classify and define ileus, evaluate the efficacy of Gastrografin in shortening its duration, predict the occurrence of prolonged ileus, and describe changes in peri-operative and post-surgical intestinal motility.

METHODS A systematic literature review and online global survey were conducted to clarify terminology and provide concise, clinically quantifiable definitions for ileus. A retrospective cohort study, narrative review, and laboratory analysis were used to inform design and execution of a double-blinded, placebo-controlled, randomised trial investigating the therapeutic value of Gastrografin in shortening duration of prolonged ileus following elective colorectal surgery. Risk factors predictive of prolonged ileus following colorectal surgery were identified by a prospective cohort study. In vivo high resolution manometry was utilised to assess changes in intestinal motility peri-operatively and post-surgically.

RESULTS Three classes of ileus can be identified and defined – post-operative ileus, prolonged post-operative ileus, and recurrent post-operative ileus. In an episode of prolonged ileus, orally-administered Gastrografin accelerates resolution of lower gastrointestinal symptoms (abdominal distension; absence of flatus and stool) but does not affect upper gastrointestinal symptoms (nausea and vomiting; intolerance of an oral diet). Independent predictors for prolonged ileus include male gender, decreasing pre-operative albumin, open/converted technique, increasing wound size, operative difficulty and bowel handling, total intravenous crystalloid, red cell transfusion, and day of first mobilisation. Ileus is underpinned by cyclic motor activity which occupies the majority of the immediate post-operative period; by contrast, short and long single motor patterns appear infrequently and sporadically. Those who have previously undergone segmental colorectal resection (and preserved normal bowel function) exhibit a normal colonic meal response with evidence of coordinated trans-anastomotic motor activity.

CONCLUSIONS Three classes of ileus can be broadly identified and defined; Gastrografin is not clinically useful in shortening an episode of prolonged ileus; predictive scoring systems may identify individuals at risk of developing prolonged ileus; ileus is characterised by ubiquitous cyclic motor activity of likely myogenic origin; and normal motility is eventually restored in patients who have undergone segmental colorectal resection.
To my brother, Sehllo, and parents, Bhavna and Mahat, for their unfaltering support and encouragement through all my endeavours.
I wish to thank my supervisor and mentor A/Prof Ian Bissett for his unequivocal support, counsel and guidance. I continue to be inspired by A/Prof Bissett’s ability to mix enthusiasm and ambition with humility and integrity, and hope that I am one day able to emulate this.

This research would not have been possible without the academic guidance of my good friends Tarik Sammour, Arman Kahokehr and Greg O’Grady – all surgeons who have completed doctoral research at the University of Auckland.

I am grateful to A/Prof Phil Dinning (Senior Scientist, Flinders University, Australia) for his academic input and direction, and Rachel Josephson (Research Nurse) for assisting with data collection.

I wish to thank my fiancée Mayuri Haribhai for her encouragement, companionship, and ensuring that I did not miss the wood for the trees.

I feel fortunate to have undertaken this thesis at Auckland Clinical School. More than provide an environment conducive to academic output, there was an element of camaraderie which provided endless amusement even on hard days. I would specifically like to thank Riyaz Bhikoo (Research Fellow), Parag Bhatnagar (Database Manager), Lisa Brown (Research Fellow), Scott Aitken (Department Manager), Sayali Pendharkar (Research Fellow), and Lois Blackwell (PA) for their friendship.

Research was facilitated by the clinical staff at Auckland City Hospital. I wish to thank the Colorectal Surgeons, Nursing Staff, Booking Clerks, and Gastroenterology Unit for their congeniality and making an effort to accommodate me even when overworked.

I would like to acknowledge the Royal Australasian College of Surgeons (RACS) for allowing me deferral from training to complete this research. I am also grateful to RACS and the Health Research Council for providing generous personal funding via scholarship. Research was made possible by project grants awarded by the Colorectal Surgical Society of Australia and New Zealand, Auckland Medical Research Foundation, and Maurice and Phyllis Paykel Trust.

Finally, I wish to thank the patients who participated in this research. Even though at a difficult stage in their lives, all selflessly offered their time and effort, and for that I am genuinely grateful and indebted.


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Chapter 3 - Retrospective cohort study - ‘prolonged’ post-operative ileus following elective colorectal surgery


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Extent of contribution by PhD candidate (%): 90%

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**Chapter 4 - Systematic review and global survey - defining post-operative ileus**


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Chapter 5 - Narrative review - conservative management of prolonged post-operative ileus

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**Chapter 5 - Laboratory analysis - quantitative stability testing of Gastrografin**


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## GLOSSARY

### Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>%</td>
<td>Percentage</td>
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<tr>
<td>Δ</td>
<td>Delta value</td>
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<tr>
<td>°C</td>
<td>Degrees Celsius</td>
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<tr>
<td>$\chi^2$</td>
<td>Chi squared (Chi $^2$) test</td>
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### A

- **ADHB**: Auckland District Health Board
- **ANOVA**: Analysis of Variance
- **ASA**: American Society of Anaesthesia
- **AUC**: Area Under Curve

### B

- **BMI**: Body Mass Index

### C

- **CI**: Confidence Interval
- **cm**: Centimetres
- **CFIQ**: Comprehensive Faecal Incontinence Questionnaire
- **CNS**: Central Nervous System
- **CO**: Carbon Monoxide
CO₂ Carbon Dioxide
COX Cyclooxygenase
COX-2 Cyclooxygenase-2
CT Computed Tomography

d Days
DAMPs Damage-Associated Molecular Patterns
DTZ Diatrizoate

EPSBO Early Post-Operative Small Bowel Obstruction
ENS Enteric Nervous System
ERAS Enhanced Recovery After Surgery

fBG fibre Bragg Grating

g Grams
GI Gastrointestinal
**H**

h  Hours

HAPS  High Amplitude Propagating Sequences

HDU  High Dependency Unit

HPLC  High Performance Liquid Chromatography

HRM  High Resolution Manometry

**I**

IBD  Inflammatory Bowel Disease

ICC  Interstitial Cells of Cajal

ICH  International Convention of Harmonisation

ICU  Intensive Care Unit

IM  Intramuscular

IPLA  Intraperitoneal Local Anaesthetic

IQR  Inter-Quartile Range

IV  Intravenous

IVLA  Intravenous Local Anaesthetic

**K**

Kg  Kilograms

kCal  Kilocalorie
L

L  Litres / Left
LA  Local Anaesthetic

M

M₂  Muscarinic-2
M₃  Muscarinic-3
MED  Morphine Equivalent Dose
MEDD  Morphine Equivalent Daily Dose
MeSH  Medical Subject Heading
mg  Milligrams
Min  Minutes
Mini-lap  Mini-laparotomy
μL  Microlitres
mL  Millilitres
mm  Millimetres

N

n  Number
N  No
NGT  Nasogastric Tube
NHI  National Health Index
NO  Nitric Oxide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>NSAIDs</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
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<tr>
<td>NTS</td>
<td>Nucleus Tractus Solitarius</td>
</tr>
<tr>
<td>OT</td>
<td>Operation / Operating Theatre</td>
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<tr>
<td>OWSC</td>
<td>Oral Water-Soluble Contrast</td>
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<tr>
<td>PACU</td>
<td>Post-Aneesthesia Care Unit</td>
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<tr>
<td>PAMPs</td>
<td>Pathogen-Associated Molecular Patterns</td>
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<tr>
<td>PCA</td>
<td>Patient Controlled Analgesia</td>
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<tr>
<td>PO</td>
<td>Oral</td>
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<tr>
<td>POI</td>
<td>Post-Operative Ileus</td>
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<tr>
<td>PPOI</td>
<td>Prolonged Post-Operative Ileus</td>
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<tr>
<td>PN</td>
<td>Parenteral Nutrition</td>
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<tr>
<td>PTNS</td>
<td>Percutaneous Tibial Nerve Stimulation</td>
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<td>R</td>
<td>Right</td>
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<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<td>RBC</td>
<td>Red Blood Cell</td>
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<td>RH</td>
<td>Relative Humidity</td>
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<td>ROC</td>
<td>Receiver Operating Characteristic</td>
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| T  | T test | Students T test |

<table>
<thead>
<tr>
<th>V</th>
<th>VAS</th>
<th>Visual Analogue Scale</th>
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<tr>
<td>VIP</td>
<td>VIP</td>
<td>Vasoactive Intestinal Peptide</td>
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<td>Vs</td>
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| Y  | Y      | Yes                   |
CHAPTER 1:
INTRODUCTION
There is an obligatory period of gastrointestinal dysfunction following major abdominal surgery which resolves variably and unpredictably between patients. This has been termed post-operative ileus (POI) and is clinically manifest as a mix of nausea and vomiting, inability to tolerate an oral diet, abdominal distension, and the delayed passage of flatus and stool. The indistinct and often transitory nature of these symptoms post-operatively have led to an inadequate characterisation of POI as a clinical syndrome. This in turn has hindered understanding of its pathophysiologic basis and the identification of effective preventive and therapeutic strategies. This chapter presents an account of the aetiology of post-operative gut dysfunction, with a focus on its clinical correlates and potential approaches to its management.

1.1 Pathophysiology

The aetiology of gastrointestinal dysfunction following abdominal surgery is believed to be multifactorial with inflammatory cell activation, autonomic dysfunction (both primarily and as part of the surgical stress response), agonism at gut opioid-receptors by exogenous narcotics, modulation of gastrointestinal hormone activity, and electrolyte derangements all being implicated. A final common pathway for these effectors is impaired contractility, gut wall oedema, and relative intestinal ischaemia (Figure 1-1).

1.1.1 Inflammatory Response

It has been postulated that an early event in the pathogenesis of POI is the release of pro-inflammatory mediators, initially due to peritoneal breach and later due to bowel handling.[1, 2] Although the composition of the inflammatory environment is relatively well known (histamine, prostanoids, interleukin-6 and interleukin-8 feature prominently) the cell types triggering the inflammatory response are less well-defined.[3] Mast cells have been found in peritoneum and the muscularis propria of the intestinal wall, and there is a growing body of evidence supporting the role these cells play in the genesis of the inflammatory cascade.[4, 5] Indeed, a murine model of POI revealed that animals pre-treated with mast cell stabilisers experienced reduced manipulation-induced inflammation and improved gastric emptying; mast-cell deficient animals likewise exhibited a diminished inflammatory response to surgery.[4] Preliminary work in humans has correlated laparoscopic surgery to reduced mast cell activation, and has attributed this finding to a reduced degree of intestinal handling.[2] Circulating monocytes and resident macrophages have also been implicated in the inflammatory response,[6, 7] and activation of these cells within the bowel wall is believed to be in part caused by damage-associated molecular patterns (DAMPs) and pathogen-
Figure 1-1 Pathophysiologic basis for the development of post-operative ileus
associated molecular patterns (PAMPs).

The former are macromolecules released in response to mechanical or chemical cellular injury (for example, physical manipulation of the gut); the latter can be found on commensal intestinal flora and are postulated to translocate through the gut wall as a consequence of the increased permeability associated with inflammation.

The mechanisms by which bowel wall inflammation may cause dysmotility are three-fold. First, several molecules involved in the inflammatory cascade are potent smooth muscle relaxants (especially the COX-2 dependent prostaglandin E2 and nitric oxide (NO)), and therefore have a direct effect on contractility. Second, bowel wall oedema is believed to contribute to the existing dysmotility by mechanically impairing the efficacy of myotonic contraction. Oedema is thought to be primarily mediated by the local inflammatory response, although it has been shown that overzealous peri-operative fluid administration may also contribute. Finally, there is preliminary evidence to suggest that relative intestinal ischaemia may play a role in ileus, and occurs either as a by-product of the inflammatory state or via direct reduction in arterial blood flow. A murine study found that a reduction in oxidative stress (effected by CO-releasing molecules) was associated with reduced development of POI. The role of relative intestinal ischaemia in POI is also supported by clinical studies from two separate groups, who have found hyperbaric oxygen therapy confers a potential benefit in POI.

1.1.2 Neural Derangement

Disturbances in neural activity play an integral role in the pathophysiological gut response to surgery, and extend to the somatic, autonomic and enteric nervous systems. Changes in neural function are also thought to be closely coupled to the immunologic/inflammatory response outlined above, and these factors have collectively been termed the "surgical stress response". Neural derangements impact upon both afferent and efferent pathways.

1.1.2.1 Afferent pathways

Two types of wounds are caused by surgery – i) a 'somatic wound' created by incision at the abdominal wall; and ii) a 'visceral wound' created by incision of peritoneum and handling of gut, further detailed as follows:

i. **Somatic wound** – the abdominal wall receives sensory innervation from the anterior and lateral branches of the ventral rami of the lower intercostal and upper lumbar nerves. Nociceptive stimuli associated with the creation of a somatic
wound are carried via sensory neurons (with cell bodies in dorsal root ganglia) to synapse in the posterior column of the spinal cord.[8] Release of the excitatory neurotransmitter glutamate at this site activates spinothalamic projections that invoke the perception and localisation of pain, and incites a local autonomic response that is mediated by sympathetic efferents with cell bodies in the lateral horn.[17, 19]

ii.  
**Visceral wound** – the peritoneum is a metabolically active tissue lining the abdomen and enveloping intestinal viscera. Injury to peritoneum leads to the activation of inflammatory and immunologic cascades as described above.[20] By contrast, contained within intestinal viscera are a dense interconnected network of neurones – the enteric nervous system (ENS) – that derive information from a variety of mechanoreceptors and chemoreceptors.[8, 21] “Silent nociceptors” which are located within the extrinsic sensory innervation of the gastrointestinal tract and remain quiescent in the absence of intestinal injury or inflammation may also be activated with gut handling.[22] Sensory information from viscera and peritoneum are conveyed primarily by the vagus nerve, which has been shown histologically at the sub-diaphragmatic level to be over 80% afferent.[23] In addition to receiving input from nociceptors, paraganglia cells within the parasympathetic ganglia of the vagus nerve express interleukin-1 receptors, thus making the nerve sensitive to the early humoral changes associated with inflammation.[24, 25] Vagal afferents travel to the nucleus tractus solitarius (NTS) of the brain stem, which is considered a major ‘relay centre’ of the neuro-immuno-humoral response to injury.[24] The importance of the vagus nerve in transmitting visceral afferents has been demonstrated in animal models which have shown blunting of a supraspinal response to intra-abdominal manipulation following vagotomy, but not after sectioning of the spinal cord.[25-27]

1.1.2.2  *Efferent pathways*

Neurogenically-mediated gastrointestinal dysmotility following surgery is brought about by an autonomic shift favouring sympathetic over parasympathetic outflow. This is postulated to occur initially as part of a local reflex response and may be perpetuated by activation of supraspinal centres. Specifically, both the hypothalamus and NTS have been implicated in central inhibition of gut motility, with activation occurring via neural afferents and circulating inflammatory metabolites.[28-30]
Parasympathetic efferents originate in neural circuits connecting the NTS to the vagal motor nucleus and nucleus ambiguous within the brainstem.[24] Outflow to the gastrointestinal tract travels via the vagus nerve and pelvic splanchnic nerves, which meet at the splenic flexure.[18] Postganglionic neurons release acetylcholine which, via activation at $M_2$ and $M_3$ muscarinic receptors, serve to increase smooth muscle excitability and contractility.[24, 31]

Thoracolumbar sympathetic efferents originate from the lateral horn of the spinal cord.[32] Their activation occurs as part of a reflex adrenergic response to nociception as well as supraspinal excitation.[21, 33, 34] Release of catecholamines within the gut leads to activation of $\alpha_2$ adrenoceptors which act on presynaptic parasympathetic cholinergic nerves to inhibit release of acetylcholine and directly on myocytes to stimulate production of NO. These pathways serve to reduce myocyte tonicity and contractility.[35-38] Additionally, evidence has emerged for a non-adrenergic non-cholinergic vagally-mediated pathway that impairs motility via local release of NO and vasoactive intestinal peptide.[39, 40]

It is important to note the significant visceral sensory and motor contribution of the vagus nerve in this context and to appreciate that it is a direct extension of the central nervous system (CNS), with its passage to the abdomen occurring sequentially through neck, thorax and diaphragm. Therefore, while epidural blockade may attenuate the initial somatically-mediated gastrointestinal response to nociceptive stimuli, the blockade does little to obliterate the more prolonged vagally-mediated inhibition associated with visceral handling.[8] High epidural local anaesthetic blockade nevertheless still accelerates gastrointestinal recovery after surgery by interrupting contributing spinal afferent and efferent signals.[41-44]

1.1.3 Disruption of Intestinal Continuity

POI is a significant problem following procedures involving resection of gut viscera.[45, 46] It has been shown that creation of an end-to-end anastomosis profoundly impairs downstream intestinal motility in the post-operative period when compared to non-anastomotic surgery of similar severity.[47] While it is postulated that this effect is related to disruption of enteric neuromuscular continuity, return of gut function even in the presence of an anastomosis generally occurs within 3-4 days post-operatively.[48] Gut recovery at this point is therefore less likely to be due to neural regeneration and more likely due to establishment of propagating motor activity distal to the anastomosis after delivery of intestinal contents and intraluminal bolus distension. Work in animal models has shown that tissue healing and longitudinal nerve trunk regeneration occur at sites of bowel wall anastomosis,[49] but there is limited literature investigating electrical or pressure wave propagation across these joins in
the immediate post-operative period. It is feasible that the disruption of neural continuity caused by visceral resection directly impairs downstream intestinal motility by creating a physical barrier to electro-mechanical coupling. This theory has been evaluated in a murine model of small bowel resection, which described acute disruptions to interstitial cells of Cajal (ICC) networks, slow waves and phasic contractions.[50] Preliminary observations of a similar effect have also been made in other animals,[51] and a human study which investigated distal colonic motility post resection.[47]

Essential to gut motility are the inter-related functions of the ICC and ENS within the gut wall. ICC form a continuous cellular network through the gut wall and their function includes generating and propagating slow waves that pattern myocyte depolarisation.[52] In the small bowel, ICC pattern contractility, but the integrated motility response is also strongly modulated by the ENS. This co-regulation is exemplified by the myenteric stretch response which underpins peristalsis.[53, 54] Conversely, although colon and rectum possess networks of ICC, their coordinated function appears to depend more on extrinsic regulatory neural stimulation.[21, 55-57] The comparative independence and resilience of myenteric motility mechanisms of the upper gut may in part explain why procedures involving colorectal resection have a longer duration of POI when compared to more proximal surgery.[45, 48]

Literature which has endeavoured to qualify the pattern of gastrointestinal (and in particular large bowel) motility following resection is limited. While it was initially postulated that an ileus was underpinned by reduced intestinal tone or ‘atony’, a study by Huge et al. that utilised barometry showed increasing colonic tone in humans following surgery.[58] It was consequently hypothesised that the colon may assume a state of tonic non-phasic contraction post-operatively. However, an important limitation of Huge et al.’s work was the absence of pre-operative barometric recordings, and it was therefore unclear whether the observed increasing colonic tone was a rise from or return to baseline tone. Indeed, it was demonstrated in two other human studies that intestinal motility is reduced following surgery but increased in response to early oral feeding.[59, 60] Understanding of peri-operative changes in intestinal tone and motility is imprecise, making this an important area for further research.

1.1.4 Disturbances of Gastrointestinal Hormones and Neuropeptides

Both the operative insult and lack of early oral intake after surgery modulate release of gastrointestinal hormones and neuropeptides. Those of greatest interest are motilin, substance P (SP) and vasoactive intestinal peptide (VIP) – each of which play a role in normal gut motility.[61] Cyclical increases in the hormone motilin are central to the genesis
of the migrating motor complex and were found to be absent in a canine model of POI.[61] Conversely, antagonism at receptor sites or prevention of release of the enteric neurotransmitters SP and VIP in animal models has been shown to accelerate recovery of post-operative gut function.[62-64] These findings are somewhat contradictory when considering SP is a potent tachykinin known to stimulate gastrointestinal motility via direct action on smooth muscle and excitation of neurons within the ENS.[65] However, SP is also involved in excitatory neurotransmission of visceral afferents and is believed to play a key role in mediating the neuro-immuno-humoral inflammatory response to tissue injury.[65-67] It is therefore feasible that blockade of these mechanisms in the peri-operative setting underpin the efficacy of SP antagonists. VIP is thought to have several different effects on gut motility, although precise mechanisms and overall action have not yet been clearly defined.[68] VIP is a smooth muscle relaxant, possibly explaining the efficacy of VIP antagonists in accelerating post-operative gut recovery.[62, 64] However, VIP also acts as a major anti-inflammatory agent[68] and there is a growing body of evidence supporting its role as an excitatory secretomotor neurotransmitter within the ENS (most notably in the context of intraluminal enterotoxins).[69-72] The role of each of VIP’s mechanisms of action and their degree of involvement in the pathogenesis of an ileus is therefore unclear. Accurate profiling of serum hormone and neuropeptide levels in humans is needed in the first instance in order to define this further.

1.1.5 Electrolyte Derangement

Peri-operative electrolyte disturbances may play a central role in the aetiology of an ileus.[73] This hypothesis is supported by the well-described effects of electrolyte variations on gut motility[56] and the observation that such disturbances often occur during an episode of POI.[73, 74] An editorial published in 1971 identified hypokalaemia as a probable contributing cause for ileus in a small series of post-operative patients, with correction being associated with resumption of gut functioning.[75] In a recent retrospective analysis Kronberg et al. noted a significant association between ileus and post-operative hypokalaemia and hypocalcaemia; hypermagnesemia was also associated but not significantly.[45] Importantly, the retrospective nature of these studies has made it difficult to determine direction of causality – although it is plausible that electrolyte disturbances cause myenteric dysfunction, it is also possible that gastrointestinal fluid shifts during POI contribute to electrolyte derangements.[2, 76]
Exogenous substances administered within the peri-operative period may significantly impact gastrointestinal function. While intravenous fluid and various antiemetics or prokinetics have been correlated with the occurrence of POI,[77, 78] there is no consistent evidence to support a causal role for any. Conversely, the negative impact of narcotic analgesia on gastrointestinal motility has now been well-defined. This was initially described in a non-surgical population,[79] but has since been evaluated in the post-operative setting where it is now widely considered to be a key contributor to both the development and maintenance of ileus.[45, 80] The surgical insult induces a spike in endogenous opioids, while exogenous opioids are administered to reduce post-operative pain.[81] The analgesic properties of opioids are caused by direct action on the CNS, while their gastrointestinal side effects result from agonism at the peripheral \( \mu \)-opioid receptor.[82] Activation of these latter receptors occur at the level of the myenteric plexus, and serve to inhibit release of acetylcholine from nerve endings thereby decreasing smooth muscle tone and impairing gut motility.[83]

The importance of narcotic-related dysmotility is demonstrated by the success of the drug Alvimopan in accelerating post-operative gastrointestinal recovery.[84] Alvimopan is a synthetic, orally-administered, peripherally-acting \( \mu \)-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.[85, 86] Several high-quality trials have been performed to investigate its clinical effect, and meta-analysis of these data have shown that when compared to placebo, a 12mg dose of Alvimopan accelerates time to tolerance of an oral diet after surgery, time to passage of first bowel motion after surgery, and time to discharge both within and outside of Enhanced Recovery After Surgery (ERAS) programs.[84, 87] Alvimopan has been approved by the Food and Drug Administration and is widely used in the USA for this purpose.[88]

1.1.7 Mechanisms of Panenteric Dysfunction

Despite differing recovery times for stomach, small bowel, and large bowel after surgery,[8] all gastrointestinal segments appear to be affected by ileus. It is therefore important that these are not considered discretely, but rather as a common recipient of a generalised response to surgery.

The panenteric effects of narcotic use or electrolyte imbalance are self-evident. Likewise, it is feasible that local neural afferents initiate reflex arcs in the CNS with efferents acting on
other parts of the gastrointestinal tract. Indeed, it has been shown in a murine model that isolated handling of the small bowel generates inhibitory neural efferents that delayed gastric emptying.[89] Panenteric inflammation has been postulated as a mechanism for generalised dysmotility, and may be the consequence of three major pathways – i) intra-peritoneal dissemination of mast cell mediators upon peritoneal entry;[4, 5, 8] ii) intramural production and haematogenous circulation of T helper type 1 memory cells;[90] or iii) translocation of intraluminal commensal endotoxins to the muscularis propria with generation of a local and systemic inflammatory response.[91]

1.1.8 Changes in Gastrointestinal Motility

It has been shown that following major abdominal surgery motility typically returns first in the small bowel (<24 hours), then in the stomach (24-48 hours), and finally in the large bowel (>48 hours).[92] However, recovery of large bowel function occurs much less predictably than in other parts of the gut, and the passage of flatus and stool have therefore traditionally been used as endpoints indicating complete clinical resolution of post-operative gastrointestinal dysfunction.[48] In healthy human controls, colonic transit and defaecation are associated with circular muscle contractions, commonly referred to as propagating motor events.[93-95] Marked increases in propagating motor activity have been shown to occur in response to consumption of calorie-rich meals, morning waking and electrical stimulation, suggesting that they are neurogenically mediated.[96-100]

Understanding of how pathophysiologic disturbances impact actual intestinal contractility is limited and it is postulated that an ileus represents an absence or attenuation of neurogenic motor activity. Clinical symptoms such as nausea, vomiting and absence of flatus and stool may be readily explained when presented in the context of radiologically proven gut dilation and fluid sequestration; however, it is unclear if this dysfunction results from intestinal hypomotility, dysmotility, or the complete absence of motility.[73, 92, 101, 102]

Techniques currently used to define normal or abnormal gut motility are largely confined to manometry (described later) and transit studies. Transit studies involve radiologic, fluoroscopic or scintigraphic tracking of radio-opaque markers as they move through the gastrointestinal tract.[103] This has recently been superseded by the ‘SmartPill’ (WMC SmartPill Corporation, Buffalo, New York, USA) – an ingestable capsule that senses changes in luminal pH allowing investigators to determine transit times through stomach, small bowel or colon.[104] However, while these transit techniques allow information to be collated on gross movement between anatomical segments of the gut, they do not qualify...
spatiotemporal pressure characteristics within segments and are therefore of little use in defining the local intraluminal changes in motility that accompany an ileus.
1.2 Clinical Characterisation of Ileus

1.2.1 Clinical Features

The clinical syndrome of an ileus is recognisable by the presence of characteristic gastrointestinal symptom clusters occurring within the immediate post-operative period. Cessation of 'normal' contractility is ostensibly coupled with the emergence of aberrant motility patterns, leading to clinical manifestations which are best conceptualised by considering segments of the gut discretely.[92-95]

Dysfunction affecting the stomach and proximal small bowel leads to 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 duodenum to stomach. Indeed, it has been suggested that a change in the colour of nasogastric drainage from green to clear may signal the return of normal antegrade motility and resolution of an ileus.[105]

Dysfunction affecting the mid-distal small bowel and the large bowel leads to abdominal distension and may be accompanied by the absence of flatus and stool. Distension is often self-reported as a distressing symptom and is qualified clinically by direct observation and elicitation of abdominal tympany on percussion.[105, 106] Although the aberrations in motility which underpin an ileus have not yet been characterised, the occurrence of distension and obstipation serve as clinical markers of the absence of the normal antegrade flow of intestinal content.

Characteristic radiologic features of an ileus may be observed on abdominal plain film or computed tomography (CT) and include generalised gut dilation with air-fluid levels and the absence of a transition point. Although these findings are non-specific for an ileus their occurrence in the appropriate clinical context has the dual role of improving diagnostic certainty and excluding alternate or precipitating pathology.[105, 107, 108]

It is important to appreciate that while clinical features are typically described as occurring in synchrony, it is also possible for symptom clusters to be confined to the upper or lower gastrointestinal tract. A recent Clinical Consensus group has suggested that POI may be classified into three types:[48]

- Type I – comprising panintestinal ileus (no flatus or bowel movement in the presence of nausea or vomiting).
- Type II – comprising upper gastrointestinal symptoms (nausea or vomiting with the passage of flatus).
• Type III – comprising lower gastrointestinal symptoms (absence of flatus or stool but the ability to tolerate an oral diet).

A final consideration is the duration of an ileus. There is a degree of obligatory gastrointestinal dysfunction following all abdominal procedures. However, in a majority of patients, symptoms are mild and self-limiting, typically resolving within two to three days. This must be differentiated from the more clinically problematic and pathologically significant entity of a 'prolonged' post-operative ileus which typically presents with florid symptoms lasting several days to weeks.[48, 109, 110]

1.2.2 Definition

An internationally accepted, standardised clinical definition for POI is lacking. Furthermore, terminology used when describing POI is inconsistent. This may be attributed to the nebulous nature of its symptoms coupled with the difficulty of identifying a specific time-point at which an ileus is deemed to become prolonged.

It is valuable to temporally qualify the clinical syndrome of an ileus using the three sub-headings listed below. [45, 48, 111, 112] While each of these is readily recognisable clinically, confusion and ambiguity arises from interchangeable terminology and difficulty identifying the point of transition from one form to another:

• ‘Normal’ POI or ‘Physiologic’ POI or ‘POI’ [not further specified] – the period of gastrointestinal dysfunction which occurs immediately after surgery.
• ‘Prolonged’ POI or ‘Paralytic’ POI or ‘Pathologic’ POI or ‘POI’ [not further specified] – the occurrence, in some cases, of post-operative gastrointestinal dysfunction extending past the expected timeframe following surgery.
• ‘Recurrent’ POI or ‘Paralytic’ POI – the apparent resolution of post-operative gastrointestinal dysfunction after surgery followed by a reoccurrence of its symptoms and signs.

There remains much scope for clarifying the terminology of POI and for the provision of concise, clinically quantifiable definitions. Prior to this topic being addressed in this thesis, reference is made to various ileus syndromes in the text using inverted commas as follows – ‘normal’ POI, ‘prolonged’ POI, and ‘recurrent’ POI.

1.2.3 Incidence

The proportion of patients undergoing major abdominal surgery who subsequently develop ‘prolonged’ POI has been quoted as falling between 3-32%. [45, 46, 112-117] It is clear from
this broad range that there has been difficulty in reliably and consistently estimating incidence. This may be attributed to three factors – i) an inherent variability in incidence depending on the type of surgery; ii) a lack of distinction with respect to type of POI being described; and most importantly iii) heterogeneity between definitions for a specific type of POI. This latter reason is well exemplified by considering three recent reviews which investigated risk factors for ‘prolonged’ POI following colorectal surgery. All studies used alternate definitions – one classifying it as an absence of bowel function on Day 5 post-operatively,[45] another on Day 6 post-operatively,[46] and the third describing it as being the length of time above the 3rd quartile for a ‘normal’ post-operative ileus.[111]

‘Prolonged’ POI occurs most frequently following intra-abdominal surgery but may also appear after procedures that do not involve breach of the peritoneum. This most notably includes orthopaedic spinal procedures, where between 5-12% develop ‘prolonged’ POI.[118] Incidence following lower limb arthroplasty is typically lower at <1%, but one study notably found that this lasted more than 3 days in approximately half the affected patients.[119] Symptoms of gastrointestinal dysfunction occurring in the post-operative time period are likewise more pronounced following abdominal vs. non-abdominal procedures.[118, 120] Abdominal surgery may involve resection and handling of a variety of viscera – enteric (oesophagus, stomach, small bowel and large bowel), hepatopancreaticobiliary, gynaecologic (ovaries and uterus) or urologic (kidneys, ureters, bladder and prostate). Large bowel resection and subsequent anastomosis have been shown to more profoundly impact post-operative gastrointestinal function than surgery of similar severity not involving resection.[47, 112, 115]

1.2.4 Risk Factors

Peri-operative and patient factors that predict which patients will develop a ‘prolonged’ ileus are poorly delineated in the literature. While it is valuable to consider the pathophysiologic mechanisms which may underpin risk factors, a risk stratification system based wholly on clinical determinants could facilitate targeted early institution of preventive measures, thereby attenuating or potentially circumventing an episode of ‘prolonged’ POI following surgery.

Anecdotally, patients at greatest risk include those who are more comorbid and of an older age; those undergoing procedures involving major visceral resection with extensive gut handling; and those requiring higher quantities of opioids post-operatively.[48, 111, 116] There is however little consistent evidence to support these assertions, and furthermore, these factors are all susceptible to considerable confounding by the index procedure type.
Focused consideration of ‘prolonged’ POI following colorectal surgery reveals a handful of clinical factors that appear to be emerging as associations. These include: increasing age, male gender, pre-existing chronic airway disease, increasing peri-operative narcotic consumption, increasing intra-operative blood loss and the formation of an ileostomy (Table 1-1).[45, 46, 111, 121] However, the retrospective design of these studies, small sample sizes of most, and differing definitions of POI have limited the ability to confidently qualify and quantify the significance of potential risk factors.

<table>
<thead>
<tr>
<th>Year</th>
<th>Definition</th>
<th>Incidence</th>
<th>Independent predictors for ‘prolonged’ POI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artinyan 2008</td>
<td>Number of days above the 3rd quartile</td>
<td>22 / 88 (25%)</td>
<td>-Estimated blood loss during surgery -Post-operative opiate dose</td>
</tr>
<tr>
<td>Kronberg 2011</td>
<td>Absence of bowel function for &gt;5 days post-op OR re-insertion of NG tube after commencing an oral diet</td>
<td>42 / 413 (10.2%)</td>
<td>-Increasing patient age -Chronic pre-operative opiate use -Previous abdominal surgery</td>
</tr>
<tr>
<td>Millan 2011</td>
<td>Absence of flatus for &gt;6 days post-op</td>
<td>123 / 773 (15.9%)</td>
<td>-Male gender -Procedures requiring formation of stoma -Pre-existing airways disease</td>
</tr>
<tr>
<td>Chapuis 2013</td>
<td>Distension, nausea or vomiting, or absence of flatus or stool for &gt;3 days post-op</td>
<td>336 / 2400 (14%)</td>
<td>-Male gender -Procedures requiring formation of stoma -Pre-existing airways disease -Pre-existing peripheral vascular disease -Acute procedures -Increasing procedure duration</td>
</tr>
</tbody>
</table>

Table 1-1 Incidence of and independent predictors for the occurrence of ‘prolonged’ POI following colorectal surgery in four recent retrospective reviews.[45, 46, 111, 121]
1.3 Clinical Corollaries of Ileus

1.3.1 Consequences to Patient

‘Prolonged’ POI has been shown to negatively impact patient outcomes, and is currently the most common cause of delayed hospital discharge following abdominal surgery.\cite{101, 121} It is associated with an increased incidence of atelectasis and pneumonia, postulated to occur as a consequence of abdominal hypertension with reduced tidal volume and impaired deep breathing.\cite{73, 122, 123} Poor oral intake accompanied by vomiting may lead to nutritional and electrolyte deficiencies which in turn have been linked to delayed wound healing.\cite{123-125} Patients with ‘prolonged’ ileus are frequently encumbered by nasogastric tubes and intravenous lines thereby limiting mobilisation and placing them at an increased risk of developing thrombotic complications.\cite{73, 123, 126} Other infectious complications (most notably anastomotic leak) are also consistent associations.\cite{107, 112, 127}

A valuable consideration is whether these conditions are truly sequelae of an ileus or whether they are causal. For example, respiratory complications are often associated with hypoxia and systemic sepsis, both known at the gastrointestinal level to be precipitants of an ileus. Similarly, fluid shifts in the peri-operative setting typically incite rapid fluctuations in electrolyte levels, which are believed to directly impact intestinal motility. Correlations of ‘prolonged’ POI with other post-operative complications are largely underpinned by retrospective work and it is important to appreciate that this limits the ability to confidently ascertain direction of causality.\cite{45, 46, 111, 121}

A significant but understated corollary of ‘prolonged’ POI is its psychological impact on patient recovery. A protracted post-operative in-patient admission is associated with increased patient fatigue, decreased satisfaction with care, and negative self-perception of clinical progress. This in turn may contribute to the development of psychological barriers to recovery.\cite{128-132} The importance of ‘barriers’ in surgical convalescence is well exemplified by considering current ERAS protocols, where strong emphasis is placed on routinely counselling patients before surgery on expectations of recovery and addressing any accompanying denial or anxiety.\cite{125, 133} Psychological state is intimately related to immunologic function, and has been shown to play a major role in physical outcomes such as wound healing after surgery.\cite{132, 134, 135}

1.3.2 Consequences to Hospital

‘Prolonged’ POI imparts a significant financial and resource-intensive burden on healthcare institutions. It has been estimated by Goldstein et al. that the cost of its management in the
USA alone approaches $US1.5 billion annually.[112] Importantly, this figure is based on a procedural cost-accounting coding system and is therefore likely to be an underestimate. Goldstein et al. showed that both the length of hospital stay and cost per hospital stay were approximately doubled in ‘prolonged’ ileus-coded patients when compared to their non-ileus counterparts. Additionally, the number and cost of readmissions was greater in the ‘prolonged’ POI group.[112] Similar findings have also been observed in other studies investigating the economic impact of POI.[117, 136]
1.4 **Therapeutic Management of Ileus**

The substantial clinical and economic burden conferred by ileus appears to have been acknowledged by the surgical community, with the recent emergence of many clinical trials examining potentially therapeutic strategies. However, a majority of these have yielded disappointing or conflicting results. A recent Cochrane review investigated 15 prokinetic agents across 39 trials and found only one (Alvimopan – a selective μ-opioid receptor antagonist) showed a reproducible therapeutic benefit. The remaining drugs were not recommended due to lack of evidence or absence of effect.[77] Moreover, it is important to note that the clinical outcome evaluated in almost all these studies was time to return of gastrointestinal function post-surgery (i.e. a shortened duration of ‘normal’ post-operative ileus) with no reference to incidence or shortened duration of ‘prolonged’ ileus.

It is valuable to draw attention to the recent success of ERAS protocols in optimising peri-operative patient outcomes and shortening length of hospital stay. ERAS programs have been shown to consistently accelerate time to the occurrence of clinical markers which indicate gastrointestinal recovery following surgery.[137-139] However, given the multimodal nature of these programs it is difficult to transparently attribute improved gut recovery to any discrete intervention. Epidural analgesia, fluid restriction, early oral feeding, and careful electrolyte monitoring are all facets of contemporary ERAS protocols and each have a sound pathophysiologic basis to explain their benefit.[125, 140] ERAS protocols may also have a role in the prevention of ‘prolonged’ POI. Although a recent consensus review listed this as a ‘key objective’, [125] few data are available to support the efficacy of ERAS for this purpose and may be related to an imprecise appreciation of the true incidence of ‘prolonged’ POI.[45]

The following text considers selected novel treatment strategies that may prove useful in the management of ‘normal’, ‘prolonged’ and/or ‘recurrent’ POI.

1.4.1 **Neural Blockade with Local Anaesthetic or Sympathetic Antagonists**

The peri-operative administration of local anaesthetic (LA) is mostly administered in the form of epidural anaesthesia and lessens the effects of post-operative gut dysfunction via three principal mechanisms: i) reduced need for narcotic analgesia; ii) blockade of somatosensory afferents; and iii) transient chemical sympathectomy.[141] The former two mechanisms may be sufficiently achieved by epidural placement at either thoracic or lumbar location, but sympathetic blockade is only achieved by placement at mid-high thoracic level. Epidural analgesia sited here diminishes sympathetic thoracic outflow to the gut while having no effect on parasympathetic vagal efferents, ostensibly allowing a shift in autonomic balance conducive to gut motility.[142, 143]
Alternate therapeutic strategies utilising local anaesthetic involve systemic intravenous administration (IVLA) or local intra-peritoneal administration (IPLA). Peri-operative administration of IVLA has been shown to have analgesic [144] and anti-inflammatory properties,[145] and it is postulated that these mechanisms account for the accelerated return of normal gastrointestinal function.[146, 147] Although antecedent studies have been subject to considerable heterogeneity with respect to type of surgery investigated and outcomes assessed, it appears IVLA may eventually provide a valuable clinical tool in the management of an ileus.[148]

IPLA has likewise been investigated as a therapeutic measure following abdominal surgery, and it has been hypothesised that the local administration of LA may blunt the autonomically-mediated visceral nociceptive response to gut handling.[17] A recent systematic review found that IPLA appeared to expedite return of gut function following surgery but recommended further research given the difficulty collating data from acute vs. elective, laparoscopic vs. open, and upper gastrointestinal vs. lower gastrointestinal vs. gynaecologic procedures.[149]

Transient sympathectomy in the post-operative period may also be achieved by adrenergic blocking agents. Propranolol is a non-selective β-blocker which to date has been investigated in four clinical trials (two examining propranolol alone,[150, 151] and two examining propranolol in conjunction with the parasympathomimetic neostigmine [152, 153]). All studies exhibited methodologic or reporting deficiencies, with a Cochrane review concluding inconsistent and insufficient evidence to support a role for propranolol in enhancing gut recovery following surgery.[77] As described previously, the effect of sympathetic outflow to the gut is primarily mediated by activation of α-2 adrenoceptors and a potential explanation for propranolol’s absence of effect relates to its exclusive antagonism at the β-1 and β-2 adrenoceptors. This hypothesis was recently validated by a rodent model of POI that showed that both the non-selective adrenergic antagonist guanethidine and the α-2 adrenoceptor antagonist yohimbine improved colonic transit after surgery, while propranolol had no discernible effect when compared to placebo.[154] The clinical value of selective adrenergic antagonism in mitigating gut dysfunction following surgery therefore merits investigation.

1.4.2 Suppression of the Inflammatory Cascade

Inflammation and immunologic activation are thought to be sentinel events in the pathophysiology of POI. Immunosuppression may be achieved by a ‘blanket’ approach –
perhaps by systemic administration of corticosteroids; or a focused approach – whereby specific pathways in the surgical inflammatory response are targeted.

There is limited literature investigating the effect of short-course corticosteroids on post-operative gut dysfunction. Indeed, while a recent review found a single pre-operative dose of glucocorticoid reduced complications in major abdominal surgery via blunting of the postsurgical inflammatory response, no specific comment was made on return of bowel function.[155] Although delivery of steroid in the pre-operative setting is likely to prevent initiation of an inflammatory cascade,[1] its selective use following surgery in confirmed cases of ‘prolonged’ POI theoretically stands to deliver a therapeutic benefit and warrants prospective clinical appraisal.

Directed anti-inflammatory treatments may likewise be beneficial in POI, with a recent review suggesting that all stages of the activation process from chemoattraction to inducible hypoxic enzymes to intracellular signalling may be viable therapeutic targets.[8] As outlined previously, mast cells play a central role in the pathogenesis of ileus,[2, 4, 5] and it has been demonstrated that prevention of mast cell degranulation significantly improves gastrointestinal recovery in a murine model.[89, 156] This subsequently led to a pilot study in human patients investigating the therapeutic value of the mast cell stabiliser ketotifen. While ketotifen shortened duration to scintigraphically-assessed gastric emptying, there was no discernible effect on colonic transit.[157] Resident macrophages likewise play a key role in the innate immunologic response, and depletion of these cells in a rodent model by chlodoronate liposomes has yielded promising results.[158] Similarly, electrical stimulation of the vagus nerve in mice reduced inflammation by impairing macrophage activation.[159] An elegant human trial by Wattchow et al. evaluated the therapeutic benefit of prostaglandin inhibition in ileus using COX inhibitors. It was demonstrated that the COX-2 inhibitor celecoxib (but not the non-specific COX inhibitor diclofenac) significantly reduced incidence of ‘prolonged’ POI without affecting duration of ‘normal’ POI.[160]

1.4.3 Manipulation of Gastrointestinal Neuropeptides

Octreotide is a somatostatin analogue believed to inhibit the release of many gastrointestinal hormones via direct action on neurons in the ENS.[161-163] Octreotide has been shown in a canine model to accelerate post-operative gastrointestinal transit at low doses, although at higher doses paradoxically inhibited gastric emptying.[161] A subsequent study investigating administration of octreotide in healthy human volunteers found it accelerated gastric emptying but delayed mouth-to-caecum transit time.[162] It has been postulated that suppression of postprandial hormones (notably cholecystokinin) may be partly
responsible.[162, 164] An important initial step in considering the therapeutic potential of octreotide in POI would therefore involve a detailed assessment of its effects on individual gut hormones.

Four trials have investigated the effect of the cholecystokinin-like drugs cerulean and ceruletide,[165-168] with a systematic review concluding that there is inconsistent evidence to support a reduction in post-operative gut recovery time.[77] VIP and SP receptor antagonists have been shown to improve post-operative intestinal transit in a rat model,[62, 64] but have not been tested in humans. A blinded trial of intravenously infused motilin vs. normal saline in patients following open cholecystectomy revealed no improvement in gut function.[169] Erythromycin is a motilin agonist and its prokinetic side effects when administered as an antibiotic are well known.[170] However, four trials investigating its use in the post-operative period were consistent in their findings of having no treatment effect.[171-174]

A more generalised approach to the manipulation of gastrointestinal neuropeptides in the post-operative period may be achievable by gum-chewing. It was initially postulated that this ‘sham feeding’ would stimulate the cephalic phase of digestion, and produce a neurohormonal milieu conducive to gut recovery.[175] Several randomised trials have since endeavoured to evaluate the effect of gum-chewing immediately after surgery, with a recent meta-analysis concluding that although this intervention accelerates time to first flatus and first bowel motion, the clinical benefit is unclear with only a non-significant trend towards reduction in length of hospital stay.[176]

More recently, considerable attention has been given to ghrelin – an endogenous ligand (with structural similarity to motilin) at the growth hormone secretagogue receptor, released from gastric and pancreatic epithelium.[177] The ghrelin agonist ‘TZP-101’ has been shown in recent Phase II trials to safely and effectively reduce upper and lower gastrointestinal dysfunction in patients following partial colectomy.[178, 179] It has been hypothesised that these findings are primarily attributable to its potent prokinetic effect,[180] although the relative significance and transferability of ghrelin’s ability to down-regulate pro-inflammatory cytokines in a sepsis model is unclear.[181, 182] Results of Phase III testing are awaited.

1.4.4 Mechanical reduction of oedema

The above discussion largely addresses strategies that may be useful in attenuating the initial stages of an ileus. However, it is of far greater clinical significance to consider therapies that may be utilised in established cases of ‘prolonged’ POI. Dysmotility at this point is likely to be in part due to bowel wall oedema, and administration of agents able to
counteract this oedema in a site-specific manner merit investigation. Oral water-soluble contrast (OWSC) media have been shown to confer a predictive and therapeutic benefit in adhesive bowel obstruction.[183] It has been proposed that the remedial properties of orally or rectally administered contrast media relate to their hypertonicity – fluid is drawn out of the gut wall into the lumen, thereby reducing gastrointestinal contractile dysfunction and promoting peristalsis.[183, 184] Appearance of contrast media within the large bowel 4–24 hours after administration predicts resolution of obstruction with a sensitivity of 96% and specificity of 98%. It reduces the need for surgery by more than a third and shortens length of in-patient hospital stay.[183] Given the pathophysiologic similarities of ileus to bowel obstruction, it is feasible that OWSC media may exert an equivalent therapeutic effect.

Gastrografin is a commercially available OWSC agent formulated for use as radiologic contrast media. It is packaged as a 100mL solution, with each dose containing 100mg sodium diatrizoate and 660mg meglumine diatrizoate, and may be administered orally or rectally.[185] Sodium and meglumine diatrizoate (DTZ) salts each contain a benzene ring carrying three iodine atoms.[186] Gastrografin is primarily utilised as a contrast agent in abdominal computed tomography, where it has been shown to improve diagnostic accuracy by more precisely delineating the gastrointestinal tract from surrounding organs.[187] Its overall formulation has been designed to combine the lower toxicity of the meglumine salt with the lower viscosity and higher iodine content of the sodium salt.[188] Gastrografin appears well suited to its roles as contrast agent and therapeutic tool in adhesive bowel obstruction, as it is minimally absorbed across the gastrointestinal mucosa (bioavailability <3%) and remains largely within the gut lumen. DTZ has a highly ionised structure, and molecules that have entered the systemic circulation therefore do not bind significantly to serum proteins and are excreted unchanged, primarily via glomerular filtration.[189-191] The water-soluble nature of Gastrografin makes it a valuable tool for radiologic investigation of post-operative anastomotic leak; unlike barium sulphate, Gastrografin which inadvertently passes into the abdominal cavity is readily absorbed across peritoneum and renally excreted.[185, 191] Furthermore, it has a generally favourable side effect profile with the major risk being dehydration and more serious adverse events such as aspiration and hypersensitivity reactions occurring relatively rarely.[185, 192]

The clinical value of Gastrografin in ‘prolonged’ POI is not clear, with previous studies being limited to small patient numbers, heterogeneous inclusion criteria and outcome measures, and conflicting results.[193-195] Appropriately powered, randomised and blinded prospective appraisal is required to adequately assess the efficacy of this potential intervention.
1.5 **Summary**

POI is a clinically and economically important consequence of abdominal surgery. The pathophysiologic basis of an ileus is multifactorial, and key contributing factors include generation of an inflammatory response, administration of opioids, autonomic dysfunction, disturbances in gastrointestinal hormone activity, and electrolyte derangements. The gastrointestinal dysfunction that underscores ileus especially in the context of visceral anastomosis is unclear and remains to be characterised. There is considerable heterogeneity with respect to terminology and definition of POI; however, ‘prolonged’ ileus is the more pathologically significant and clinically problematic entity, and requires specific consideration. An accurate risk prediction tool for this syndrome would facilitate early institution of preventive measures and warrants investigation. Clinical appraisal of novel therapeutic strategies that target individual pathways in the pathogenesis of ileus such as neural blockade, suppression of inflammation, gut neuropeptide manipulation and mechanical reduction of oedema will continue to inform management.
CHAPTER 2:
THESIS OBJECTIVES & OVERVIEW
Chapter 1 has summarised the clinical and pathophysiologic aspects of post-operative ileus and highlighted several areas that require further investigation. The research outlined in this thesis aims to improve insight into ileus by answering the following specific questions:

1. How should ileus be classified and clinically defined?

2. What are best-practice recommendations for the conservative management of ‘prolonged’ ileus?

3. Is Gastrografin useful in shortening an established episode of ‘prolonged’ ileus?

4. Which clinical factors predict the development of ‘prolonged’ ileus?

5. How does intestinal motor activity change during the peri-operative period, and does motility ever return to ‘normal’ after segmental resection and anastomosis?

This was to be achieved by reviewing and amalgamating current literature; prospectively appraising a potentially therapeutic intervention; constructing a risk prediction system; and characterising peri-operative and post-surgical changes in intestinal motility.

Chapter 3 is a retrospective account of ‘prolonged’ ileus following elective colorectal surgery at Auckland District Health Board over a single year. This study aimed to provide local pilot data on the incidence, duration, risk factors and management of ‘prolonged’ ileus, thereby informing design and power calculations for the planned clinical trial and prospective risk stratification work.

The next chapter (Chapter 4) clarifies terminology and provides concise, clinically quantifiable definitions for ileus. This was achieved by performance of a systematic review of randomised trials investigating ileus published between 1996 and 2011, and by execution of a global survey obtaining the opinions of authors published in the field. Data were amalgamated to provide concise definitions for ‘post-operative ileus (POI)’, ‘prolonged post-operative ileus (PPOI)’, and ‘recurrent post-operative ileus’.

Chapter 5 presents a narrative review of the current literature directed at identifying best-practice conservative management strategies which may aid resolution of PPOI. Concise recommendations were synthesised and accompanied by Strength of Recommendation Taxonomy (SORT) gradings.
A double-blinded clinical trial was to be executed appraising the ability of Gastrografin to precipitate resolution of PPOI by reducing intestinal oedema. A critical step in trial development was ensuring Gastrografin re-packaged during the blinding process remained active under anticipated storage conditions. Chapter 6 describes the use of simple and rapid reverse phase High Performance Liquid Chromatography to appraise the 30-day stability of opened and re-packaged Gastrografin under standard storage conditions (25°C, 60% relative humidity, no light).

Chapter 7 presents a double-blinded, placebo-controlled, randomised trial investigating the therapeutic value of Gastrografin in shortening duration of PPOI following elective colorectal surgery. Participants were uniformly diagnosed with PPOI using the definition outlined in Chapter 4 and were allocated to receive either 100ml of Gastrografin (Exposure Group) or flavoured distilled water (Control Group) administered enterally. Other aspects of management were standardised in line with the recommendations of Chapter 5. Resolution of PPOI was assessed 12-hourly. The primary outcome was duration of PPOI.

A prospective observational study delineating risk factors for the development of PPOI and construction of a novel predictive tool is described in Chapter 8. In total, 92 variables were prospectively investigated in an elective colorectal surgical cohort with uniform application of the definition of PPOI presented in Chapter 4. Independent predictors for PPOI were assimilated to generate score-based risk stratification systems. The discriminative capacity of each system was appraised using Receiver Operating Characteristic (ROC) analysis.

Chapter 9 describes an in vivo high resolution manometry study which characterises changes in intestinal motility during the pre-, intra- and immediate post-operative periods in human patients undergoing elective right hemicolecotony. A fibre-optic high resolution manometry (HRM) catheter was used to assess motor activity of the distal colon and rectum. Manometric events were qualified as cyclic, short single, or long single motor patterns and were quantified with respect to frequency, velocity, extent and amplitude.

The final chapter (Chapter 10) presents a further in vivo high resolution manometry study which endeavours to identify whether colorectal motility returns to baseline in patients who have previously undergone anterior resection and preserved normal bowel function. An HRM catheter was placed in the distal colorectum of these patients. The colonic motor response to a standardised 700kCal meal was quantified and compared to data previously acquired from healthy controls. The presence of coordinated trans-anastomotic motor activity was also determined.
CHAPTER 3:
RETROSPECTIVE COHORT STUDY –
‘PROLONGED’ POST-OPERATIVE ILEUS FOLLOWING ELECTIVE
COLORECTAL SURGERY
3.1 **Background**

Research presented in subsequent chapters of this thesis attempts to utilise prospective work to facilitate pathophysiologic and clinical insights into ileus. Chapter 7 describes the execution and findings of a randomised trial investigating a potentially therapeutic intervention for ‘prolonged’ POI. Aspects critical to study design include a sound understanding of relevant institutional clinical protocols and their adherence to by clinical staff, and the identification of potential pitfalls in trial implementation. Likewise, Chapter 8 details the development of a novel risk stratification tool predicting the occurrence of ‘prolonged’ POI. A retrospective analysis of features associated with ileus would assist in identifying variables which could be contributory, thereby ensuring they are adequately investigated on prospective data collection.

An additional consideration is the selection of an appropriate surgical cohort within which to conduct clinical research. It is necessary, for the purposes of the anticipated work, that index procedures within the source population conform to the following requirements – i) ‘prolonged’ POI must occur in a sufficient proportion of patients after surgery to make research feasible; ii) there must be an adequate number of cases being undertaken on a regular basis at the site of research; and iii) surgery must occur on an elective schedule to ensure patients have ample time to provide informed consent prior to enrolment. It is proposed that surgery undertaken by the Colorectal Unit at Auckland District Health Board (ADHB) fulfil these criteria. A significant proportion of patients undergoing colorectal surgery develop ‘prolonged’ ileus,[45, 46, 48, 111, 121] and ADHB’s Colorectal Unit carry out several elective procedures every week.

3.2 **Study Objectives**

The aim of this study was to obtain baseline retrospective data for the anticipated patient cohort – namely, those undergoing elective colorectal surgery at ADHB – to ensure that planned prospective work was methodologically robust in terms of both study design and study setting.

Specific objectives were first, to provide pilot data on ‘prolonged’ POI within the local patient cohort to inform design and power calculations for the planned clinical trial; and second, to identify peri-operative risk factors which may be associated with the development of ‘prolonged’ POI following elective intra-abdominal surgery within a colorectal unit.
3.3 Methods

3.3.1 Ethical Approval

Ethics approval was obtained from the Ministry of Health’s National Ethics Committee (NTX/12/EXP/036) and Auckland District Health Board’s Multidisciplinary Research Review Committee (A+ 5439) prior to data extraction.

3.3.2 Study Population

A prospectively maintained register of all elective colorectal operations undertaken at ADHB was retrospectively accessed (Figure 3-1). Consecutive intra-abdominal procedures performed electively between 1st January and 31st December 2011 (inclusive) by this unit were identified via the acquisition of unique patient National Health Index (NHI) numbers. Intra-abdominal procedures were defined as any operation involving breach of the peritoneum, and therefore included standard colonic resection (right hemicolectomy; extended right hemicolectomy; left hemicolecotomy; sigmoid colectomy; sub-total colectomy; and total colectomy), standard rectal resection (high, low and ultra-low anterior resection; and abdominoperineal resection), ventral mesh rectopexy, and formation or reversal of small and large bowel stomas. Both open and laparoscopic cases were included. Excluded operations were hernia repairs, stoma revision or re-siting, and diagnostic or staging procedures.

3.3.3 Data Extraction

Patient NHI numbers were used to extract information from ADHB’s online patient portal ‘Concerto’ for an assortment of peri-operative parameters as detailed below. Data was directly input into an electronic database.

3.3.3.1 Patient Characteristics

These included patient age at the time of surgery (calculated by recording date of birth and date of surgery), gender, American Society of Anaesthesiologists (ASA) grade and body mass index (BMI).

3.3.3.2 Operative Characteristics

Variables recorded were procedure type, operating surgeon, operative technique (open vs. laparoscopic vs. converted procedure), indication for surgery, procedure duration, formation of stoma, previous abdominal surgery, use of a pre-operative epidural or spinal block, and intra-operative narcotic administration.
Figure 3-1 Patient catchment area covered by Auckland District Health Board (reproduced from ADHB website – http://www.adhb.govt.nz/about/population_stats.htm)
3.3.3.3 **Haematologic and Biochemical Indices**

Haemoglobin and creatinine were recorded pre-operatively (the ‘pre-operative’ period was defined as the two weeks preceding index surgery). Variables interrogated post-operatively were Day 1 haemoglobin and Day 1-3 lowest haemoglobin, lowest potassium, lowest sodium, highest white cell count and highest creatinine. Change in haemoglobin concentration from pre- to post-operatively was expressed as a percentage and used as a proxy for operative blood loss. Percentage change in creatinine concentration before and after surgery was likewise noted. Albumin was not recorded as it is not routinely carried out at ADHB either pre- or post-operatively.

3.3.3.4 **Post-operative Markers of Recovery**

These included oral and intravenous narcotic consumption from Day 0-3, day of first flatus, occurrence of concomitant post-operative complications (graded according to the Clavien-Dindo classification)[196] and total length of hospital stay. Intra-operative and post-operative opiate use was collated and expressed as the Morphine Equivalent Daily Dose (MEDD), a validated and sensitive measure of narcotic consumption (Figure 3-2).[197-199]

<table>
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**Figure 3-2** Morphine Equivalent Daily Dose (MEDD) = (Opioid dose) x (MEDD-factor).
3.3.4 Primary Outcome

The primary outcome was the occurrence of ‘prolonged’ POI during the post-operative inpatient admission. This binary outcome was used to identify peri-operative risk factors associated with its development.

‘Prolonged’ POI was recorded as occurring if it was clinically diagnosed and documented by the overseeing surgical team on or after Day 3 post-operatively. As outline in Chapter 1, no clear definitions exist for when a ‘normal’ ileus becomes prolonged, or the time point at which a diagnosis of ‘prolonged’ POI can be feasibly made. However, its occurrence in the post-operative period is typically apparent to the examining clinician and a label of ‘ileus’ may be more reliably recorded by staff in the clinical notes where incipient symptoms and signs are not. This formed the rationale for using a clinician-based diagnosis in this retrospective study. Diagnosis involved a variable combination of nausea or vomiting, inability to tolerate an oral diet, abdominal distension and absence of flatus or stool, with or without radiologic confirmation. Resolution of ‘prolonged’ POI was defined as occurring when patients no longer experienced nausea or vomiting with the nasogastric tube removed, were tolerating a solid or semi-solid diet, were passing flatus or stool, and had no abdominal distension.

3.3.5 Secondary Outcomes

Secondary outcomes included the duration of ‘prolonged’ POI, method of resolution (i.e. spontaneously with conservative measures only or requirement for intervention), and adherence or reference to guidelines for the management of ‘prolonged’ POI.

3.3.6 Peri-operative Care

Peri-operative care did not conform to an Enhanced Recovery After Surgery (ERAS) or multimodal ‘fast-track’ rehabilitation programme. However, several aspects of patient care were protocolised at ADHB including stepwise analgesia progression, restrictive post-operative intravenous fluid therapy, subcutaneous thromboprophylaxis, early post-operative feeding, and structured post-operative mobilisation regimens in conjunction with physiotherapy.

3.3.7 Statistical Analysis

Statistics were performed using SPSS for Windows (Version 19; SPSS, Chicago, Illinois, USA). Analysed variables were stratified according to the presence or absence of ‘prolonged’ POI. Missing data were excluded in a listwise fashion from all further analyses.
Parametricity was determined using the Shapiro-Wilk test, with normally distributed data being expressed as mean ± standard deviation (SD) and non-parametric data as median ± interquartile range (IQR). Univariate analysis was carried out using the $\chi^2$ test for categorical variables, the Mann-Whitney $U$ or Kruskal Wallis tests for non-parametric continuous variables, and an independent samples $t$-test for parametric continuous variables. All variables which were significant or near significant ($p<0.10$) on univariate analysis were entered into a logistic regression model. An omnibus test of model coefficients was carried out prior to performance of logistic regression with subsequent identification and insertion of a constant. Results were considered statistically significant if $p<0.05$. 
3.4 Results

3.4.1 Data Retrieval

Information pertaining to the peri-operative inpatient stay was thoroughly and consistently recorded. Data were largely extracted from ADHB’s electronic information system portal (Concerto); remaining data were accessed via the electronically-linked ‘3M Viewer’ which contained scanned picture files of clinical notes that were hand-written during a patient’s admission. Overall variable extraction for the final electronic dataset was 99.2% complete.

3.4.2 Incidence of ‘Prolonged’ POI

In total, 255 consecutive patients underwent elective intra-abdominal surgery by the Colorectal Unit in the 2011 year, of whom 50 (19.6%) developed ‘prolonged’ POI.

3.4.3 Significant Correlates (Univariate Analysis)

Basic descriptive statistics of peri-operative variables and the strength of their associations to ‘prolonged’ POI can be found in Table 3-1. The median age of the overall patient population was 66 years with a female preponderance. Those who developed ‘prolonged’ POI were significantly older than those who did not (72 vs. 65 years; p=0.024), although no significant differences were noted between these groups with respect to gender, BMI, ASA and previous abdominal surgery. The most common procedures performed were colonic resections and reversal of small bowel stomas, with distribution of procedure types being significantly different between groups (p=0.004). However, there were no significant differences in technique, surgeon, indication, use of regional anaesthesia, or duration of surgery. Patients who developed ‘prolonged’ POI had a significantly lower post-operative haemoglobin (101.9 vs. 107.8; p=0.022), lower post-operative sodium (135 vs. 136; p=0.033), higher pre-operative creatinine (81.5 vs. 71; p=0.019), and higher maximum post-operative white cell count (12.0 vs. 10.3; p=0.001). Total intra- and post-operative opiate consumption was significantly greater in those who went on to develop ‘prolonged’ POI (MEDD 52.7 vs. 46.3; p=0.021). There was a significant difference in complication occurrence between the two groups (p=0.002), with 28/50 patients with ileus (56%) and 60/205 patients without ileus (29.3%) having a Clavien-Dindo classification related to another complication of ≥2. Post-operative intra-abdominal sepsis was recorded in 3/50 patients in the ‘prolonged’ POI group (6%) and 9/205 in the remainder (4.4%); this difference was not statistically significant. Sepsis was most frequently due to anastomotic leak. Length of stay was expectedly protracted in those with ‘prolonged’ POI (13 vs. 6 days; p<0.001).
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<th>Ileus (n=50)</th>
<th>Total (n=255)</th>
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<td>66±28</td>
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<td>24 (16.8%)</td>
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<tr>
<td>III</td>
<td>63 (72.4%)</td>
<td>24 (27.6%)</td>
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<tr>
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<td>12 (17.4%)</td>
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**Table 3-1 Peri-operative variables associated with developing 'prolonged' POI.**

All continuous variables were non-parametric except those starred (*).

Parametric variables are expressed as mean±SD; non-parametric variables as median±IQR.
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<th>Hb</th>
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<td>Epidural 31 (77.5%)</td>
<td>132±129</td>
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<td>125.4±19.0</td>
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<td>138 (87.9%)</td>
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<td>10.3±4.4</td>
<td>136±4</td>
<td>71±27</td>
<td>138 (87.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiate MEDD</td>
<td>46.3±42.8</td>
<td>52.7±29.9</td>
<td>49±43</td>
<td>125.4±19.0</td>
<td>12.0±4.5</td>
<td>136±4</td>
<td>71±27</td>
<td>138 (87.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Regional anaesthesia | Epidural 31 (77.5%) | Spinal 5 (71.4%) | 132±129 | 46.3±42.8 | 125.4±19.0 | 10.3±4.4 | 136±4 | 71±27 | 138 (87.9%) |
|                      | Spinal 5 (71.4%) |                       |                    |             |    | 12.0±4.5         | 135±6.3             | 3.7±0.5           |            |                               |               |
|                      | None 169 (81.3%) |                       |                    |             |    | 10.75±4.3        | 136±5               | 3.7±0.5           |            |                               |               |

| Original indication for surgery | Neoplasia 118 (79.2%) | Epidural 31 (77.5%) | 132±129 | 46.3±42.8 | 125.4±19.0 | 10.3±4.4 | 136±4 | 71±27 | 138 (87.9%) |
| J | IBD 33 (75%) | Spinal 5 (71.4%) | 166.5±143.5 | 49±43 | 125.4±19.0 | 12.0±4.5 | 136±4 | 71±27 | 138 (87.9%) | 6±3 | 13±10 | 6±6 | <0.001* |

| Clavien-Dindo Complication Grade | nil 138 (87.9%) | 1 (12.1%) | 157 | 0.002* |
|                                  | 1 7 (70%) | 3 (30%) | 10 |       |
|                                  | 2 40 (63.5%) | 23 (36.5%) | 63 |       |
|                                  | 3 15 (78.9%) | 4 (21.1%) | 19 |       |
|                                  | 4 3 (100%) | 0 (0%) | 3 |       |
|                                  | 5 2 (66.7%) | 1 (33.3%) | 3 |       |

Table 3-1 (Continued)
3.4.4 Independent Predictors (Logistic Regression)

Logistic regression analysis identified increasing age (OR 1.032 [per year], 95% CI 1.004–1.061; p=0.026) and increasing drop in maximum pre- to post-operative haemoglobin (OR 1.043 [per unit percent change], 95% CI 1.002 – 1.085; p=0.037) as the only independent predictors for developing ‘prolonged’ POI. Maximum pre- to post-operative change in haemoglobin and lowest post-operative haemoglobin were input exclusively in two separate regression models to avoid erroneous correction. Likewise, complication grade was excluded from regression analysis because correction of causal factors for this variable would have compromised the quantitative predictive value of factors independently associated with ‘prolonged’ POI.

3.4.5 Secondary Outcomes

The mean duration for an episode of ‘prolonged’ POI following its clinical diagnosis was 4.54 days (SD 2.21 days; range 1-15 days); a graphical depiction of frequency and duration can be found in Figure 3-3. Of the 50 identified cases, 49 resolved spontaneously with conservative measures only (98%) and a single patient (2%) underwent laparotomy on Day 5 post-operatively for gross small bowel distension with impending perforation. Clinical decisions made regarding the management of all 50 patients with ‘prolonged’ POI were undertaken wholly at the discretion of the overseeing clinical team without any documented reference by medical, nursing, or allied health personnel to standardised or best-practice recommendations.
Figure 3-3 Duration of ‘prolonged’ POI.
3.5 Discussion

It is valuable to acknowledge the importance of establishing an internationally accepted, standardised, clinical definition for ‘prolonged’ POI as a means to ensure uniformity and validity in study reporting. Three reviews published prior to the execution of this study investigated risk factors for developing ‘prolonged’ POI following colorectal surgery, with all using alternate definitions – one classified it as an absence of bowel function on Day 5 post-operatively,[45] another on Day 6 post-operatively,[46] and a final described it as being the length of time above the 3rd quartile for a ‘normal’ post-operative ileus.[111] These definitions all specify ‘time to clinical events’ and appraise lower gastrointestinal symptoms only. The clinical manifestation of an ileus is most frequently a complex and variable cluster of upper and lower gastrointestinal symptoms, and this has formed the rationale for the present study’s use of a clinician-based diagnosis made upon patient assessment. It is intuitively apparent that a diagnosis made at the time of occurrence is more likely to be associated with a clinically significant episode of ileus than one made by inference in retrospect.

Although diagnosis by the overseeing clinician may be the most reliable method of identifying an episode of ‘prolonged’ POI in this retrospective work, it is still a subjective measure open to interpretation by differing observers. The introduction of this heterogeneity in turn may preclude externally valid appraisal and objective comparison of risk factors. However, this does not necessarily completely diminish the applicability of study findings to other patient populations. The pathophysiologic process and clinical manifestations of a ‘prolonged’ ileus do not change between different cohorts; it is just the manner in which these manifestations are assessed which varies.

Understanding of risk factors associated with the development of ‘prolonged’ POI is nebulous, with only a limited number of retrospective studies attempting to qualify this. In one review of consecutive patients who had undergone laparoscopic colectomy, Kronberg et al. identified increasing age, chronic pre-operative narcotic use and previous abdominal surgery as independent predictors for ‘prolonged’ POI on regression analysis.[45] Conversely, a regression model created by Millan et al. in a similar analysis found male gender, formation of ileostomy and pre-existing obstructive airways disease as the only independent predictors.[46] Park et al. investigated predisposing factors for ‘prolonged’ POI following radical cystectomy and interestingly found that type of pre-operative bowel preparation used was the only difference,[200] while a more general review of ileus following abdominal surgery by Artinyan et al. concluded intra-operative blood loss and peri-operative opiate consumption were significant associations.[111] Although the present series identified
several risk factors as significant correlates of 'prolonged' POI, only age and maximal haemoglobin drop remained as independent predictors. While these findings are consistent with previous literature, the retrospective design and relatively small sample sizes of each of these works have limited the ability to confidently identify risk factors.

As outlined in Chapter 1, the aetiology of ileus following abdominal surgery is believed to be multifactorial. Handling of the gut has the dual effect of causing bowel wall inflammation (and therefore oedema) via mast cell activation, and arterial vasospasm leading to relative ischaemia.[8, 12, 13, 15, 201] The consequent dysfunction is further augmented by peri-operative use of opiate analgesia, which causes aberrant motility via activation of peripherally acting µ-opioid receptors.[84, 87, 202] The present study's finding of raised post-operative white cells, increased pre- to post-operative haemoglobin drop, and increasing opiate usage all being significant associations of 'prolonged' POI lends credence these hypotheses. Post-operative electrolyte disturbances are thought to diminish intrinsic small bowel myogenic and neural activity,[56, 73, 74] and it is interesting to note that this is the first study to associate low sodium with ileus. Although a pre- to post-operative drop in haemoglobin may be a function of intra-operative blood loss, its coupling with the relative hyponatremia observed here suggests haemodilution secondary to overzealous intravenous fluid administration as a cause. The gut wall oedema this is known to precipitate is believed to be a significant contributory factor to the development of 'prolonged' POI.[10] Indeed, a restrictive post-operative intravenous fluid prescription has been shown to be associated with a significantly accelerated return to gastrointestinal function when compared to standard intravenous fluid therapy.[11]

It has been consistently shown that laparoscopic surgery is associated with a shorter duration of 'normal' post-operative ileus.[203-205] However, this has led to the inference that laparoscopic surgery must therefore be associated with a reduced incidence of 'prolonged' POI. The findings of Millan et al. and the present study do not support this assumption, with both identifying not even an association on univariate analysis.[46] Though it is possible that this was due to inadequate study powering or retrospective design, the independent significance of factors such as age, intra-operative blood loss and respiratory deconditioning raise the important question of whether the occurrence of prolonged gut dysmotility is an inverse relation of the body's capacity to recover from the surgical insult, rather than a relation of the degree of bowel handling or peritoneal breach. These latter two elements are difficult to interrogate retrospectively and there remains much scope to qualify and quantify their influence on the development of ileus.
An important limitation of this study is its retrospective nature. This has hindered the ability to confidently identify risk factors for ‘prolonged’ POI by introducing heterogeneity in the method with which it is defined. Secondly, it is not possible to determine the prevalence and significance of possible confounders particularly with respect to direction of causality (for instance, it was not clear whether complications are a cause or an effect of ileus). However, recording of all patient characteristics, intra-operative factors, post-operative narcotic consumption, and peri-operative biochemical parameters did not extend past Day 3 post-operatively. Given diagnoses of ‘prolonged’ POI were only made after Day 3, it can be inferred that identified variables remain a cause rather than effect. A prospective risk appraisal tool which categorises variables temporally (i.e. pre-, intra-, or post-operatively) may help mitigate this issue.
3.6 Conclusions

The incidence of ‘prolonged’ POI following elective intra-abdominal surgery in the ADHB colorectal cohort was 19.6%. Increasing age and increasing drop in haemoglobin across surgery were independent predictors for developing ‘prolonged’ POI. Procedure, morphine equivalent daily dose, pre-operative creatinine, highest post-operative white cell count, lowest post-operative sodium, and Clavien-Dindo complication grade were all significant associations, but were not found to be independent predictors on logistic regression. The retrospective design and lack of uniform endpoint reporting with respect to occurrence of ‘prolonged’ POI limit the veracity of this study’s findings.

Reporting of ‘prolonged’ POI incidence and risk factors were based on retrospectively identified clinician assessments. This definition lacks transparency and limits the applicability and reproducibility of study results in other colorectal populations. There is a clear requirement for the provision of objective, concise and clinically-quantifiable definitions for ileus to facilitate standardisation of endpoint reporting.

Management of an established episode of ‘prolonged’ POI at ADHB appears to be wholly at the discretion of the overseeing clinician without reference to best-practice guidelines. In the context of the planned randomised trial, there is hence also a need for the provision of concise evidence-based recommendations to standardise clinical management of ‘prolonged’ POI.

The development of an accurate risk stratification system will need meticulous prospective recording of factors pertaining to patient, procedure and peri-operative care with application of a standardised definition of ‘prolonged’ POI. Clinical variables which could not be assessed adequately in this study and require careful evaluation in prospective work include haematological and biochemical markers (specifically – albumin, calcium, and magnesium), estimated intra-operative blood loss, quantifiable indices of intra-operative difficulty and bowel handling, fluid regimen, and wound size. Consideration of variables by temporal separation into the pre-operative, intra-operative and post-operative periods are most conducive to the construction of a predictive tool.
CHAPTER 4:
SYSTEMATIC REVIEW & GLOBAL SURVEY –
DEFINING POST-OPERATIVE ILEUS
4.1 Background

The debilitating impact of POI on patients and healthcare systems alike appears to have been acknowledged by the surgical community with the recent emergence of a plethora of clinical trials investigating potentially therapeutic interventions. However, despite this there remains a lack of an internationally accepted, standardised clinical definition for POI. Moreover, terminology used when describing POI is inconsistent, with little distinction being made between the ‘normal’ obligatory period of gastrointestinal dysmotility following surgery, and the more clinically significant entity of a ‘prolonged’ post-operative ileus which may last several days.

Ambiguity surrounding the definition of POI has made it difficult to reliably and consistently estimate incidence and identify risk factors.[45, 46, 111, 121] However, perhaps the most concerning aspect of this imprecision is the effect it has had on the external validity of clinical trials. Although many trials have examined interventions for POI, there is considerable heterogeneity with respect to the outcomes being used as surrogate markers of its occurrence and resolution. This has consequently made it difficult to compare the relative efficacy of competing therapies and raises questions as to the ultimate applicability of an intervention. This is echoed in Chapter 3 where a key conclusion was the importance of establishing a standardised clinical definition of ileus, especially in the context of the anticipated prospective work.

Studies investigating POI have traditionally based their definitions on ‘time to specified clinical events’. In the context of colorectal surgery, these clinical ‘events’ are most frequently exclusive to the lower gastrointestinal tract (for example – time to flatus and/or time to stool).[41, 45, 46, 111, 206, 207] While this definition modality of ileus offers transparency and reproducibility, its use in the prospective or retrospective identification of a clinical phenomenon characterised by a complex and transitory cluster of clinical manifestations is perhaps misplaced. This is exemplified by a Clinical Consensus published in 2006 which sub-classified ileus based on the relative prominence of presenting symptom clusters.[48] In descending prevalence – Type I ileus was represented by ‘panintestinal’ symptoms (no flatus or bowel movement, presence of nausea and vomiting); Type II by upper gastrointestinal symptoms exclusively (nausea, vomiting, and flatus present); and Type III by lower gastrointestinal symptoms exclusively (no flatus or bowel movement, tolerance of a diet). There is hence a niche for the development of a definition capable of reliably and reproducibly diagnosing ileus despite varying clinical presentation.
4.2 Study Objectives

The aim of this study was to clarify the terminology of POI and propose concise, clinically quantifiable definitions which may be used in the planned prospective work and future studies from other units. This was to be achieved by determining the frequency with which various diagnostic criteria are used in the scientific literature and obtaining opinions of authors who have published in the field.
4.3  **Methods**

A systematic review was conducted and then followed by an online global survey seeking the opinions of authors published in the field.

4.3.1  **Provisional Terminology for Reference**

For clarity and expedience, the term ‘normal’ POI has been used through the following text to denote the period of gastrointestinal dysfunction occurring immediately after surgery; ‘prolonged’ POI refers to this dysfunction continuing past the expected timeframe; and ‘recurrent’ POI refers to a reoccurrence of this dysfunction after apparent resolution.

4.3.2  **Systematic Review**

4.3.2.1  **Systematic Literature Search**

A high-sensitivity, low precision systematic literature search was conducted through the Ovid MEDLINE, EMBASE, CINAHL, Cochrane Collaboration and National Guideline databases in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[208] The search spanned the timeframe January 1996 – December 2011 (inclusive). Studies were limited to randomised controlled trials, systematic reviews and meta-analyses investigating post-operative ileus in humans. There were no language limits. Conference abstracts were not included.

4.3.2.2  **Search Strategy**

Boolean AND/OR operators were used to combine keyword and database-specific indexed subject headings as appropriate. For Ovid MEDLINE and EMBASE, the following search criteria were used: keywords (post-operative ileus.mp OR postsurgical ileus.mp), Medical Subject Heading (MeSH) search terms (Ileus/ OR Intestinal Pseudo-obstruction/; AND Post-operative complication/). For CINAHL, ‘Ileus’ was searched as a keyword and ‘Intestinal Pseudo-obstruction/’ as an indexed subject heading. For both the Cochrane Database of Systematic Reviews and National Guidelines Databases the term ‘ileus’ was searched with a filter to reviews.

4.3.2.3  **Inclusion and Exclusion Criteria**

Inclusion criteria were all publications looking at POI as a *primary* endpoint following abdominal surgery. This meant papers referencing POI as one of several outcomes when examining unrelated interventions were to be excluded. Publications were to evaluate POI using clinically appraisable measurements with specific reference to at least one of the
following: nausea, vomiting, abdominal pain, abdominal distension, presence of bowel sounds, passage of flatus, passage of stool, ability to tolerate an oral diet, need for nasogastric tube placement or radiologic features of ileus. Exclusion criteria were all publications looking at bowel ‘motility’ only without clearly making a link to POI, ileus occurring after non-abdominal procedures, and studies without clinical endpoints.

4.3.2.4 Data Abstraction

Two reviewers (Ryash Vather, Sid Trivedi) independently carried out searches, using titles and abstracts to exclude irrelevant publications and collate a list of those requiring full-text evaluation. This list was compared prior to acquisition of full-texts and then again after reading through them, with any discrepancies on which to include being resolved by discussion and consensus or, if required, arbitration by a senior academic (Ian Bissett). A manual search of the reference lists from systematic reviews and meta-analyses as well as retrieved randomised trials was conducted to identify any other potentially relevant studies. Articles which were to undergo extraction were to be the original published trials – definitions from collated data in systematic reviews and meta-analyses were not used.

The two reviewers independently extracted data from each acquired full-text manuscript. Parameters recorded included year of publication, whether endpoints were for ‘normal’, ‘prolonged’ or ‘recurrent’ POI; primary and secondary clinical criteria used to signal onset or resolution of POI; and type of surgery. If ‘prolonged’ or ‘recurrent’ POI were used, the time point in days at which this definition became applicable was also recorded.

4.3.2.5 Validity Assessment

Qualitative assessment of included publications was not performed as the information of interest was the definition used, and not outcome data.

4.3.3 Online Global Survey

4.3.3.1 Author identification

A high-sensitivity, low precision Ovid MEDLINE search was conducted using the keyword ‘post-operative ileus.mp’. The search was limited to humans, had no language restrictions and spanned the period between January 2001 and December 2011 (inclusive). This time frame was chosen as corresponding authors were to be contacted via email, and this information was not consistently cited in corresponding author information prior to 2001. Publications of interest were those investigating POI as a primary and clinically appraisable endpoint following abdominal surgery, and in contrast to the systematic review, included
retrospective studies as well as prospective studies and reviews. Relevant articles were identified by screening through titles and abstracts with full-text evaluation being undertaken if required.

Email addresses of corresponding authors were electronically extracted from included publications which were in most instances available in the abstract or full-text. If not present, a Google search of the corresponding author’s name was performed to retrieve this. A database was created with author name, institution, specialty, and primary email address. The final list of authors to be approached was significantly broader than those identified in the above systematic review.

4.3.3.2 Survey Construction

A survey was constructed in English to collect information spanning five sections as outlined below. Writing in italics illustrates the wording of ileus-related questions actually posed to participants. A complete survey can be found in Appendix A.

1) Participant personal information [Free-text]
   1. Name.
   2. Specialty.

2) ‘Normal’ ileus [Selection Template]
   *After intra-abdominal surgery almost all patients have a period of physiologic gastrointestinal (GI) dysfunction.*
   1. Terminology
      1) Do you have a specific term for this? If YES, what do you call it.
   2. Definitions.
      1) Which essential criteria must be met in order for you to define a resolution of this gut dysfunction? Please tick as many boxes as necessary.

3) ‘Prolonged’ ileus [Selection Template]
   *In some cases, post-operative GI dysfunction can extend past the expected timeframe.*
   1. Terminology
      1) Do you have a specific term for this? If YES, what do you call it.
   2. Definitions.
i) Which essential criteria must be met in order for you to define this as ongoing post-operative GI dysfunction, which has not yet resolved? Please tick as many boxes as necessary.

ii) What is your expected timeframe (in days) for physiologic post-operative GI tract dysfunction? (i.e. at what time point does this ongoing gut dysfunction stop being physiologic?) If in your opinion this varies with procedure, please list the maximum duration.

4) ‘Recurrent’ ileus [Selection Template]

A final scenario is where post-operative GI dysfunction appears to resolve, only for there to be a reoccurrence of the symptoms & signs indicating GI dysfunction.

1. Terminology
   i) Do you have a specific term for this? If YES, what do you call it.

2. Definitions.
   i) Which essential criteria must be met in order for you to define this as a reoccurrence of post-operative GI dysfunction? Please tick as many boxes as necessary.

5) Questions and comments [Free-text]

Parts 1 and 5 contained free-text boxes where participants were able to electronically enter information if they wished. There were no character or word limits for these sections. Parts 2-4 contained a Selection Template where participants were asked to choose from a list of pre-specified options. If participants were unable to find a suitable choice, an 'other' check box with an adjoining free-text field could be found at the end of the option list thereby allowing participants to manually specify their answer.

4.3.3.3 Survey Publication

The survey was converted to HTML format and published online using Survey Monkey (Palo Alto, California, USA) – a validated and independent commercial service.[209] A single round of beta-testing was commenced by consultant general surgeons at ADHB. Survey feedback was provided electronically by beta-testers, with suggestions for improvement focusing primarily on formatting and layout. A final HTML iteration of the survey was then readied for dissemination.
4.3.3.4 Survey Dissemination

A uniform email template inviting participation was personalised in the salutation to each identified corresponding author (Appendix A). The text of this email contained a link to the online survey. No academic or financial incentives were offered for completion. Emails were sent out to corresponding authors individually, with a follow-up reminder email 2 weeks later to those who did not respond. The online survey was closed 4 weeks after the original invitation was emailed to authors. Survey responses were collated and downloaded as an electronic database file.

4.3.4 Statistics

Basic descriptive statistics were used to summarise data for the systematic review and online global survey, each within their own POI subset. Graphical depictions of information were utilised where appropriate to facilitate ease of interpretation. Given the descriptive nature of this study, no tests of statistical significance were performed.
4.4 **Results**

4.4.1 **Systematic Review**

A total of 3,234 publications were identified for screening using the predefined search strategy, with 3,043 of these being excluded based on titles and abstracts (Figure 4-1). Duplicates were then excluded from the 190 publications exported. Systematic reviews and meta-analyses were identified and their references searched for relevant articles, before also being excluded. Full-texts were acquired for 66 publications, of which 14 were excluded. The reasons for this were assessment of POI as a secondary outcome (n=6), evaluation of POI using a non-clinical approach (n=3), lack of a definition for POI (n=3), inclusion of non-abdominal procedures (n=1), and lack of randomisation (n=1). Final extraction was performed on the remaining 52 publications.[41, 141, 146, 160, 172, 173, 178, 210-254]

'Normal' POI was defined in 44 publications;[41, 141, 146, 160, 172, 173, 178, 210-247, 255] 'prolonged' POI in 5 publications;[250-254] and definitions for both found in 3 publications.[160, 248, 249] No publications referenced recurrent POI. Seven studies used composite endpoints to define POI with six using the GI-3 (passage of flatus, passage of stool, and toleration of oral diet) and one using the GI-2 (passage of stool and toleration of an oral diet).[214, 219, 228, 242, 243, 246, 247] These were split into their individual clinical components before being entered into the data sheet. All remaining publications outlined specific clinical criteria in their definitions.

4.4.1.1 **'Normal' POI**

The relative frequency of clinical criteria used to define resolution of 'normal' POI in the 47 publications identified are outlined in Figure 4-2.[41, 141, 146, 160, 172, 173, 178, 210-249, 255] The most commonly used criteria were the passage of flatus (83%) and stool (79%), followed by ability to tolerate an oral diet (28%) and presence of bowel sounds (13%). All remaining criteria were used to define resolution of 'normal' ileus in less than 10% of identified publications. These included absence of nausea or vomiting (9%), absence of abdominal pain (9%), absence of abdominal distension (6%), radiological evidence of resolution (4%), and removal of nasogastric tube (6%).

Most studies investigated 'normal' POI in colonic (75%) or rectal (43%) procedures with a smaller proportion describing its occurrence in the gynaecologic (17%), hepatobiliary (6%), vascular (4%), and urologic (4%) cohorts. The open technique (57%) was employed more frequently than laparoscopic (15%) or mixed/unstated (28%) techniques in the publications analysed.
Figure 4-1 PRISMA flow chart illustrating the identification, screening and exclusion process.
Figure 4-2 ‘Normal’ POI – systematic review.
Relative frequency of clinical criteria used to define resolution of ‘normal’ POI in the 47 publications identified in the systematic review.
Figure 4-3 ‘Prolonged’ POI – systematic review.
Relative frequency of clinical criteria used to define onset of ‘prolonged’ POI in the 8 publications identified in the systematic review.
4.4.1.2 ‘Prolonged’ POI

Eight publications were identified which contained definitions for ‘prolonged’ POI (Figure 4-3).[160, 248-254] Absence of passage of flatus (50%) and stool (88%) were the primary means of diagnosing ‘prolonged’ POI, followed by ongoing nausea and vomiting (25%) and need for nasogastric tube insertion (25%). Less frequently cited criteria were inability to tolerate and oral diet (12.5%), absence of bowel sounds (12.5%), ongoing abdominal pain (12.5%), ongoing abdominal distension (12.5%), and radiologic evidence of ileus (12.5%). The time point at which the definition for ‘prolonged’ POI was applied varied considerably (range 1-7 days) with a mean of 3.9 days and median of 4 days.

Most publications investigated ‘prolonged’ POI after colonic (63%) or rectal (38%) surgery, with a smaller number describing its occurrence after small bowel (25%), urologic (12.5%) and vascular (12.5%) cases. The open technique (63%) was employed more frequently than mixed open/laparoscopic or unstated (38%) technique in the publications analysed.

4.4.1.3 ‘Recurrent’ POI

None of the identified publications referenced ‘recurrent’ POI.

4.4.2 Online Global Survey

4.4.2.1 Survey Response

A total of 118 individual corresponding authors were identified and invited to participate in the online survey. Upon termination of the survey 4-weeks after dissemination, 45 authors had responded (38% response rate) with 44 completing the survey in its entirety. Of these, 31 belonged to a surgical specialty (69%), 7 to anaesthesiology or peri-operative medicine (16%), 4 to a medical specialty (9%), and the remaining 3 to emergency medicine, obstetrics and gynaecology, and full-time academia. In total, 22 countries were represented with respondents being based mostly in either the United States (13 participants; 29%) or United Kingdom (4 participants; 9%).

4.4.2.2 ‘Normal’ POI

A specific term for ‘normal’ POI was used by 31 respondents (71%), with over half referring to it as ‘post-operative ileus’ not further specified (Table 4-1). Other terminology were used less commonly to describe this syndrome and included ‘adynamic ileus’ (13%), ‘physiologic ileus’ (13%), ‘normal POI’ (10%), ‘post-operative dysmotility’ (3%), and ‘GI tract dysfunction’ (3%).
Responses to the question: "If you have a specific term for the period of gastrointestinal dysfunction seen immediately after intra-abdominal surgery, what do you call it?"

Passage of flatus (68%) and tolerance of an oral diet (61%) were the most commonly quoted essential criteria to be met when defining its resolution (Figure 4-4). Other criteria cited less frequently included absence of nausea and vomiting (36%), absence of distension (34%), passage of stool (30%), presence of bowel sounds (25%), radiologic evidence of ileus (9%), absence of abdominal pain (5%), and removal of nasogastric tube (5%).

4.4.2.3 ‘Prolonged’ POI

A total of 34 respondents (74%) reported having a specific term for this syndrome with 47% referring to it as ‘prolonged POI’ (Table 4-2). Less frequently used terminology included ‘POI [not further specified]’ (21%), ‘paralytic POI’ (15%), ‘pathologic POI’ (6%), ‘severe POI’ (3%), ‘adynamic ileus’ (3%), ‘prolonged GI tract dysfunction’ (3%), and ‘prolonged post-operative dysmotility’ (3%).

Responses to the question: "In some cases, post-operative gastrointestinal dysfunction can extend past the expected timeframe. If you have a specific term for this, what do you call it?"

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Number of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged POI</td>
<td>16 (47%)</td>
</tr>
<tr>
<td>POI [not further specified]</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Paralytic POI</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>Pathologic POI</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Severe POI</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Adynamic ileus</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Prolonged GI tract dysfunction</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Prolonged post-operative dysmotility</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 4-2 ‘Prolonged’ POI – global survey.

Responses to the question: "If you have a specific term for the period of gastrointestinal dysfunction seen immediately after intra-abdominal surgery, what do you call it?"
Figure 4-4 ‘Normal’ POI – global survey.

Responses to the question: “After intra-abdominal surgery almost all patients have a period of gastrointestinal dysfunction. Which essential criteria must be met in order for you to define a resolution of this gut dysfunction? Please check as many boxes as necessary”.

- Passage of flatus: 68%
- Passage of stool: 30%
- Tolerance of an oral diet: 61%
- Presence of bowel sounds: 25%
- Absence of nausea or vomiting: 36%
- Absence of abdominal pain: 5%
- Absence of abdominal distension: 34%
- Radiologic evidence: 9%
- Removal of NG tube: 5%
Figure 4-5 ‘Prolonged’ and ‘Recurrent’ POI – global survey.

Collated responses to the questions “Which essential criteria must be met in order for you to define this as ongoing post-operative GI dysfunction, which has not yet resolved? Please check as many boxes as necessary” – displayed as ‘prolonged’ POI; and “Which essential criteria must be met in order for you to define a reoccurrence of post-operative GI dysfunction which appeared to have previously resolved? Please check as many boxes as necessary” – displayed as ‘recurrent’ POI.
Figure 4-6 ‘Prolonged’ POI – global survey.

Responses to the question: “What is your expected timeframe (in days) for physiologic post-operative GI tract dysfunction? (i.e. at what time point does this ongoing dysfunction stop being physiologic?). If in your opinion this varies with procedure, please list the maximum duration.”
Most commonly cited essential criteria to be met when defining a ‘prolonged’ POI (Figure 4-5) were inability to tolerate an oral diet (82%), absence of flatus (70%), ongoing nausea and vomiting (61%), and ongoing abdominal distension (52%). Criteria cited less frequently included absence of stool (39%), absence of bowel sounds (32%), need for nasogastric tube insertion (27%), radiologic evidence of ileus (20%), and ongoing abdominal pain (16%).

When asked at what point an ileus moved from being ‘normal’ to ‘prolonged’, responses ranged from 1-7 days, with a mean of 3.9 days and median of 4 days (Figure 4-6). Out of the 44 respondents, three stated this depended on whether surgery was laparoscopic or open without providing a specific time point.

4.4.2.4  ‘Recurrent’ POI

A total of 26 respondents (59%) indicated they had a specific term for this syndrome with 46% labelling it ‘recurrent POI’ (Table 4-3). Other terminology used less commonly to describe the syndrome included ‘paralytic POI’ (15%), ‘pathologic POI’ (15%), ‘POI [not further specified]’ (8%), ‘adynamic ileus’ (4%), ‘GI tract dysfunction’ (4%), ‘small bowel obstruction’ (4%), and ‘primary POI’ (4%).

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Number of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent POI</td>
<td>12 (46%)</td>
</tr>
<tr>
<td>Paralytic POI</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Pathologic POI</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>POI [not further specified]</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Adynamic ileus</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>GI tract dysfunction</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Primary POI</td>
<td>1 (4%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26</strong></td>
</tr>
</tbody>
</table>

Table 4-3 ‘Recurrent’ POI – global survey.

Responses to the question: “A possible scenario is where post-operative GI dysfunction appears to resolve, only for there to be a reoccurrence of the symptoms and signs indicating GI dysfunction. If you have a specific term for this, what is it?”.

Essential criteria to be met in order to define an ileus as recurrent echoed that for defining a ‘prolonged’ POI (Figure 4-5), with the most common being inability to tolerate an oral diet (77%), ongoing nausea and vomiting (68%), absence of flatus (61%), and ongoing abdominal distension (59%). Other criteria were cited less frequently included absence of stool (39%), radiologic evidence of ileus (30%), ongoing abdominal pain (27%), need for
nasogastric tube insertion (25%), and absence of bowel sounds (20%). In the free-text section of this question, four of the 44 respondents stated a diagnosis of recurrent POI could only be made after excluding a surgical complication as an underlying cause.
4.5 **Recommended Definitions**

Data from the systematic review and global survey were amalgamated to propose the following terminology and definitions for post-operative ileus.

4.5.1 **“Post-operative ileus (POI)”**

Defined as the interval from surgery until *both* the following criteria are met:

a. Passage of flatus OR stool
b. Tolerance of an oral diet.

These events should occur before Day 4 post-operatively.

4.5.2 **“Prolonged post-operative ileus (PPOI)”**

Defined if *2* or more of the following *5* criteria are met on or after Day 4 post-operatively without prior resolution of “post-operative ileus” (as described above):

a. Nausea OR vomiting
b. Inability to tolerate an oral diet
c. Absence of flatus AND stool
d. Abdominal distension
e. Radiologic confirmation.

Concordance of this definition with the global survey was 80%, with 35 out of 44 participants citing two or more of these as essential criteria.

4.5.3 **“Recurrent post-operative ileus (Recurrent POI)”**

Defined if *2* or more of the following *5* criteria are met *after* an apparent resolution of “post-operative ileus” (as described above):

a. Nausea OR vomiting
b. Inability to tolerate an oral diet
c. Absence of flatus AND stool
d. Abdominal distension
e. Radiologic confirmation.

Concordance of this definition with the global survey was 75%, with 33 out of 44 participants citing two or more of these as essential criteria.
4.6 Discussion

The present study has shown that a majority of clinical trials published over the last 15 years focused on shortening the duration of a 'normal' POI, with only a few addressing the problem of a 'prolonged' POI. A perceptible degree of concordance was noted in the systematic review and global survey with respect to defining the resolution of a 'normal' ileus, with passage of flatus, passage of stool and tolerance of an oral diet being principal elements. The small number of trials investigating 'prolonged' POI and the broad distribution of essential criteria made a systematic review of little use when attempting to standardise a definition for this syndrome. Conversely, the global survey revealed that for both 'prolonged' and 'recurrent' POI, ongoing nausea and vomiting, inability to tolerate an oral diet, absence of flatus and stool, and distension were key elements of diagnosis. Both systematic review and global survey identified a prolonged POI as one which continues past Day 4 post-operatively.

Definitions extracted from publications identified in the systematic review are likely to have been used by respective authors prior to study execution. Given there is no standardised definition for POI, the results of this systematic review are therefore analogous to those from the global survey in that both are fundamentally a collation of academic opinion. It is proposed that the broad opinion base on which this study’s recommended definitions were constructed may mean they hold greater generalizability to other authors and institutions.

'Ileus' takes its origins from the ancient Greek verb 'eileos', whose literal meaning is to 'twist or squeeze'.[256] It is clear that in the context of post-operative ileus this is a misnomer, as the primary pathological process appears to be one of atony or hypomotility. Over the last century 'ileus' (as a single word) has frequently been used as an alternate term for bowel obstruction, and it is only recently that the jargon for these distinct clinical entities has differentiated appropriately. The ambiguity with which this has evolved has perhaps foreshadowed the interchangeable and somewhat confusing terminology currently used to describe POI, and is exemplified well by noting the heterogeneity with which definitions were applied by clinical trials and academics who have published in the field.

Post-operative ileus is a clinical diagnosis which has traditionally been associated with a variable combination of upper and lower gastrointestinal symptoms.[105, 109] Radiologic investigations may be used in conjunction with clinical diagnosis to confirm POI but are often more importantly reserved to exclude bowel obstruction or a precipitating cause.[48] While most studies in the systematic review outlined individual clinical criteria, seven publications used the GI-2 or GI-3 – gastrointestinal functional recovery composite endpoints – to define
a resolving POI. Although these composite endpoints lend elegance and expediency to outlining a definition, they make reference to the same criteria as other publications and do not add to the standardisation of a definition.

A clinical consensus update published in 2006 by Delaney et al. has endeavoured to provide definitions for POI. It makes a distinction between primary and secondary POI, and also classifies it as Type I-III depending on the relative prominence of upper or lower gastrointestinal symptom clusters. The clinical consensus describes POI as being the interval between surgery and passage of flatus or stool and tolerance of an oral diet, which is consistent with our proposed definition. It is suggested that an ileus is ‘prolonged’ if it extends past Day 5 post-operatively for open abdominal surgery or Day 3 for laparoscopic abdominal surgery, and recurrent if there is nausea or vomiting, bloating, and absence of flatus or stool after apparent resolution.[48] Our proposed definitions for these are two or more of nausea/vomiting, inability to tolerate oral diet, absence of flatus and stool, distension or radiologic confirmation – occurring on or after Day 4 post-operatively for prolonged POI, and in the case of recurrent POI occurring after an apparent resolution of POI. Importantly, despite the proficiency of the Clinical Consensus committee, it appears the attempt at standardisation has been unsuccessful with the present study finding only 6 of the 31 trials published since 2006 conforming to them.[160, 173, 214, 218, 246, 247]

Perhaps the biggest drawback of a non-standardised definition is the inability to impartially compare competing therapeutic interventions. For instance, a Cochrane review examining systemic prokinetics for the treatment of POI meta-analysed data from 39 randomised trials. Primary outcomes evaluated by individual trials differed considerably, revolving mainly around a variable mixture of time to stool, time to flatus, toleration of an oral diet, or a collation of these expressed as composite endpoints.[77] It is not possible to objectively meta-analyse related interventions or contrast competing interventions when subtle differences exist in their outcome measures. A degree of homogeneity with respect to endpoints is therefore necessary in future trials to prevent potential bias.

It is pertinent to note that most identified literature evaluated interventions in the context of ‘normal’ POI, and used this as a proxy for anticipated outcomes in prolonged POI. It is the latter of these two entities which is clinically and financially significant, and deserves greater attention. Variability with respect to terminology and definitions has led to a ‘generic grouping’ phenomenon, and this has subsequently made it difficult to consider incidence, risk factors, patient outcomes and fiscal burden as they relate to ‘normal’ and prolonged POI individually. This inconsistency is also likely to diminish the internal and external validity of
any institutional audit practices (further compounded by the fact that coding of POI in most centres is wholly at the discretion of the clinician).[257] Indeed, much emphasis is given in the literature to Goldstein et al.’s estimation of the annual $US1.5 billion cost of managing POI in the United States. Identification of cases of POI in this study were based retrospectively on *coded* data, and the authors make the clear point that “studies on POI have been limited, because no standardized nomenclature or grading system is available to objectively define the clinical scope and the clinical relevance of this common post-operative problem”. The authors also go on to state that “patients with prolonged POI are expected to undergo a greater number of interventions and are at greater risk for complications associated with the prolonged hospital stay”. [112] Much scope therefore remains for trials examining interventions in this group of patients exclusively.

The present study has considered ileus following abdominal surgery only. However, POI is a recognised entity after procedures not involving breach of the peritoneum, most notably spinal operations. The pathogenesis of POI in this group is poorly elucidated, but is presumed to also relate to narcotic analgesia, autonomic shift, fluid imbalances and the surgical stress response.[105] It may therefore be plausible to extend the proposed definitions to apply to POI following non-abdominal surgery, and indeed standardisation with respect to endpoint reporting may serve to similarly improve the external validity of trials conducted in this patient cohort.
4.7 Conclusion

There is considerable heterogeneity with which terminology and definitions of post-operative ileus are used. Three classes can be broadly identified – post-operative ileus, prolonged post-operative ileus and recurrent post-operative ileus. A prolonged post-operative ileus is one which continues past Day 4 post-operatively. Clinical definitions have been proposed based on the available literature and author opinion. Standardisation of endpoints in future studies is required in order to accurately determine the incidence of prolonged POI, identify risk factors for its occurrence, and to allow objective comparison between competing interventions.
CHAPTER 5:
NARRATIVE REVIEW –
CONSERVATIVE MANAGEMENT OF PROLONGED
POST-OPERATIVE ILEUS
5.1 **Background**

Studies published over the last decade have focused almost exclusively on the evaluation of novel therapies to reduce the duration of a ‘normal’ ileus following abdominal surgery. By contrast, literature outlining standard best-practice management strategies for prolonged post-operative ileus (PPOI) is still nebulous and inconsistent. This appears to have perpetuated the ‘drip and suck’ panacea widely utilised as first line management by clinicians.[258-260] As previously described, there is a growing body of evidence which demonstrates that PPOI runs a much more sinister course than ‘normal’ POI whereby it prolongs patient recovery after surgery, increases risk of post-operative morbidity, and confers a financial and resource-intensive burden on healthcare institutions.[112, 121, 261, 262] In the absence of effective therapeutic measures for an episode of PPOI it is therefore valuable to identify conservative management strategies which may be conducive to its resolution.

A second consideration relates to the findings of the retrospective cohort study outlined in Chapter 3. It appeared that patients at ADHB who had developed PPOI following surgery were managed by the overseeing clinical team without reference to any guidelines. While this does not necessarily translate to suboptimal patient care, it is proposed that the circulation of a protocol which summarises literature and provides clinical recommendations for the management of PPOI may aid junior medical, nursing and allied health staff, particularly during on-call hours. It was also surmised in Chapter 3 that the construction of such guidelines is central to the design of the planned clinical trial, where it is necessary to standardise patient management in differing treatment arms.

Distilled and concise evidence-based recommendations for the management of PPOI are hence valuable for general readership, local practice, and the anticipated prospective research.

5.2 **Study Objective**

The aim of this text was to perform a narrative review of the current literature to identify conservative management strategies which may aid resolution of PPOI. This information was then used to generate succinct recommendations with associated Strength of Recommendation Taxonomy.
5.3 **Methods**

5.3.1 **Literature Search**

A high sensitivity, low precision literature search was conducted through the Ovid MEDLINE, EMBASE, Google Scholar and Cochrane Collaboration databases from inception to July 2012. Filters were set in each database limiting searches to human subjects and publication in the English language. No limits were placed on study type with all of the following being screened: meta-analyses, systematic reviews, randomised controlled trials, case-control studies, consensus guidelines, observational cohort studies, case-reports, and anecdotal evidence. A systematic review was not performed as this would require repeated tailored literature searches and data abstraction for each recommendation, and is therefore outside of the scope of a review aimed at providing a concise overview of management strategies described in the literature.

5.3.2 **Search Strategy**

Boolean AND/OR operators were used to combine keyword and database-specific indexed subject headings as appropriate. For Ovid MEDLINE and EMBASE, search criteria utilised either keywords (post-operative ileus.mp OR postsurgical ileus.mp) or MeSH terminology (Ileus/ OR Intestinal Pseudo-obstruction/; AND Post-operative complication/). Google Scholar was searched using free-text keyword entries, checking the ‘all of the words’ or ‘exact phrase’ options as appropriate. Identified literature included patents, indexed articles, and relevant book chapters. The Cochrane Database of Systematic Reviews was searched for the term ‘ileus’ with a filter to reviews.

5.3.3 **Inclusion and Exclusion Criteria**

Inclusion criteria were all publications examining ‘normal’ ileus, prolonged ileus or gastrointestinal dysmotility after surgery. This low precision approach was adopted because, as outlined in Chapter 4, there is considerable heterogeneity with respect to terminology and definitions used for different forms of ileus. It was assumed that an intervention capable of conferring a beneficial effect in ‘normal’ ileus could reasonably be anticipated to aid or expedite resolution of an episode of PPOI. Exclusion criteria were all studies describing gut dysfunction not related to the post-operative period and studies investigating experimental or unproven interventions.
5.3.4 Data Abstraction

Articles identified on respective databases were screened by a single reviewer (Ryash Vather) using title and abstract. Full-texts were acquired for those with content potentially relevant to the intended narrative review. A manual search of the reference lists from these full-texts was conducted to identify any other potentially relevant publications.

5.3.5 Strength of Recommendation Taxonomy

Review of the literature was followed by a summary of relevant findings and synthesis of concise recommendations for the management of PPOI. These were in turn accompanied by Strength of Recommendation Taxonomy (SORT) gradings of A, B or C (Table 5-1). SORT ratings consider the quality, quantity and consistency of evidence and allow authors to rate individual articles or bodies of evidence. The principal focus of the taxonomy are changes in patient-oriented outcomes as measured by morbidity and mortality.[263]

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<tr>
<th>Strength of Recommendation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>A</td>
<td>Recommendation based on consistent and good quality patient-oriented evidence.</td>
</tr>
<tr>
<td>B</td>
<td>Recommendation based on inconsistent or limited quality patient-oriented evidence.</td>
</tr>
<tr>
<td>C</td>
<td>Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, and case series for studies of diagnosis, treatment, prevention, or screening.</td>
</tr>
</tbody>
</table>

Table 5-1 Strength of Recommendation Taxonomy (SORT). [263]
5.4 **Recommendations**

5.4.1 **Electrolyte Correction**

*Patients with PPOI warrant regular review and correction of the following electrolytes: sodium, potassium, magnesium and calcium (Grade B).*

It has been postulated that electrolyte derangement is a critical step in the pathogenesis of ileus.[73] This hypothesis has arisen as a culmination of the well described effects of electrolyte disturbances on gastrointestinal motility[56] and the observation that such disturbances are often seen to occur during an episode of PPOI.[73, 74]

A seminal editorial published in 1971 identified hypokalaemia as a possible cause for refractory ileus in 18 post-operative patients, with its correction being associated with resolution. This study however lacked a control arm and it is unclear if the result reflected restoration of normal motility due to electrolyte correction or spontaneous resolution.[75] A retrospective review by Kronberg et al. investigating risk factors for the occurrence of prolonged ileus noted significant correlations between PPOI and post-operative hypokalaemia and hypocalcaemia; hypermagnesaemia was also correlated although this trend was not significant.[45] It was likewise demonstrated in the retrospective cohort study outlined Chapter 3 that post-operative hyponatremia was a significant correlate of PPOI. Importantly, the associations in both studies did not persist as independent predictors of PPOI on logistic regression analysis. Moreover, the retrospective nature of these studies has hindered the ability to establish direction of causality. While it is possible that electrolyte fluctuations precipitate myenteric dysfunction, it is equally feasible that the gastrointestinal fluid sequestration known to occur in PPOI initiates and/or perpetuates these derangements.[2, 76]

5.4.2 **Review Analgesia Prescription**

*Patients with PPOI require review of their analgesic prescription. Narcotic pain relief should be weaned and substituted sequentially with regular paracetamol, regular non-steroidal anti-inflammatory drugs (NSAIDs) if not contraindicated, and regular or as-required Tramadol. Opiates are to be reserved for breakthrough pain (Grade A).*

Paracetamol (acetaminophen) is a safe, tolerable and effective first-line medication for the management of post-operative pain, and should be used to establish a ‘baseline level’ of analgesia.[264] NSAIDs are effective in managing post-operative pain, and importantly have been shown to reduce the risk of developing PPOI (independent of narcotic use) with no
increase in post-operative complications. This is believed to relate to their ability to inhibit the COX enzyme, thereby reducing formation of pro-inflammatory prostanoids. The preventive properties of NSAIDs have not yet been proven to extend to a therapeutic role in PPOI, although they are postulated to be beneficial in this setting both primarily and by reducing need for narcotic analgesia. Relative contraindications to the prescription of NSAIDs include increasing patient age, concurrent renal impairment or a history of peptic ulcers. A prescription combining paracetamol and NSAIDs has been shown in a qualitative systematic review of 21 studies to provide more effective analgesia than either modality alone.

Tramadol is a monoaminergic reuptake inhibitor and weak centrally acting μ-opioid receptor agonist, which has little influence on gastrointestinal motor function. It has been shown to be of comparable or greater efficacy than paracetamol when administered orally for post-operative pain, and importantly exhibits fewer gastrointestinal and respiratory side effects than morphine. It is hence well suited as an intermediary step between basic and opiate analgesia.

The influence of narcotic analgesia on gastrointestinal dysmotility has been well described in nonsurgical populations and has been extrapolated to the post-operative setting where it is thought to be a fundamental step in the pathogenesis of an ileus. This supposition is strongly corroborated by the recent success of Alvimopan – a peripheral-acting μ-opioid receptor antagonist – in accelerating time to gut function post-operatively. An analgesic prescription which minimises opiate use in favour of more basic forms of analgesia will therefore not exacerbate the gastrointestinal dysfunction seen in PPOI.

5.4.3 Nasogastric Tube Insertion

Patients who develop PPOI with nausea or vomiting as a prominent feature will benefit from nasogastric decompression (Grade C).

A considerable body of Grade A evidence now exists to support selective vs. routine nasogastric tube insertion following surgery. Routine post-operative nasogastric placement has been associated with a prolonged return to normal gastrointestinal function and a significantly higher risk of developing pneumonia, atelectasis, and fever. No evidence exists to suggest routine nasogastric insertion is associated with a higher incidence of PPOI, although studies investigating this have been subject to confounding or have taken place within a multimodal enhanced recovery programme. Selective vs. no nasogastric decompression in patients with post-operative nausea and vomiting has never
been investigated. The presumed benefits of nasogastric insertion in this patient group are symptomatic relief and reducing risk of aspiration by draining stomach contents.

5.4.4 Intravenous Fluid Therapy

*Isotonic dextrose-saline crystalloid solution administered within a restrictive regimen (1-1.25ml/kg/hr) is the post-operative maintenance fluid of choice (Grade B). Nasogastric losses or vomiting as a result of gut sequestration in PPOI should be replaced in approximately equivalent volume with normal 0.9% saline or balanced isotonic crystalloid solution containing supplemental potassium (Grade C).*

5.4.4.1 Maintenance

The use of isotonic dextrose-saline crystalloid solution as a maintenance fluid is common practice post-operatively.[273, 274] Dextrose serves to provide a carbohydrate substrate for metabolism and the low salt content of such solutions prevent sodium over-infusion.[275-277] The question of whether to administer maintenance fluid within a restrictive or standard regimen has however become a contentious issue. Overzealous peri-operative intravenous fluid administration is known to precipitate gut wall oedema, and it has been postulated that this is a significant contributory factor to the development of ileus.[10] Lobo et al. initially showed that a restrictive post-operative fluid prescription following colonic resection was associated with a significantly expedited return of gastrointestinal function (i.e. a shortened duration of ‘normal’ POI) when compared to standard intravenous fluid therapy.[11] This finding appeared to contradict the long held surgical dogma that liberal intravenous fluid administration was necessary to offset peri-operative hypotension (due to either anaesthesia, dehydration or blood loss) and therefore maintain adequate organ perfusion.[274] A recent meta-analysis comparing the effects of restrictive vs. standard maintenance fluid regimens showed that a restrictive prescription significantly reduced post-operative morbidity but not mortality.[78] However, only four of the nine trials identified in this review specifically investigated the effect of post-operative fluids, or intra- and post-operative fluids on gastrointestinal function,[11, 278-280] with only one showing a significant improvement with restrictive fluid administration.[11] There is limited literature which has extended to specifically validate the efficacy of a restrictive fluid prescription in reducing the duration of an established case of PPOI. However, given the probable beneficial effects of such a regimen in shortening ‘normal’ POI (and the detrimental effects of a liberal regimen in the same), it can be reasonably assumed that a restrictive prescription will be conducive to recovery from PPOI or at worst, not perpetuate it.
5.4.4.2 Replacement

Nausea and vomiting are central features of PPOI, and are the result of extracellular fluid sequestration in the stomach and small bowel. Fluid losses are therefore typically rich in electrolytes (specifically sodium, potassium and chloride), and replacement has traditionally involved administration of an equivalent volume of sodium and potassium rich crystalloid solution.[273, 274] Emerging evidence has however begun to support the use of a balanced isotonic crystalloid solution (such as Ringer’s Lactate or Plasma-Lyte 148) as a replacement fluid. Balanced crystalloids have an electrolyte composition which more closely resembles plasma, and circumvent the hyperchloraemic acidosis which may occur with the administration of 0.9% saline.[275, 281, 282] It has also recently been demonstrated that infusion of 0.9% saline in healthy adults is associated with a reduced renal plasma flow and cortical perfusion pressure when compared to equivalent administration of balanced crystalloid.[283] This finding has however yet to be translated to patients who are fluid-deplete. Volume of gastric losses should be used as an adjunct to clinical assessment of hydration status when evaluating the degree of intravascular depletion and replacement of deficit.[275]

5.4.5 Ambulation

It is advisable for patients who develop PPOI to ambulate regularly, with assistance as necessary (Grade C).

It was initially thought that ambulation exerted a prokinetic effect on gastrointestinal motility, which despite a lack of scientific evidence, led to it becoming a central component of the conservative management of PPOI. To date, a single study has directly investigated the effects of ambulation following laparotomy and found that this did not confer any significant differences in myoelectric activity in the stomach, small bowel or colon.[284] However, it is believed that mobilisation is beneficial in reducing the risk of developing post-operative respiratory complications (by increasing tidal volume and preventing or reversing alveolar collapse) and thrombotic complications (by promoting intravascular blood flow particularly from the extremities). This has led it to its inclusion in multimodal enhanced recovery programmes.[101, 285] While such programmes have consistently shown a reduced incidence of PPOI, it is not possible to directly attribute this to any single intervention.[286] It is therefore recommended that patients with PPOI ambulate regularly.
5.4.6 Parenteral Nutrition

*Parenteral nutrition should be commenced in patients who are unable to tolerate an adequate oral intake due to PPOI for more than 7 days post-operatively (Grade A). Upon resolution of PPOI and resumption of an oral diet, parenteral nutrition may be ceased without weaning (Grade A).*

An important consequence of PPOI is the inability to tolerate an oral diet, and therefore failure to meet daily caloric needs. Post-operative nutritional depletion has been consistently associated with poorer outcomes following surgery (especially those related to sepsis and wound healing),[287, 288] and this is thought to be exacerbated in the context of pre-operative malnutrition.[289, 290]

Both the European and American Societies for Parenteral and Enteral Nutrition have published guidelines recommending administration of parenteral nutrition after 7 days of inadequate oral intake.[291, 292] Parenteral formulations should aim to deliver between 25-30kcal/kg of energy per day, in a protein:fat:carbohydrate caloric ratio of 20:30:50.[292] Importantly, calculations should be based on *ideal* body weight to avoid caloric surplus in obese patients.[293] No clear evidence exists for inclusion of vitamins or minerals in short-term parenteral formulations although this is recommended by both guidelines.[291, 292]

Post-operative enteral feeding is associated with a lower rate of complications and length of hospital stay when compared to parenteral nutrition, and should therefore be recommenced as soon as it becomes a viable option.[294] Weaning of parenteral nutrition was previously recommended for fear of rebound hypoglycaemia.[295] However, recent studies have shown that this does not occur upon abrupt cessation,[296] with blood glucose levels normalising within 60 minutes.[297]

5.4.7 Exclusion of Precipitating Pathology or Alternate Diagnoses

*Sepsis is a common precipitant of PPOI, and early post-operative small bowel obstruction may easily be mistaken for it. Suspicion of either entity warrants exclusion using clinical assessment and appropriate imaging (Grade C).*

A distinction has been made in the literature between primary and secondary post-operative ileus – the former occurring in the absence and the latter in the presence of a precipitating complication (such as an anastomotic leak or other sepsis).[48] It is of great importance to sufficiently differentiate these entities, given the propensity of one to resolve spontaneously with conservative measures and the other to require additional intervention. Likewise, early
post-operative small bowel obstruction (EPSBO) must be distinguished from PPOI, as its clinical similarity has previously led to under-diagnosis and therefore mismanagement.\[108\]

No clear algorithm exists for confidently differentiating secondary ileus or EPSBO from primary ileus, although a combination of clinical assessment and radiologic evaluation has been proposed as the most feasible means.\[48, 108\]

Post-operative fever in conjunction with tachycardia, hypotension or raised inflammatory markers suggest a source of sepsis, and in the setting of intra-abdominal surgery should prompt investigation to exclude intra-abdominal, wound, chest or urinary infection.\[107\] Importantly, PPOI occurs several days after surgery, and a fever at this time is therefore separate and distinct from ‘early post-operative fever’, which occurs 0-48 hours post-surgery and is most frequently attributable to the metabolic response to injury.\[298\] If a clear source of infection is not identified on examination, site-specific culture or plain radiography, then computed tomography (CT) is advisable to exclude intra-abdominal sepsis.\[107\]

It has been suggested that EPSBO may be partly distinguished from PPOI if there is initial passage of flatus and stool followed by complete cessation. Nausea, vomiting and distension may be features of both entities, although the presence of colicky abdominal pain points more towards obstruction. Differentiation based on symptoms and signs are unreliable, and imaging is recommended if EPSBO is clinically suspected.\[108\] Plain abdominal radiography may reveal the ‘classical’ findings of an ileus – distended small and large bowel, with air-fluid levels. In contrast, dilated small bowel with paucity of gas in the colon is more indicative of an obstruction. However, plain film interpretation is often not clear-cut, and in this setting the use of CT (shown in one study with a cohort of 36 patients to differentiate between PPOI and EPSBO with 100% sensitivity and specificity) is a viable option.\[299\]
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<tbody>
<tr>
<td>Delaney et al.</td>
<td>2006</td>
</tr>
<tr>
<td>Frager et al.</td>
<td>1995</td>
</tr>
</tbody>
</table>

**Table 5-2** Summary of key publications used to formulate recommendations.
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular review of electrolytes.</td>
<td>B</td>
</tr>
<tr>
<td>Review analgesic prescription with weaning of narcotics and substitution</td>
<td>A</td>
</tr>
<tr>
<td>with paracetamol, non-steroidal anti-inflammatories, and Tramadol.</td>
<td></td>
</tr>
<tr>
<td>Nasogastric decompression for those with nausea or vomiting.</td>
<td>C</td>
</tr>
<tr>
<td>Intravenous fluid administration:</td>
<td></td>
</tr>
<tr>
<td>Maintenance fluids – isotonic dextrose-saline crystalloid solution administered</td>
<td>B</td>
</tr>
<tr>
<td>within a restrictive regimen (1-1.25ml/kg/hr).</td>
<td></td>
</tr>
<tr>
<td>Replacement fluids – normal saline or balanced isotonic crystalloid solution</td>
<td>C</td>
</tr>
<tr>
<td>containing supplemental potassium, in equivalent volume to losses.</td>
<td></td>
</tr>
<tr>
<td>Regular ambulation.</td>
<td>C</td>
</tr>
<tr>
<td>Parenteral nutrition if inadequate oral intake for &gt;7 days post-operatively.</td>
<td>A</td>
</tr>
<tr>
<td>Cessation of parenteral nutrition without weaning upon resumption of oral diet.</td>
<td>A</td>
</tr>
<tr>
<td>Exclusion of precipitating pathology or alternate diagnoses.</td>
<td>C</td>
</tr>
</tbody>
</table>

Table 5-3 Summary of Recommendations.
5.5 Conclusions

Concise recommendations for the conservative management of PPOI have been described (Table 5-2 & Table 5-3) and may serve to standardise in-patient care. Several of these strategies however are “based on consensus, usual practice or opinion” thereby classifying them as evidence of Grade C strength. Further research is required to validate many of the outlined management recommendations for PPOI.
CHAPTER 6:
LABORATORY ANALYSIS –
QUANTITATIVE STABILITY TESTING OF GASTROGRAFIN
6.1 Background

Gastrografin is a commercially available medication packaged as a 100mL solution, with each dose containing 100mg sodium diatrizoate and 660mg meglumine diatrizoate.[185] Sodium and meglumine diatrizoate salts each contain a benzene ring carrying three iodine atoms (Figure 6-1 & Figure 6-2) and are responsible for the compound’s hyperosmolarity.[186] It has been proposed that the remedial properties of orally or rectally administered contrast media such as Gastrografin relate to their hypertonicity – fluid is drawn out of the gut wall into the lumen, thereby reducing gastrointestinal contractile dysfunction and promoting peristalsis.[183, 184]

![Figure 6-1 Sodium diatrizoate.](image1)

![Figure 6-2 Meglumine diatrizoate.](image2)
There are at present no therapeutically effective measures for shortening the duration of an established episode of PPOI. A central component of this thesis is, by way of a double-blinded randomised trial, to prospectively appraise the value of Gastrografin in mitigating PPOI-associated intestinal oedema, thereby precipitating its resolution. Equipoise, rationale, and methodological design of this study are thoroughly described in Chapter 7.

A critical step in trial development was to ensure a robust blinding process (detailed in Chapter 7). This was to be effected by re-packaging of Gastrografin and placebo into uniformly labelled tinted glass bottles. However, there are no reports on the stability of the active diatrizoate salts (DTZ) in Gastrografin after opening and re-packaging. Moreover, it is unclear which conditions are best for storage of the re-packaged drug. This information is central to the accurate appraisal of Gastrografin as a therapeutic tool in PPOI and must be ascertained prior to commencing the planned clinical trial.

6.2 Study Objective

The aim of this study was to assess the 30-day stability of DTZ salts in re-packaged Gastrografin and provide guidance as to optimal storage conditions during trial execution. This was to be achieved by developing, validating, and utilising a rapid reverse phase High Performance Liquid Chromatography (HPLC) analytical method for the assay of DTZ.
6.3 Methods

6.3.1 Drugs and Chemicals

Sodium diatrizoate and meglumine diatrizoate of greater than 99% purity were purchased from Sigma-Aldrich (Auckland, New Zealand). Potassium dihydrogen phosphate, sodium hydroxide and analytical grade acetonitrile were obtained from Merck Pharmaceuticals (Auckland, New Zealand). Gastrografin and placebo (matrix without active) were purchased from manufacturers Bayer Shering Pharma (Berlin, Germany).

6.3.2 Chromatographic Conditions

A published HPLC method for the assay of meglumine amidotrizoate injection described in the Japanese Pharmacopeia was adapted and partially validated.[300] Modifications to this technique included alteration of the mobile phase to optimise detection of the analyte and utilisation of multiple dilutions to achieve a sample suitable for analysis.

All analytical work was carried out at AnQual Laboratories, a Good Laboratory Practice compliant facility at the University of Auckland. Reverse phase HPLC was performed for the quantification of DTZ in Gastrografin solution. A Shimadzu (Kyoto, Japan) HPLC VP series (LC 10AD) system comprising an autosampler maintained at 4°C (SIL-10AD), a quaternary pump, and a photo-diode detector (SPD-M20A) were used for analysis with detection at 254nm. Separation of the sample was achieved using a 10 micron C18 Kromasil Column (250mm x 4.6mm) maintained at 25°C in a column oven (CTO-10AS). The injection volume was 20μL; the sample run time was 10 minutes with the analyte eluting at 5 minutes.

The mobile phase was also used as the diluent for all the samples and consisted of phosphate buffer (pH 7.0) and acetonitrile in a ratio of 36:10. The buffer comprised 62.5% 0.1M potassium dihydrogen phosphate and 36.4% sodium hydroxide, with milliQ water to 100%. Preparation utilised magnetic stirring, filtration and sonication of the solution prior to use. A neutral pH was maintained throughout to minimise degradation of DTZ. The mobile phase was delivered isocratically at 0.5mL/min at a standard pressure of 47 bar.

6.3.3 Preparation of Standard Solutions

Standard solutions were prepared immediately prior to study execution. Sodium diatrizoate and meglumine diatrizoate reference standards were weighed and dissolved in the mobile phase separately. These were subsequently mixed together with step wise dilution in the mobile phase to produce a reference standard final solution containing 100μg/ml of sodium diatrizoate and 660μg/ml of meglumine diatrizoate.
6.3.4 Validation of HPLC Method

6.3.4.1 Specificity

Specificity was chromatographically assessed by examining the matrix of the product without active component. A sample of matrix prepared in exactly the same way as the active drug was injected into the system and the response monitored.

6.3.4.2 Linearity

Assessment of linearity was performed to verify that sample solutions were in a concentration range where analyte response was directly proportional to concentration. A calibration curve was constructed using five concentrations of standard sample solutions over the expected concentration range. Linearity was determined by quantifying the peak area response using least squares regression and correlation coefficients.

6.3.4.3 Accuracy

Accuracy was determined by pipetting the active drug (95 µg/mL) into the blank matrix of the formulation to obtain samples containing 80% (3.2mL), 100% (4.0mL) and 120% (4.8mL) of the expected concentrations of analyte. The expected concentration of analyte was 38 µg/mL and the matrix was therefore correspondingly pipetted with active drug to produce samples of 30.4 µg/mL, 38.0 µg/mL and 45.6 µg/mL. Accuracy was expressed as the mean percentage recovery of analyte from each sample with an acceptable margin of error being ±5% at each concentration level as specified in the United States Pharmacopeia.[301]

6.3.4.4 Precision

System precision was assessed by injecting six replicates of a single sample while method precision was evaluated by triple injection of samples at three different concentrations. Precision is considered acceptable if the standard deviation of all tests is ≤3%.

6.3.5 Preparation of Samples

Gastrografin samples were stored in their original containers under variable conditions (described below) and in concordance with International Convention of Harmonisation (ICH) guidelines.[302] At defined time intervals (Days 3, 7 and 30) samples were removed and diluted step wise in mobile phase to produce solutions containing 5 µg/ml of sodium diatrizoate and 33 µg/ml of meglumine diatrizoate. Samples therefore theoretically containing 38 µg/mL of DTZ were analysed. The stationary phase was appropriately conditioned prior to running of the samples, and all samples were analysed in triplicate.
6.3.5.1 Sample One

Exposure to 25ºC, 60% relative humidity and no light – examined on Days 3, 7 and 30. This was intended to mimic storage in a locked cabinet – the condition most likely to be encountered during the planned clinical trial.

6.3.5.2 Sample Two

Exposure to 25ºC, 60% relative humidity and 1.2 million lux hours of ultraviolet light (corresponding to approximately 1 week of daylight)[302] – examined on Days 3 and 7. The length of exposure to UV/Vis is governed by the ICH Guidelines which state that the photostability of a product is assessed by its exposure to visible light providing overall illumination of at least 1.2 million lux hours and ultraviolet energy of at least 200 watt hours per square meter. The chambers used were fitted with bulbs providing 6800 lux of light with 5.1 watts of ultraviolet energy.

6.3.5.3 Sample Three

Exposure to 4ºC, minimal humidity (<10%) and no light – examined on Days 3, 7 and 30. This environment was selected to mimic storage in a refrigeration unit, which could serve as an alternative to the conditions outlined in Sample One.

6.3.6 Funding Sources

The Foundation for Surgery Research Scholarship (consumables allocation) awarded by the Royal Australasian College of Surgeons via competitive application was used to fund this work.
6.4 Results

6.4.1 Validation of HPLC Method

6.4.1.1 Specificity

DTZ from both salts eluted as a single peak at 5 minutes. There was no interference from excipients at the 20,000 fold dilution used in the preparation of samples. Injected placebo samples diluted in mobile phase to the same extent as Gastrografin samples; however, they showed no peak at 5 minutes indicating this method was specific for DTZ.

6.4.1.2 Linearity

Injected sample concentrations of between 9.5-95 µg/mL produced a calibration curve with a correlation coefficient of 0.999. This confirmed the linearity of the method.

6.4.1.3 Accuracy

The average recovery of analyte was 30.2 µg/mL for the 80% sample, 38.4 µg/mL for the 100% sample and 46.4 µg/mL for the 120% sample. This corresponded to recoveries of 99%, 101% and 103% respectively, and were within the ±5% accepted margin of error thereby confirming method accuracy.

6.4.1.4 Precision

The injection of six replicates to determine system precision produced results with a standard deviation of 0.18%. Three determinations at three concentrations to establish method precision produced relative standard deviations of 0.79%, 0.90% and 0.55%. These were all within the ≤3% acceptable limit thereby validating system and method precision.

6.4.2 Stability Testing

6.4.2.1 Sample One

Gastrografin stored at 25°C, 60% relative humidity and exposed to no light maintained integrity throughout the 30 day study duration with no physical change to the solution (Table 6-1). Analysis at Days 3, 7 and 30 showed DTZ content of 103%, 104% and 102% respectively, all of which fell within the 95-105% margin of acceptability stipulated by the United States Pharmacopeia.[301]
Table 6-1 Stability of Sample One – DTZ stored at 25°C, 60% humidity and no light.

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Day 3 Concentration of DTZ (µg/mL)</th>
<th>Day 7 Concentration of DTZ (µg/mL)</th>
<th>Day 30 Concentration of DTZ (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>38.811</td>
<td>39.613</td>
<td>38.547</td>
</tr>
<tr>
<td>Test 2</td>
<td>40.181</td>
<td>39.364</td>
<td>37.557</td>
</tr>
<tr>
<td>Test 3</td>
<td>38.383</td>
<td>39.548</td>
<td>39.933</td>
</tr>
<tr>
<td>Average Conc.</td>
<td>39.125</td>
<td>39.508</td>
<td>38.679</td>
</tr>
<tr>
<td>Expected Conc.</td>
<td>38.000</td>
<td>38.000</td>
<td>38.000</td>
</tr>
<tr>
<td>Content (%)</td>
<td>102.961</td>
<td>103.969</td>
<td>101.787</td>
</tr>
</tbody>
</table>

6.4.2.2 Sample Two

Gastrografin stored at 25°C, 60% relative humidity and exposed to 1.2 million lux hours showed DTZ content of 97% on Day 3 and 95% on Day 7 (Table 6-2). Exposure to light therefore caused a slight reduction in analyte recovery although this remained within the acceptable limit.[301]

Table 6-2 Stability of Sample Two – DTZ stored at 25°C, 60% relative humidity and exposed to 1.2 million lux hours of light.

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Day 3 Concentration of DTZ (µg/mL)</th>
<th>Day 7 Concentration of DTZ (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>32.904</td>
<td>36.861</td>
</tr>
<tr>
<td>Test 2</td>
<td>35.047</td>
<td>34.827</td>
</tr>
<tr>
<td>Test 3</td>
<td>42.796</td>
<td>36.812</td>
</tr>
<tr>
<td>Average Conc.</td>
<td>36.915</td>
<td>36.167</td>
</tr>
<tr>
<td>Expected Conc.</td>
<td>38.000</td>
<td>38.000</td>
</tr>
<tr>
<td>Content (%)</td>
<td>97.146</td>
<td>95.176</td>
</tr>
</tbody>
</table>

6.4.2.3 Sample Three

Gastrografin stored at 4°C, minimal humidity (<10%) and exposed to no light showed DTZ content of 100% on Day 3 (Table 6-3). This subsequently fell to 95% on Day 7 due to microscopic crystallisation of the solution which was not visible. On Day 30, macroscopic crystallisation of the sample was evident and vigorous agitation was required to homogenise the sample. Subsequent analysis revealed a DTZ concentration of 97%. Therefore, while
crystallisation of the drug occurs at 4°C this may be readily reversed by agitation and does not affect its stability.

<table>
<thead>
<tr>
<th></th>
<th>Day 3 Concentration of DTZ (µg/mL)</th>
<th>Day 7 Concentration of DTZ (µg/mL)</th>
<th>Day 30 Concentration of DTZ (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>36.356</td>
<td>37.629</td>
<td>36.128</td>
</tr>
<tr>
<td>Test 2</td>
<td>42.899</td>
<td>35.964</td>
<td>37.328</td>
</tr>
<tr>
<td>Test 3</td>
<td>35.169</td>
<td>35.682</td>
<td>39.145</td>
</tr>
<tr>
<td>Average Conc.</td>
<td>38.141</td>
<td>36.425</td>
<td>37.534</td>
</tr>
<tr>
<td>Expected Conc.</td>
<td>38.000</td>
<td>38.000</td>
<td>38.000</td>
</tr>
<tr>
<td>Content (%)</td>
<td>100.372</td>
<td>95.855</td>
<td>98.773</td>
</tr>
</tbody>
</table>

Table 6-3 Stability of Sample Three – DTZ stored at 4°C, minimal humidity (<10%) and exposed to no light showed DTZ.
6.5 Discussion

No reports on the chemical stability of Gastrografin could be identified in the literature. It was therefore elected to investigate this via HPLC – a method commonly used for the pharmaceutical analysis of non-volatile substances. Chromatographic analysis has been successfully employed previously in the Japanese Pharmacopoeia for the assay of meglumine amiditrizoate injection.[300] Additionally, liquid chromatography has been used in biodegradability analysis of contrast media and the separation of sodium diatrizoate from its impurities in a final drug product.[186, 303]

The hyperosmotic and radio-opaque properties of Gastrografin and other water-soluble media have lead to their use as first-line agents in adhesive small bowel obstruction.[183] Other therapeutic indications for Gastrografin have included its selective utilisation in the treatment of neonatal meconium ileus,[304] intestinal obstruction secondary to tapeworm or roundworm infection,[305, 306] and to relieve distal intestinal obstruction in children with cystic fibrosis.[307] Its uses in these conditions have however been largely superseded by more directed and efficacious therapies. Gastrografin is well-suited as a contrast media when barium based agents are not feasible or potentially dangerous (most notably in the context of suspected visceral perforation).[185] This is particularly valuable in the context of prolonged ileus where anastomotic leak may be a precipitant or occur concurrently.[48]

A limitation of this study was its relatively short 30 day duration; stability testing is usually conducted over a 6 month period.[300, 301] However, the principal objective of this research was to determine the integrity of opened and re-packaged Gastrografin in the context of a clinical trial, and to this end complied with the rigorous guidelines stipulated by the ICH.[302] Secondly, this analysis was performed under strictly controlled conditions which may not accurately reflect packaging or storage conditions in the field. However, care was taken through study conception and design to ensure that experimental conditions closely mimicked those which would be encountered in the clinical setting.
6.6 Conclusion

Using a simple and rapid reverse phase HPLC methodology it has been demonstrated that, after opening and re-packaging, Gastrografin remains stable and active for a minimum of 30 days under standard storage conditions (25°C, 60% humidity, no light).

Gastrografin also remains stable for 7 days when exposed to 25°C, 60% relative humidity and 1.2 million lux hours of light. Crystallisation of Gastrografin may occur when stored at 4°C, minimal humidity (<10%) and no light, but is readily reversed by agitation and has no discernible effect on drug stability up to 30 days.
CHAPTER 7:
DOUBLE-BLINDED RANDOMISED CONTROLLED TRIAL – GASTROGRAFIN IN PROLONGED POST-OPERATIVE ILEUS
7.1 Background

As outlined in Chapter 1, the aetiology of PPOI is thought to be multifactorial with skin and peritoneal incision, bowel handling, formation of new anastomosis and exogenous administration of fluid and opioid all being implicated. These in turn precipitate a localised and systemic inflammatory response, induce autonomic shift, and create direct physical barriers to normal gastrointestinal motility. A final common pathway for these effectors is intramural oedema and impaired intestinal contractility (Figure 1-1).

It is valuable to note that while there is discrete evidence to support each of the processes described in this model, the cohesive sequence of pathophysiologic events between root cause (corresponding clinically to initial surgery) and end-organ effect (corresponding clinically to the appearance of PPOI symptoms) has not been accurately defined. Moreover, PPOI only occurs in a subset of the post-surgical cohort, and at present there is no clear understanding of which patients are at increased risk and which factors predispose them to its development.\cite{45, 46, 111, 121} It is therefore proposed that, in the context of these pathophysiologic and clinical discernments, a potentially therapeutic intervention being investigated as part of a clinical trial may be best delivered in the early stages of an established episode of PPOI, and should target the end-organ effect which can be reliably assumed to have occurred at this timepoint.

OWSC media such as Gastrografin have been shown to confer a therapeutic benefit in adhesive small bowel obstruction.\cite{183} This salutary property is believed to relate to its hypertonicity – fluid is drawn out of the gut wall into the lumen, thereby reducing oedema-related gastrointestinal contractile dysfunction and promoting distension-induced peristalsis.\cite{184} OWSC media are hence theoretically well-suited to the management of PPOI by mitigating intramural oedema in a site-specific manner (Figure 7-1). Previous literature evaluating the use of OWSC agents in ileus have been limited by small patient numbers, heterogeneous inclusion criteria and outcome measures, and conflicting results.\cite{193-195} but despite this there remain anecdotal accounts of its administration for this purpose.

7.2 Study Objective

The aim of this study was to therefore perform a double-blinded placebo-controlled randomised trial investigating the hypothesis that Gastrografin given enterally would shorten the duration of established PPOI following elective colorectal surgery.
Figure 7-1 Postulated therapeutic action of luminally administered hyperosmotic OWSC media.
7.3 Methods

7.3.1 Ethics Approval and Trial Registration

Ethics approval was obtained from the Ministry of Health’s National Ethics Committee (NTX12/06/054) and Auckland District Health Board’s Multidisciplinary Research Review Committee (A+5600) prior to trial commencement. The trial was prospectively registered with http://clinicaltrials.gov (identifier: NCT01648972, US National Library of Medicine, 8600 Rockville Pike, Bethesda, Maryland, USA).

7.3.2 Study Population

The source population included all New Zealand citizens and permanent residents living within the catchment area of Auckland District Health Board. All patients aged 18 years or older scheduled to undergo elective laparoscopic or open colorectal surgery for any indication between September 2012 and June 2014 were screened for eligibility.

7.3.2.1 Inclusion Criteria

Included patients were those undergoing segmental colonic or rectal resection, abdominoperineal resection, total or sub-total colectomy, and formation or reversal of ileostomy or colostomy.

7.3.2.2 Exclusion Criteria

Exclusion criteria were participants with an ASA of 4 or greater; previous allergic or adverse reaction to Gastrografin or iodinated contrast agents; manifest hyperthyroidism; those on pre-operative parenteral nutrition; and those who could not participate in trial assessments due to dementia, post-operative delirium, or language difficulties. Participants with anastomotic leak were not excluded unless they required percutaneous or operative intervention. Leak was defined according to Rahbari et al. as either i) anastomotic dehiscence identified on re-operation; ii) intra-abdominal collection next to the anastomosis on computed tomography; or iii) discharge of faeculent material from abdominal wound or drainage tube.[308] Patients requiring re-operation prior to commencement of formal Day 4 assessments for PPOI were not randomised; those requiring re-operation during an episode of PPOI were excluded from subsequent analysis.

7.3.3 Recruitment and Consent

All patients were seen on an individual basis pre-operatively by the study investigator (Ryash Vather) and provided with verbal information on trial rationale and protocol. Patients were
also given a Participant Information Sheet which included investigator contact details (Appendix B). Written informed consent was obtained prior to surgery.

7.3.4 Participant Assessment

Patients were assessed for the occurrence of PPOI between 8-9am on a daily basis from Day 4 post-operatively until discharge. The day of surgery was considered ‘Day 0’. Those who met diagnostic criteria for PPOI were enrolled, allocated study medication, and then assessed 12-hourly for resolution of PPOI. These assessments were independently made by a single, blinded investigator (Ryash Vather) who was not affiliated with the overseeing clinical team to ensure standardisation of data collection (Appendix C).

7.3.4.1 Simulated Patient Assessments

A definition of PPOI was proposed in Chapter 4 based on systematic review and global survey as follows: two or more of nausea/vomiting, inability to tolerate an oral diet, absence of flatus and stool, abdominal distension, or radiologic confirmation – occurring on or after Day 4 post-operatively. Although the symptoms and signs outlined in this definition were constructed from a broad opinion base they are inherently subjective. It was therefore deemed important to ensure that, prior to trial commencement, criteria were made as transparent, objective, and reproducible between clinicians as possible. This was effected by a series of simulated assessments on post-operative colorectal surgical patients over the course of two weeks in August 2012. Patients were consented by the study investigator (Ryash Vather) to participate in ‘dry runs’ comprising a brief directed history and focused examination during their post-operative stay. These patients were not approached for recruitment or enrolment in the clinical trial. The results of these assessments were used to inform and refine definitions for diagnosis and resolution of PPOI as outlined below.

7.3.4.2 Diagnosis of PPOI

PPOI was defined as occurring if patients met 2 or more of the following 5 criteria on or after Day 4 post-operatively:

- **Nausea OR vomiting over the preceding 12 hours.**
  Nausea was self-assessed by patients and graded as either ‘mild’, ‘moderate’ or ‘severe’; or on a 0-10 point Likert scale with 1-3 corresponding to ‘mild’, 4-7 ‘moderate’, and 8-10 ‘severe’. Patients who had experienced nausea of ‘moderate’ or ‘severe’ intensity, or ≥4/10 on a scale, over the preceding 12 hours were classified as meeting this criterion.
• Inability to tolerate a solid or semi-solid oral diet over the preceding two mealtimes.
  Patient assessments were made between 8-9am on a daily basis; the preceding two mealtimes therefore referred to breakfast that morning (delivered between 7-7.30am) and dinner the night before. Patients were deemed to have met this criterion if they consumed less than 25% of their self-reported pre-operative meal quantity.

• Abdominal distension.
  This was clinician-defined as increased abdominal girth from baseline with tympany on percussion, and was graded as ‘mild’, ‘moderate’ or ‘severe’. Those identified as having ‘moderate’ or ‘severe’ distension met this criterion. Baseline examination was undertaken pre-operatively either at pre-admission clinic or upon arrival to the Pre-operative Assessment Unit immediately before surgery.

• Absence of flatus AND stool over the preceding 24 hours.
  Patients were asked this directly. In those with ileostomy or colostomy this was defined as the absence of air or bowel contents in the stoma bag over the preceding 24 hours.

• Radiologic evidence of ileus on abdominal plain film or CT over the preceding 24 hours.
  Patients were deemed to have met this criterion if two or more of the following three features were noted on plain film or CT – gastric distension, presence of air-fluid levels, and dilated small or large bowel loops without a transition point.

7.3.4.3 Resolution of PPOI

PPOI was defined as having resolved when all 4 of the following criteria were met:

• Absence of nausea AND vomiting for 12 hours with nasogastric tube (NGT) spigotted or removed.
  ‘Absence’ of nausea included that of ‘mild’ intensity or ≤3/10 on a Likert scale as described above.
• Ability to tolerate a solid or semi-solid oral diet at the preceding mealtime. Patients were assessed 12-hourly and preceding mealtimes therefore referred to breakfast for 8-9am morning assessments and dinner for 8-9pm evening assessments. More than 25% of self-reported pre-operative meal quantity was to have been consumed to meet this criterion.

• Absence of abdominal distension. ‘Absence’ of distension included those with clinician-determined ‘mild’ distension as described above.

• Passage of flatus OR stool over the preceding 24 hours. Participants were asked this directly. In those with a stoma this was defined as the presence of air or bowel contents in the stoma bag over the preceding 24 hours.

7.3.5 Interventions

7.3.5.1 Surgery

All patients underwent routine elective in-patient abdominal surgery either by, or under the supervision of, a specialist colorectal surgeon at Auckland City Hospital. All procedures were carried out under general anaesthetic. Anaesthetic protocol and technical aspects of the operative procedure were left to the discretion of the anaesthetic and surgical teams respectively.

7.3.5.2 Immediate Post-operative Care

Several aspects of post-operative care for patients undergoing elective surgery within the Colorectal Unit at ADHB were protocolised. This included stepwise analgesia progression with early weaning of intravenous narcotics, restrictive post-operative maintenance fluid therapy, subcutaneous thromboprophylaxis, early post-operative feeding, and structured mobilisation regimens in conjunction with physiotherapy. A multimodal ERAS programme was piloted in the unit during the execution of this study, initially enrolling selected patients and procedures, and later extending to involve most cases. All aspects of post-operative care which occurred prior to a diagnosis of PPOI were left to the discretion of the overseeing clinical team.
7.3.5.3 Study Medication

Patients were assessed daily from Day 4 post-operatively for the occurrence of PPOI, and upon diagnosis were enrolled and prescribed a single 100ml dose of study medication. This was given orally or via NGT within 4 hours of diagnosis by a ward nurse not associated with the study. If administered via NGT this was spigotted for at least 2 hours but switched back to free drainage earlier if the patient experienced nausea or vomiting.

Participants in the Exposure Group received 100ml of undiluted Gastrografin (Bayer Schering Pharma, Berlin, Germany). Each 1ml of solution contained 100mg sodium diatrizoate and 660mg meglumine diatrizoate in aqueous solution with flavouring agents and saccharin.[185]

Participants in the Control Group received 100ml of placebo consisting of 1ml concentrated anise solution (2% anise oil, 72% ethanol, 26% water), 40ml glycerol, and 59ml distilled water. This solution mimicked the smell, taste and consistency of Gastrografin but lacked its hypertonicity. It has been previously validated as an appropriate placebo counterpart.[309]

7.3.5.4 Standardised Management Guidelines for PPOI

The clinical management of enrolled trial participants conformed to the standardised evidence-based recommendations outlined in Chapter 5, and are briefly summarised below.

A NGT was inserted if vomiting was a feature. This was initially set to free drainage, and then spigotted with 6-hourly aspirates when output was less than 600mls/24 hours. When output fell below 300ml/24 hours the NGT was removed. Electrolytes (specifically sodium, potassium, magnesium and calcium) were monitored and corrected on a daily basis. Analgesia prescription was reviewed with weaning of opiates and progressive substitution with regular paracetamol, regular tramadol and regular or as-required non-steroidal anti-inflammatory drugs. Opiates were reserved for breakthrough pain only. Maintenance fluid therapy of Dextrose 4% and Saline 0.18% with KCl was prescribed at 1ml/kg/hr. NGT losses or vomits greater than 500mls were replaced ml for ml with 0.9% Saline + 30mmol KCl at a maximum infusion rate of 330ml/hr. Fluid therapy in participants with clinical dehydration, acute renal impairment, fluid overload or haemodynamic instability was left to the discretion of the surgical team. If feasible, patients were asked to ambulate at least three times a day with assistance from nursing or physiotherapy staff as necessary. Parenteral nutrition (PN) was commenced if patients were unable to sustain adequate oral intake for more than 7 days, or after 5 days if nutritionally deplete. PN was discontinued when participants were tolerating an oral diet. The PN prescription was determined by the nutritional support team.
### Management of Prolonged Postoperative Ileus

1. Nasogastric tube insertion (IF vomiting is a feature)
   a. Initially – free drainage.
   b. When <600ml/24 hours – sipqg with q6h aspirates.
   c. When <300ml/24 hours – remove.

2. Electrolyte correction
   a. Daily electrolyte sampling – Na, K, Mg, Ca, Cr.
   b. Replace as appropriate to within normal range.

3. Review analgesia prescription
   a. Wean opiates and substitute with:
      i. Regular paracetamol.
      ii. Regular tramadol.
      iii. PRN/Regular NSAIDs (if no contraindications).
   b. Reserve opiates for breakthrough pain.

4. Intravenous fluid therapy
   a. Maintenance
      i. Use Dextrose 4% and Saline 0.18% with KCl at 1ml/kg/hr.
   b. Replacement (NS losses or vomits)
      i. 1 ml for ml replacement of losses >500ml
      ii. Use 0.9% Saline + 30mmol KCl
         (use infusion rate 330ml/hr at this K concentration)

Fluid therapy in the management of clinical dehydration, acute renal impairment, fluid overload or haemodynamic instability will be left to the discretion of the surgical team.

5. Ambulation
   a. At least 3 times/day, with assistance as necessary.

6. Total parenteral nutrition
   a. Commence if inadequate oral intake for ≥7 days;
      or at Day 5 if nutritionally depleted.
   b. Prescription to be made by nutritional support team.
   c. Discontinue when tolerating an oral diet.

---

Figure 7-2 Standardised management guidelines inserted within the clinical notes of enrolled patients.
Nursing and allied health staff were made aware of the presence of these guidelines via formal interactive ward-based teaching sessions and one-on-one reminders to involved personnel. Junior medical staff were similarly informed and run through recommendations upon commencement of their attachment to the Colorectal Unit. A concise single-page summary of guidelines was constructed and placed on the involved wards’ staff notices board and within the written clinical notes section of each participant’s folder upon recruitment (Figure 7-2). Investigator names could be found at the bottom of these guidelines.

7.3.6 Sample Size

An *a priori* power calculation was undertaken based on the findings of the retrospective cohort study outlined in Chapter 3 which described incidence and duration of PPOI following elective colorectal surgery at ADHB. PPOI was found to occur in 50 of 255 consecutive colorectal cases over the 2011 year with a mean duration of 4.54 days (SD 2.21) per episode. It was estimated that if therapeutically active, Gastrografin may be reasonably expected to reduce the mean duration of PPOI to 3 days. A reduction from 4.5 to 3 days would also represent a shift which was clinically useful.

Using a two-tailed independent-samples t-test for the difference between two unpaired means with an alpha-error of 0.05, beta-error of 0.2, and power of 0.8 it was determined that to detect a 33% difference in duration of PPOI between groups with an allocation ratio of 1:1, 35 patients would be required in each arm. It was anticipated some participants would be excluded from analysis after administration of study medication because of diagnosis of an alternate pathology or return to theatre. A recruitment target of 40 patients in each arm was therefore set.

7.3.7 Randomisation

7.3.7.1 Sequence Generation

Allocation to Exposure and Control Groups occurred in a 1:1 ratio and randomisation was blocked into groups of eight to ensure comparable allocation in the event of early termination of the trial. Randomisation sequence generation was undertaken by a third party not associated with this study using an online purpose-built random number generator (http://www.random.org). A spreadsheet was created with consecutive numbers from 1 to 80 with treatment allocation listed adjacent to this.
7.3.7.2 *Allocation Concealment*

The spreadsheet containing treatment allocation was then sealed in an opaque envelope and signed across the seal by the third party. This envelope was delivered to Auckland City Hospital’s on-site pharmacy prior to trial commencement.

7.3.8 *Blinding*

Trial participants, study investigators, and clinical staff were all blinded to treatment allocation.

Specified participant numbers were forwarded to Auckland City Hospital’s on-site pharmacy staff on a weekly basis. After consulting the randomisation spreadsheet, pharmacy staff either formulated placebo or re-packaged Gastrografin into identical tinted glass bottles. The only discriminating feature between bottles supplied to the study investigator was the allocation number printed on its label (Figure 7-3).

![Study medication bottle.](image)

*Figure 7-3* Study medication bottle.
These bottles were then collected on a weekly basis and stored in a locked cabinet at room temperature. Prior to trial commencement independent commercial testing was undertaken to ensure opened and re-packaged Gastrografin maintained its stability and sterility. Data from this analysis showed the compound remained stable in the planned storage conditions for at least 30 days following re-packaging (Chapter 6).

Upon diagnosis of PPOI, trial participants were allocated to receive the next consecutively numbered bottle of study medication. This was collected from the locked cabinet by the study investigator (Ryash Vather) and delivered to the ward nursing staff for administration. Auckland City Hospital’s on-site pharmacy was not involved in any aspect of patient management, study design, study execution, data collection or analysis.

7.3.9 Outcomes

7.3.9.1 Baseline Data

Data were prospectively collected for an assortment of baseline characteristics including patient age at the time of surgery, gender, ASA grade, BMI, procedure type, open vs. laparoscopic vs. converted technique, operative indication and procedure duration.

7.3.9.2 Primary Outcome

The primary outcome for this study was the duration of PPOI, defined as the time in hours from diagnosis to resolution of PPOI as described above.

7.3.9.3 Secondary Outcomes

Data were collected on time until discharge criteria were met (from surgery and from diagnosis of PPOI), and actual length of hospital stay (from surgery and from diagnosis of PPOI). Discharge criteria were defined as being met when patients were able to tolerate an oral diet sufficient to meet daily nutritional needs; mobilise safely and independently (or at the level of pre-operative baseline function); independently perform Activities of Daily Living (or at the level of pre-operative baseline function); and manage pain with oral analgesia only. Occurrence of other complications were recorded and graded using the Clavien-Dindo classification system.[196] The 30-day readmission rate was also recorded.

Volume and type of intravenous fluid required over the course of the PPOI episode was recorded. Analgesia consumption was noted with total opioid use being expressed as the Morphine Equivalent Dose (MED). MED has previously been shown to be a validated and sensitive measure of narcotic use and was used to quantify opiate consumption in Chapter 3.
Antiemetic consumption was recorded with comparison being facilitated by conversion to standardised units as follows: 1 unit = 4mg ondansetron; 25mg cyclizine; 10mg metoclopramide; 0.625mg droperidol; 10mg stemetil; 4mg dexamethasone; 1.5mg scopolamine. The requirement for NGT placement was noted with data prospectively collected on total output volume and time to removal. Requirement for PN and duration of administration were also recorded.

Data were collected on the tolerability of study medication and the occurrence of any adverse effects. Aspiration was considered a sentinel event requiring unblinding of treatment allocation to the overseeing clinical team.

7.3.10 Statistical Analysis

Analysis was performed on an intention-to-treat basis. No interim or sub-group analyses were planned or undertaken. Statistical analysis was performed using SPSS for Windows (Version 19; SPSS, Chicago, Illinois, USA). Parametricity was determined using histograms, Q-Q plots and the Shapiro-Wilk test. Normally distributed data were expressed as mean ± standard deviation (SD) and non-parametric data as median ± interquartile range (IQR). Univariate analysis was carried out using the \( \chi^2 \) test for categorical variables, the Mann-Whitney \( U \) test for non-parametric continuous variables, and an independent samples \( t \)-test for parametric continuous variables. Kaplan-Meier curves were constructed for primary outcome measures with resolution of symptoms as the survival event. Differences in survival distribution were compared using the log-rank test. Results were considered statistically significant if \( p<0.05 \).

7.3.11 Funding sources

The following grants were awarded by their respective bodies via competitive application and were used to fund this clinical trial:

- Colorectal Surgical Society of Australia and New Zealand project grant (2012-2014).
- Auckland Medical Research Foundation project grant (2012-2014).
### 7.4 Results

#### 7.4.1 Patient Flow

Patient flow is detailed in the CONSORT diagram (Figure 7-4). Between September 2012 and June 2014, 351 patients were assessed for eligibility. Six patients declined consent and a further five were unable to provide consent because of dementia (n=3), psychosis (n=1) and severe Asperger’s syndrome (n=1). Four patients met exclusion criteria of receiving pre-operative parenteral nutrition (n=3) or having previous anaphylaxis to an iodinated contrast agent (n=1). Nine patients were excluded prior to commencement of formal assessments of PPOI for the following reasons: re-operation before Day 4 for wound dehiscence (n=3), abdominal sepsis (n=2), necrotising deep tissue infection (n=1), and intra-abdominal bleed (n=1); intubation and ventilation in the Intensive Care Unit (ICU) for sepsis (n=1); and post-operative ischaemic stroke on Day 2 (n=1). In total, 88 of the remaining 327 screened patients developed PPOI (incidence 26.9%).

Eight patients were excluded prior to treatment allocation for the following reasons – withdrawal of patient consent (n=1); withdrawal of clinical team consent because of concerns relating to patient age (92 years old) and frailty (n=1); haemodynamic instability of cardiac origin (n=1); transfer to geriatric ward where staff were unaware of trial protocol and standardised management guidelines (n=1); Gastrografin charted in error by on-call intern (n=1); re-operation for anastomotic leak on morning of diagnosis (n=1); vomit with aspiration of gastric contents leading to intubation and ventilation in ICU (n=1); and inability to participate in trial assessments because of post-operative delirium (n=1).

#### 7.4.2 Diagnosis of PPOI

The remaining 80 patients were randomised equally to receive either Gastrografin or placebo. Diagnostic criteria most frequently met were the presence of nausea or vomiting (n=74 [92.5%]), inability to tolerate an oral diet (n=77 [96.3%]), and abdominal distension (n=68 [85%]). Absence of flatus and stool (n=37 [46.3%]) and radiologic evidence of ileus (n=13 [16.3%]) were observed less commonly. Three or more diagnostic criteria were met in 72 (90%) patients.

#### 7.4.3 Treatment Allocation

All 80 participants were administered study medication within 4 hours of diagnosis with the exception of two (both in the Gastrografin group), who received it at 8 hours and 14 hours post-diagnosis because of nursing delay. A single patient in the placebo group consumed 50ml of study medication per orally before declining the rest because of taste; all other
Assessed for eligibility (n=351)

Excluded (n=8)
- Withdrawal of patient consent (n=1)
- Withdrawal of team consent because of concerns of patient frailty (n=1)
- Cardiogenic haemodynamic instability (n=1)
- Transfer to geriatric ward (n=1)
- Gastrografin given in error (n=1)
- Re-operation for anastomotic leak on day of diagnosis (n=1)
- Aspiration with intubation & ventilation (n=1)
- Post-operative delirium (n=1)

Enrolled and screened for PPOI (n=327)

Lost to follow-up (n=0)
Discontinued intervention (n=0)

Allocated to Gastrografin (n=40)
- Received allocated intervention (n=40)

Allocated to Placebo (n=40)
- Received allocated intervention (n=40)

Analysis

Analysed (n=35)
Excluded from analysis (n=5)
- Re-operation for:
  - Anastomotic leak (n=3)
  - Early post-operative SBO (n=1)
  - Fascial dehiscence (n=1)

Occurrence of PPOI (n=88)

Excluded (n=36)
- Re-operation for:
  - Early post-operative SBO (n=2)
  - Anastomotic leak (n=1)
  - Outlier duration of PPOI (n=1)

Figure 7-4 CONSORT flow diagram.
<table>
<thead>
<tr>
<th></th>
<th>Gastrografin (n=35)</th>
<th>Placebo (n=36)</th>
<th>All (n=71)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>62.7 (16.1)</td>
<td>66.2 (14.4)</td>
<td>64.5 (15.3)</td>
<td>0.326</td>
</tr>
<tr>
<td>Gender (M:F)</td>
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<td>23:13</td>
<td>50:21</td>
<td>0.300</td>
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<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>European</td>
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<td>27</td>
<td>52</td>
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<td>Maori</td>
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</tr>
<tr>
<td>Pacific Islander</td>
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<td>2</td>
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</tr>
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<td>1</td>
<td>1</td>
<td></td>
</tr>
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<td>19</td>
<td>21</td>
<td>40</td>
<td></td>
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<tr>
<td>3</td>
<td>16</td>
<td>14</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m$^2$)$^i$</td>
<td>28.1 (7.0)</td>
<td>29.6 (8.6)</td>
<td>28.6 (7.7)</td>
<td>0.593</td>
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<tr>
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<td>R. hemicolecotomy</td>
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<tr>
<td>APR</td>
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<tr>
<td>Total colectomy</td>
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<td>6</td>
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<tr>
<td>Reversal loop ileostomy</td>
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<td>5</td>
<td>13</td>
<td></td>
</tr>
<tr>
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<tr>
<td>end ileostomy</td>
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<td>5</td>
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<td></td>
</tr>
<tr>
<td>Technique</td>
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<td>0.687</td>
</tr>
<tr>
<td>Open</td>
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<td>26</td>
<td>48</td>
<td></td>
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<tr>
<td>Lap-assisted</td>
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<td>4</td>
<td>11</td>
<td></td>
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<td>Laparoscopic</td>
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<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Converted</td>
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<td>3</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Table 7-1 Baseline characteristics.
Parametric data (*) are expressed as mean (SD); non-parametric data (i) are expressed as median (IQR).
participants consumed the study medication in its entirety. Five patients were excluded from analysis in the Exposure Group because of re-operation for anastomotic leak (n=3), early post-operative SBO (n=1), and fascial dehiscence (n=1). Four patients were excluded in the Control Group because of re-operation for early post-operative SBO (n=2), re-operation for anastomotic leak (n=1), and occurrence of outlier data (n=1). This latter participant’s duration of PPOI was 660 hours while all remaining durations of PPOI were normally distributed between 12 and 264 hours (Figure 7-5). Data from this participant were excluded to avoid skewing results towards the Exposure Group thereby providing a more conservative estimate of any observed treatment effect.

Seventy one patients were analysed with 35 in the Exposure Group and 36 in the Control Group. There was complete follow-up for all primary and secondary endpoints.

7.4.4 Baseline Characteristics

Groups were evenly matched at baseline with no significant differences in age, gender, ethnicity, ASA grade, BMI, indication for surgery, procedure type or operative technique (Table 7-1).

7.4.5 Primary Outcome

The mean duration of PPOI did not differ significantly between the Gastrografin and placebo groups (83.7 vs. 101.3 hours; p=0.191) (Table 7-2 & Figure 7-5).

When considering individual markers of PPOI resolution, Gastrografin did not significantly affect time to resolution of nausea and vomiting (64.5 vs. 74.3 hours; p=0.404) or consumption of an oral diet (75.8 vs. 90.0 hours; p=0.297) compared to placebo. However, it accelerated time to flatus or stool (18.9 vs 32.7 hours; p=0.047) and time to resolution of abdominal distension (52.8 vs 77.7 hours; p=0.013). Kaplan-Meier analyses concordantly showed no significant difference in resolution distributions between groups for overall duration of PPOI (Figure 7-6), time to resolution of nausea and vomiting, and time to consumption of an oral diet. Time-to-event was however accelerated in the Gastrografin group for passage of flatus or stool (log-rank test p=0.029) and resolution of abdominal distension (p=0.016).
Figure 7-5 Histogram of duration of PPOI.

- Placebo
- Gastrografen

Duration of Prolonged Ileus (hours) vs. Number of patients
Table 7-2 Primary outcome measures.
All data are parametric and expressed as mean (SD).

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Gastrografin (n=35)</th>
<th>Placebo (n=36)</th>
<th>All (n=71)</th>
<th>p-value</th>
<th>log-rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of PPOI (hours)</td>
<td>83.7 (58.8)</td>
<td>101.3 (53.9)</td>
<td>92.6 (56.6)</td>
<td>0.191</td>
<td>0.311</td>
</tr>
<tr>
<td>Time to flatus or stool</td>
<td>18.9 (20.0)</td>
<td>32.7 (35.2)</td>
<td>25.9 (29.4)</td>
<td>0.047</td>
<td>0.029</td>
</tr>
<tr>
<td>Time to resolution of nausea and vomiting</td>
<td>64.5 (54.5)</td>
<td>74.3 (44.2)</td>
<td>69.5 (49.5)</td>
<td>0.404</td>
<td>0.370</td>
</tr>
<tr>
<td>Time to resolution of distension</td>
<td>52.8 (35.6)</td>
<td>77.7 (45.6)</td>
<td>65.4 (42.5)</td>
<td>0.013</td>
<td>0.016</td>
</tr>
<tr>
<td>Time to consumption oral diet</td>
<td>75.8 (61.9)</td>
<td>90.0 (52.0)</td>
<td>83.0 (57.1)</td>
<td>0.297</td>
<td>0.348</td>
</tr>
</tbody>
</table>

Figure 7-6 Kaplan-Meier survival curves for time to resolution of PPOI.
(Log-rank test p=0.311).
7.4.6 Secondary Outcomes

There were no significant differences between groups in time until objective discharge criteria were met (from surgery or diagnosis of PPOI), actual length of stay (from surgery or diagnosis of PPOI), occurrence of other complications, and 30-day readmission rate (Table 7-3). The volume of intravenous crystalloid, paracetamol and antiemetic administered over the episode of PPOI was similar between groups. There was however a trend towards increased use of opioid analgesia in the Gastrografin cohort (19.8 vs. 8.8 MED; p=0.050). An equivalent number of participants in each group required NGT insertion with a similar median duration of insertion and median total output volume. No significant differences were noted in the number of patients requiring post-operative PN or the median duration of administration if commenced.

7.4.7 Adverse Events

Study medication was generally well-tolerated with watery diarrhoea/high stoma losses being the principal adverse events in each study arm. A single patient in each group was noted to have electrolyte disturbances on serial monitoring. Two patients in the Gastrografin group developed moderate clinical dehydration during the course of PPOI requiring additional replacement fluid.
<table>
<thead>
<tr>
<th></th>
<th>Gastrografin (n=35)</th>
<th>Placebo (n=36)</th>
<th>All (n=71)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time until discharge criteria met (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From diagnosis of PPOI</td>
<td>4 (4.5)</td>
<td>3.5 (3.75)</td>
<td>3.5 (4.5)</td>
<td>0.572</td>
</tr>
<tr>
<td>From surgery</td>
<td>8.5 (4.5)</td>
<td>8.5 (3.9)</td>
<td>8.5 (4.0)</td>
<td>0.530</td>
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<tr>
<td>Actual length of stay (days)</td>
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<tr>
<td>From diagnosis of PPOI</td>
<td>8 (5.0)</td>
<td>8.5 (8.5)</td>
<td>8 (8.0)</td>
<td>0.540</td>
</tr>
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<td>From surgery</td>
<td>10 (5.0)</td>
<td>13 (7.8)</td>
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</tr>
<tr>
<td>Complications (Clavien-Dindo grading)</td>
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<tr>
<td>Nil</td>
<td>6</td>
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<td>1</td>
<td>3</td>
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<td>4</td>
<td></td>
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<tr>
<td>2</td>
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<tr>
<td>30-day readmission</td>
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<td>Intravenous crystalloid (L)</td>
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<td>3.5 (3.9)</td>
<td>3.4 (3.9)</td>
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<td>Paracetamol (g)</td>
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<td>8.5 (8.5)</td>
<td>10 (10)</td>
<td>0.881</td>
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<td>Antiemetic (units)</td>
<td>5 (12)</td>
<td>6.5 (12.1)</td>
<td>6 (11)</td>
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<td>Opioid analgesia (MED)</td>
<td>19.8 (56)</td>
<td>8.8 (51.3)</td>
<td>14 (55.5)</td>
<td>0.050</td>
</tr>
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<td>NG tube</td>
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<tr>
<td>No. requiring insertion</td>
<td>21</td>
<td>27</td>
<td>48</td>
<td>0.177</td>
</tr>
<tr>
<td>Duration of insertion after diagnosis (days)</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>2 (2.8)</td>
<td>0.554</td>
</tr>
<tr>
<td>Total output volume (L)</td>
<td>3.2 (3.7)</td>
<td>2.3 (4.1)</td>
<td>2.8 (4.1)</td>
<td>0.795</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. requiring PN</td>
<td>8</td>
<td>14</td>
<td>22</td>
<td>0.144</td>
</tr>
<tr>
<td>Duration of PN (days)</td>
<td>4.75 (4.4)</td>
<td>4.75 (3.1)</td>
<td>4.75 (3.4)</td>
<td>0.764</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td>0.359</td>
</tr>
<tr>
<td>Diarrhoea/high stoma losses</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Table 7-3 Secondary outcome measures.**
All continuous data are non-parametric and expressed as median (IQR).
7.5 Discussion

Understanding of the changes in gastrointestinal contractility which accompany PPOI is lacking, and it is hypothesised that generalised hypomotility predominates rather than dysmotility or complete atony.[73, 92, 101, 102] This is supported by the fluctuating clinical features of ileus – such as obstipation, abdominal distension, tympany, the absence of bowel sounds, and presence of air-fluid levels on imaging – as well as the predicted gastrointestinal response to the processes of inflammation, autonomic dysfunction and exogenous activation of opioid receptors thought to be central to its pathogenesis.[48] OWSC media such as Gastrografin act as osmotic laxatives, and their therapeutic properties in adhesive SBO are believed to relate to their ability to shift fluid from oedematous bowel wall to lumen, which in turn serves to improve coordinated myocyte activity, cause bolus-induced peristalsis, and create a longitudinal pressure difference across the site of obstruction.[184] It was therefore hypothesised that Gastrografin may exert an effect similar to SBO in PPOI albeit with an absence of any discrete differences in pressure.

The potential benefit of OWSC media in resolving ileus has received limited attention in the literature. Watkins et al. first published in 1985 a retrospective review of 40 patients with apparent PPOI who had received OWSC media with good effect; there was however no control arm with which this was compared.[195] This was followed a decade later with a case-control study which showed in a gynaecologic surgical cohort that OWSC media conferred no apparent benefit with respect to return of bowel function or oral intake. The incidence of PPOI was particularly high in this study with 57 of 115 screened patients meeting inclusion criteria.[194] Chen et al. performed an unblinded randomised trial investigating the routine administration of Gastrografin after colorectal surgery. With 25 patients in each arm, it was shown that Gastrografin allowed oral feeding to commence 1.5 days earlier and shortened length of stay from 10.2 to 7.6 days when compared to placebo; no inference was however made on its value in prolonged ileus.[193] The role of Gastrografin in PPOI was therefore unclear and adequately powered, randomised and blinded prospective appraisal was thought necessary to assess its clinical utility.

An important feature of this clinical trial was the attempt to use standardised and reproducible definitions for the diagnosis and resolution of PPOI. As demonstrated in Chapter 4, previous prospective work has used varying definitions for PPOI which has precluded comparison of competing interventions and translation to clinical practice. Moreover, while symptoms such as the presence or absence of flatus or stool are relatively easy to qualify, ‘softer’ symptoms such as nausea and the ability to tolerate an oral diet are
not as transparent and may be subject to differing interpretations. Diagnostic criteria have been explicitly defined in this clinical trial in what is hoped to be a clinically useful and readily appraisable manner. It is anticipated that this will serve to improve external validity and encourage homogeneity in subsequent endpoint reporting.

It was demonstrated that while Gastrografin accelerated time to flatus or stool and resolution of distension in patients with PPOI, it did not influence time to tolerance of an oral diet or resolution of nausea and vomiting. These findings were foreshadowed by a recent clinical consensus update which sub-classified ileus based on the relative prominence of presenting symptom clusters. In descending prevalence – Type I ileus was represented by 'panintestinal' symptoms, Type II by upper gastrointestinal symptoms exclusively and Type III by lower gastrointestinal symptoms exclusively. Although this classification system was designed primarily to lend expediency to the clinical description of an ileus syndrome, it also strongly alludes to the pathophysiologic mechanisms which may explain the observed results. Dysfunction associated with ileus may affect segments of the gastrointestinal tract autonomously and to varying degrees. Indeed it has been shown that after surgery motility returns first to the small bowel, then stomach, and finally large bowel. This suggests that although Gastrografin may successfully counteract oedema and promote peristalsis within the small and/or large bowel, it lacks an equivalent effect in the stomach. It is postulated that this may be related to the anatomical shape of the stomach whereby its large internal volume and non-cylindrical shape hinders Gastrografin's ability to effectively shift fluid from wall to lumen and induce sufficient distension for peristalsis. Alternatively, absence of effect may be explained by pathophysiologic mechanisms such as autonomic dysfunction or gastrointestinal hormone derangement, which are unrelated to oedema and known to manifest more prominently in the stomach than small or large bowel. Over 90% of the patients in this clinical cohort demonstrated symptoms of upper gastrointestinal dysfunction on diagnosis of PPOI and may have therefore been less susceptible to the mechanical effects of Gastrografin. A regimen which combines an intraluminal hyperosmotic agent with an agent that promotes gastric emptying may be expected to promote resolution of PPOI and warrants investigation in future research.

There was a trend towards an increased consumption of opioid analgesia in the Gastrografin cohort compared to placebo. It is speculated that this may relate to the increased peristaltic activity Gastrografin is believed to precipitate, which could feasibly be associated with increased pain in a patient who has undergone abdominal surgery.
The presentation of early post-operative small bowel obstruction (EPSBO) closely resembles that of PPOI and it may be difficult to differentiate these syndromes clinically after surgery.[108] This represents an important potential confounding factor in this trial whereby participants with self-limiting EPSBO could have been mislabelled as having PPOI and administered study medication. This in turn may partly explain the lack of statistical significance. CT has been shown to distinguish PPOI and EPSBO with high sensitivity and specificity.[108, 299] A trial which employs routine CT scanning in all patients with suspected ileus will accurately separate these entities, and may therefore yield results different to those that have been observed.

A limitation of this trial related to the administration of study medication. It was not possible to ensure medication given orally or nasogastrically remained in situ, with patients often experiencing vomits or nasogastric losses soon after administration. However, this represents what may occur in a typical clinical scenario and mirrors difficulties previously experienced in trials investigating Gastrografin in adhesive SBO.[184] A second limitation relates to the relatively broad distribution of duration of PPOI. This is likely a reflection of inherent variation in the severity of the clinical syndrome and the fact that diagnosis and resolution of PPOI required the presence and absence of separate symptom clusters. Nonetheless, the standard deviations for duration of PPOI noted here are consistent with those observed in the previous retrospective cohort study (Chapter 3). Finally, larger patient numbers would have reduced the chance of a type II error in this study. However, it was shown on sub-analyses that there was earlier occurrence of the two markers of PPOI related to resolution of small and large bowel symptoms, without any significant improvement in the remaining two markers associated with the upper gastrointestinal symptom cluster. Increased numbers may therefore not necessarily show a difference in PPOI which uses all these symptoms in its definition.
7.6 Conclusion

Gastrografin reduces the time taken to passage of flatus or stool and resolution of distension, but not the time taken to tolerance of an oral diet or resolution of nausea and vomiting. It is therefore not clinically useful in shortening an episode of PPOI characterised by all of these features. Gastrografin may however be of therapeutic benefit in the subset of patients with PPOI who display lower gastrointestinal symptoms exclusively and further prospective appraisal in this scenario is warranted.
CHAPTER 8:  
PROSPECTIVE COHORT STUDY –  
RISK STRATIFICATION OF PROLONGED POST-OPERATIVE ILEUS  
FOLLOWING COLORECTAL SURGERY
8.1 **Background**

A number of recent studies have attempted to determine risk factors associated with the development of PPOI following colorectal surgery. However, these have all reported differing incidences of PPOI (between 10-25%) in seemingly analogous cohorts, and there has been limited consistency between variables identified as independent predictors. [45, 46, 111, 121] This exemplifies the poor characterisation of PPOI as a clinical syndrome, and is postulated to relate principally to the heterogeneity with which it has been defined and the retrospective nature of antecedent literature. There is hence a niche for the performance of a prospective study employing a standardised, transparent and reproducible definition of PPOI to accurately determine its incidence and predisposing risk factors. Furthermore, it is anticipated that continued prospective application of a uniform definition within a local or external surgical cohort may also facilitate ‘incidence of PPOI’ being used as a marker of unit performance. [312]

A further consideration relates to the creation of a risk stratification tool for PPOI. As described in Chapters 1 and 5, current best-practice recommendations for the management of PPOI are conservative with potential therapeutic measures still remaining largely experimental. It is valuable, therefore, to shift attention to prevention. A sound understanding of the clinical factors which predispose a patient to PPOI form the initial step in developing a tool capable of predicting its occurrence. This in turn may facilitate identification of high-risk individuals and allow early institution of measures to attenuate or abort an episode.

8.2 **Study Objective**

The aim of this study was to identify peri-operative risk factors associated with the development of PPOI following elective colorectal surgery and use this information to create a risk stratification system predicting its occurrence. This was achieved by meticulous prospective interrogation of all potentially relevant clinical variables and the uniform application of a standardised definition of PPOI.
8.3 Methods

This prospective observational study was conducted in tandem with the randomised controlled trial described in Chapter 7. The same eligible population was screened with patients being approached for enrolment in both. A diagnosis of PPOI represented the endpoint of this prospective observational study and the commencement of the randomised trial.

8.3.1 Ethics Approval and Trial Registration

Ethics approval was obtained from the Ministry of Health’s National Ethics Committee (NTX12/06/054) and Auckland District Health Board’s Multidisciplinary Research Review Committee (A+5600) prior to study commencement.

8.3.2 Study population

The source population included all New Zealand citizens and permanent residents living within the catchment area of Auckland District Health Board. All patients aged 18 years or older scheduled to undergo elective surgery for any indication by the Colorectal Unit at ADHB between September 2012 and June 2014 were screened for eligibility. Included procedures were segmental colonic or rectal resection, abdominoperineal resection, total or sub-total colectomy, and formation or reversal of ileostomy or colostomy. Exclusion criteria were patients with an ASA of 4 or greater; those on pre-operative parenteral nutrition; those who could not participate in study assessments due to dementia, language difficulties or post-operative delirium; and those requiring re-operation for any indication prior to commencement of formal assessment for PPOI.

8.3.3 Recruitment and Consent

All patients were consented in conjunction with the clinical trial as described in Section 7.3.3.

8.3.4 Prospective Data Recording

In total, 92 assorted peri-operative variables were prospectively recorded for each enrolled patient and stored in an electronic worksheet. This data was acquired either by focused patient history and examination, direct observation of patient care, brief semi-structured interviews of involved surgical staff, or data extraction from written clinical notes or ADHB’s online ‘Concerto’ portal.
8.3.4.1 Pre-operative Variables

Pre-operative information pertained to:

- Patient demographics – age; gender; and self-reported ethnicity.
- Past medical history – previous abdominal surgery; occurrence of an episode of PPOI after previous abdominal surgery; systemic co-morbidities; and regular medications.
- Functional status – ASA grade; body mass index; and smoking status.
- Haematologic and biochemical parameters – haemoglobin, white cell count, creatinine, sodium, potassium, calcium, magnesium and albumin. These were to have been measured no more than two weeks before surgery.

8.3.4.2 Intra-operative Variables

Intra-operative variables recorded related to:

- Anaesthetic protocol – use of epidural or spinal (including level and duration of use); induction agent and dose; and intra-operative administration of medications, fluids and blood products.
- Procedure – indication for surgery; operative surgeon; open vs. laparoscopic vs. converted technique; operative duration; stoma formation (qualified as ileostomy formation; colostomy formation; or stoma reversal); specimen resection length; and wound size. Reversal of Hartmann’s procedures which entailed restoration of colonic continuity with creation of diverting loop ileostomy were considered as ‘ileostomy formation’ rather than ‘stoma reversal’ under the stoma formation heading.
- Surgeon questionnaire (Figure 8-1) – following each case the operating surgeon or first assistant completed a standardised questionnaire evaluating estimated blood loss; self-assessed procedure difficulty (1-10 uniform Likert scale: 1-very easy, 10-very difficult); self-assessed degree of bowel handling (1-10 uniform Likert scale: 1-negligible handling, 10-intensive handling); and the presence of intra-abdominal contamination of pus or faeces (if present, further qualified as minimal, moderate or major).
Figure 8-1 Surgeon questionnaire.
8.3.4.3 Post-operative Variables

Post-operative factors documented related to:

- Markers of recovery – day of first mobilisation, flatus, and stool; and conformance to Enhanced Recovery After Surgery (ERAS) protocols.

- Haematologic and biochemical parameters – haemoglobin, white cell count, creatinine, sodium, potassium, calcium, magnesium and albumin. These were recorded on Day 1 post-operatively, and Day 3 post-operatively.

- Post-operative fluid and drug therapy – amount and type of intravenous fluid, blood products, and analgesia administered. This was recorded from the time of anaesthetic emergence on ‘Day 0’ until midnight at the end of Day 3 post-operatively. Total narcotic use was expressed as the Morphine Equivalent Daily Dose (MEDD) as previously described in Chapter 3 (Figure 3-2).[197-199] NSAID use was collated and converted with 1 unit corresponding to 750mg naproxen, 1200mg ibuprofen, 100mg diclofenac, 800mg celecoxib, 50mg rofecoxib, or 1200mg aspirin.[313, 314] Antiemetic use was not recorded as it would be unable to determine whether its use in the immediate post-operative period was a cause or consequence of a developing prolonged ileus.

8.3.5 Peri-operative Care

Several aspects of peri-operative care for patients undergoing elective surgery within the Colorectal Unit at ADHB were protocolised. This included stepwise analgesia progression with early weaning of intravenous narcotics, restrictive post-operative maintenance fluid therapy, early removal of lines and catheters, subcutaneous thromboprophylaxis, early post-operative feeding, and structured mobilisation regimens in conjunction with physiotherapy. An ERAS programme was piloted in the unit during the execution of this study, initially enrolling selected patients and procedures, and later extending to involve most cases. ERAS protocols were analogous to the standard multimodal care pathway described above but included two further measures – pre-operative counselling and the provision of clear carbohydrate enriched fluids until 2 hours before surgery. A dedicated ERAS nurse visited these patients on a daily basis to ensure adherence to protocols. Peri-operative care within an ERAS vs. ‘standard’ multimodal pathway was recorded as a binary variable in analysis.
8.3.6 Primary Outcome

The primary outcome was the occurrence of PPOI. Definition of PPOI was based on the systematic review and global survey described in Chapter 4 and an account of its refinement for clinical use can be found in Section 7.3.4.1. A brief summary of diagnostic criteria are provided below but detailed description of each can be found in Section 7.3.4.2.

8.3.6.1 Diagnosis of PPOI

PPOI was defined as occurring if patients met 2 or more of the following 5 criteria on or after Day 4 post-operatively:

- **Nausea OR vomiting over the preceding 12 hours.**
  Patients who had experienced nausea of ‘moderate’ or ‘severe’ intensity, or \( \geq 4/10 \) on a 0-10 Likert scale were classified as meeting this criterion.

- **Inability to tolerate a solid or semi-solid oral diet over the preceding two mealtimes.**
  Patients were deemed to have met this criterion if they consumed less than 25% of their self-reported pre-operative meal quantity.

- **Abdominal distension.**
  This was clinician-defined as those with ‘moderate’ or ‘severe’ distension.

- **Absence of flatus AND stool over the preceding 24 hours.**
  In those with a stoma this was defined as the absence of air or bowel contents in the stoma bag.

- **Radiologic evidence of ileus on abdominal plain film or CT over the preceding 24 hours.**
  Patients were deemed to have met this criterion if two or more of the following three features were noted on imaging – gastric distension, presence of air-fluid levels, and dilated small or large bowel loops without a transition point.

8.3.7 Patient Assessment

Patients were prospectively assessed for PPOI between 8-9am on a daily basis from Day 4 post-operatively until discharge. These assessments were made independently by a single investigator (Ryash Vather) who was not affiliated with the overseeing clinical team.
8.3.8 **Statistical Analysis**

Statistical analysis was performed using SPSS for Windows (Version 19; SPSS, Chicago, Illinois, USA).

8.3.8.1 **Univariate and Logistic Regression Analyses**

Analysed variables were stratified according to the presence or absence of PPOI. Parametricity was determined using the Shapiro-Wilk test, with normally distributed data being expressed as mean ± standard deviation (SD) and non-parametric data as median ± interquartile range (IQR). Univariate analysis was carried out using the $\chi^2$ test for categorical variables, the Mann-Whitney U or Kruskal Wallis tests for non-parametric continuous variables, and an independent samples $t$-test for parametric continuous variables. All variables which were significant or near significant (p<0.10) on univariate analysis were entered into a logistic regression model. An omnibus test of model coefficients was carried out prior to performance of logistic regression with subsequent identification and insertion of a constant. Closely related parameters were input exclusively into separate regression models to avoid erroneous correction for each other. Results were considered statistically significant if p<0.05.

8.3.8.2 **Construction of a Risk Prediction Tool**

Variables identified as independent predictors of PPOI on regression analyses were then used to generate two score-based risk stratification systems – one which predicted risk incorporating variables across the pre-, intra- and the immediate post-operative period (Ileus Score 1 [I-Score 1]); and a second which could be compiled using wholly pre- and intra-operative factors (Ileus Score 2 [I-Score 2]). Multiple iterations of each scoring system were constructed using varying data point ‘cut-offs’ with the discriminative capacity of each system being interrogated using receiver operating characteristic (ROC) curves. The area under the ROC curve (c-value of discrimination) was used to appraise predictive accuracy. An area-under-curve (AUC) of 1.0 indicates a perfect test while an area of 0.5 signifies an ineffective test; an area between 0.7-0.8 represents ‘fair discrimination’ at predicting a binary outcome.[315]
8.4 Results

8.4.1 Patient Flow

Patient flow is consistent with that described in the randomised controlled trial (Section 7.4.1) and is summarised below. The single exception to this was a patient who was found at pre-admission clinic to meet exclusion criteria of the clinical trial because of previous anaphylaxis to an iodinated contrast agent; she was subsequently approached for involvement in the present prospective observational study but declined consent.

In total, 351 patients met eligibility criteria and were approached for study enrolment. Seven patients declined consent and a further five were unable to provide consent because of dementia (n=3), psychosis (n=1), and severe Asperger’s syndrome (n=1). Three patients met exclusion criteria of being on pre-operative parenteral nutrition. Nine patients were excluded prior to commencing formal Day 4 assessment of PPOI for the following reasons – re-operation before Day 4 for wound dehiscence (n=3), abdominal sepsis (n=2), necrotising deep tissue infection (n=1), or intra-abdominal bleed (n=1); intubation and ventilation in ICU for sepsis (n=1); and post-operative ischaemic stroke on Day 2 (n=1). PPOI was observed to occur in 88 of the remaining 327 patients (26.9%).

8.4.2 Database Integrity

Recording of variables for the final data set was 99.7% complete.

8.4.3 Significant Correlates of PPOI

Results of univariate analysis are presented in Table 8-1. A higher proportion of males developed PPOI than females (31.9% vs 20.4%; p=0.020) with no significant differences noted between groups in age and ethnicity. Pre-existing cardiac and renal disease were significant correlates of PPOI but regular medication and smoking status were not. The occurrence of PPOI was associated with higher pre-operative BMI (28.0 vs 25.6 kg/m²; p=0.005) and worsening ASA grade (p=0.008). Right hemicolecction, total colectomy, and reversal of Hartmann’s or end ileostomy had a higher incidence of PPOI than other procedures (p=0.003). Surgery entailing colostomy formation or reversal of loop/end ileostomy was associated with a lower rate of prolonged ileus (p=0.047). Operative technique and duration, stoma formation, use of epidural or spinal regional anaesthesia, surgeon, wound size, bowel resection length, and surgeon-assessed operative difficulty, bowel handling and estimated blood loss were all found to significantly correlate with PPOI. Patients who developed PPOI were administered significantly more intravenous crystalloid, colloid and red blood cell units before diagnosis than their non-PPOI counterparts; they were
### Table 8-1 Results of univariate analysis.

Parametric variables are daggered (†) and expressed as mean±SD; all remaining continuous variables are non-parametric and expressed as median±IQR. Variables analysed without ‘reversal of ileostomy’ are double daggered (‡). Significant p-values are starred (*).

<table>
<thead>
<tr>
<th></th>
<th>PPOI n=88 (26.9%)</th>
<th>Non-PPOI n=239</th>
<th>All n=327</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>68.4±23</td>
<td>66.1±23</td>
<td>67.0±23</td>
<td>0.205</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59 (31.9%)</td>
<td>126</td>
<td>185</td>
<td>0.020*</td>
</tr>
<tr>
<td>Female</td>
<td>29 (20.4%)</td>
<td>113</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
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<td></td>
<td></td>
<td>0.768</td>
</tr>
<tr>
<td>European</td>
<td>66 (26.2%)</td>
<td>186</td>
<td>252</td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>5 (38.5%)</td>
<td>8</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>4 (23.5%)</td>
<td>13</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>13 (28.9%)</td>
<td>32</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td><strong>Medical Co-morbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous Abdominal Surgery</td>
<td>46 (23.5%)</td>
<td>150</td>
<td>196</td>
<td>0.098</td>
</tr>
<tr>
<td>Previous PPOI</td>
<td>8 (23.5%)</td>
<td>26</td>
<td>34</td>
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</tr>
<tr>
<td>Cardiac</td>
<td>35 (34.3%)</td>
<td>67</td>
<td>102</td>
<td>0.042*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (31.8%)</td>
<td>107</td>
<td>157</td>
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</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>3 (20%)</td>
<td>12</td>
<td>15</td>
<td>0.537</td>
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<tr>
<td>Respiratory</td>
<td>26 (35.6%)</td>
<td>47</td>
<td>73</td>
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<tr>
<td>Renal</td>
<td>25 (41.0%)</td>
<td>36</td>
<td>61</td>
<td>0.006*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15 (31.9%)</td>
<td>32</td>
<td>47</td>
<td>0.403</td>
</tr>
<tr>
<td>Neurological</td>
<td>6 (26.1%)</td>
<td>17</td>
<td>23</td>
<td>0.926</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>14 (32.6%)</td>
<td>29</td>
<td>43</td>
<td>0.370</td>
</tr>
<tr>
<td><strong>Pre-operative Medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>24 (25.3%)</td>
<td>71</td>
<td>95</td>
<td>0.667</td>
</tr>
<tr>
<td>Opioid</td>
<td>6 (21.4%)</td>
<td>22</td>
<td>28</td>
<td>0.494</td>
</tr>
<tr>
<td>Steroids</td>
<td>5 (35.7%)</td>
<td>9</td>
<td>14</td>
<td>0.448</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>21 (36.2%)</td>
<td>37</td>
<td>58</td>
<td>0.078</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>33 (31.7%)</td>
<td>71</td>
<td>104</td>
<td>0.180</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>20 (30.8%)</td>
<td>45</td>
<td>65</td>
<td>0.433</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1 (14.3%)</td>
<td>6</td>
<td>7</td>
<td>0.446</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>14 (26.9%)</td>
<td>38</td>
<td>52</td>
<td>0.998</td>
</tr>
<tr>
<td>Statin</td>
<td>31 (30.4%)</td>
<td>71</td>
<td>102</td>
<td>0.339</td>
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<td><strong>Smoker</strong></td>
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<td></td>
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<td>0.174</td>
</tr>
<tr>
<td>Current</td>
<td>9 (25%)</td>
<td>27</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>45 (32.1%)</td>
<td>95</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>34 (22.5%)</td>
<td>117</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td><strong>Bloods (pre-operative)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin†</td>
<td>127.6±20.6</td>
<td>129.0±18.4</td>
<td>126.6±19.1</td>
<td>0.937</td>
</tr>
<tr>
<td>White count</td>
<td>7.2±2.5</td>
<td>6.6±2.5</td>
<td>6.8±2.5</td>
<td>0.133</td>
</tr>
<tr>
<td>Creatinine</td>
<td>75±31</td>
<td>74±22.5</td>
<td>74±24.8</td>
<td>0.129</td>
</tr>
<tr>
<td>Albumin</td>
<td>42±5</td>
<td>43±4</td>
<td>42±4</td>
<td>0.053</td>
</tr>
<tr>
<td>Sodium</td>
<td>140±3</td>
<td>140±3</td>
<td>140±3</td>
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<td>PPOI n=88 (26.9%)</td>
<td>Non-PPOI n=239</td>
<td>All n=327</td>
<td>p-value</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>Potassium†</td>
<td>4.1±0.4</td>
<td>4.2±0.4</td>
<td>4.2±0.4</td>
<td>0.126</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.3±0.2</td>
<td>2.3±0.1</td>
<td>2.3±0.1</td>
<td>0.173</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.82±0.1</td>
<td>0.84±0.1</td>
<td>0.83±0.1</td>
<td>0.157</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>28.0±7</td>
<td>25.6±6</td>
<td>26.2±6</td>
<td>0.005*</td>
</tr>
<tr>
<td>ASA grade</td>
<td></td>
<td></td>
<td></td>
<td>0.008*</td>
</tr>
<tr>
<td>1</td>
<td>1 (4.8%)</td>
<td>20</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>47 (24.9%)</td>
<td>142</td>
<td>189</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40 (34.2%)</td>
<td>77</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
<td>0.534</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>69 (28.3%)</td>
<td>175</td>
<td>244</td>
<td></td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>7 (23.3%)</td>
<td>23</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Diverticular Disease</td>
<td>3 (12.5%)</td>
<td>21</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (31.0%)</td>
<td>20</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
<td>0.003*</td>
</tr>
<tr>
<td>R. hemicolectomy</td>
<td>19 (35.8%)</td>
<td>34</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Anterior resection</td>
<td>28 (25.2%)</td>
<td>83</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>Abdominoperineal resection</td>
<td>4 (28.6%)</td>
<td>10</td>
<td>14</td>
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<tr>
<td>Total colectomy</td>
<td>7 (58.3%)</td>
<td>5</td>
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<tr>
<td>Reversal loop ileostomy</td>
<td>12 (14.8%)</td>
<td>69</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Reversal Hartmann's or end ileostomy</td>
<td>14 (45.2%)</td>
<td>17</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (16.0%)</td>
<td>21</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Technique‡</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Open</td>
<td>48 (48%)</td>
<td>52</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>20 (15.9%)</td>
<td>106</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Converted</td>
<td>8 (40%)</td>
<td>12</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Stoma Formation</td>
<td></td>
<td></td>
<td></td>
<td>0.047*</td>
</tr>
<tr>
<td>Ileostomy</td>
<td>27 (31.0%)</td>
<td>60</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Colostomy</td>
<td>4 (19.0%)</td>
<td>17</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Reversal</td>
<td>14 (16.5%)</td>
<td>71</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>43 (32.1%)</td>
<td>91</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>Regional anaesthesia‡</td>
<td></td>
<td></td>
<td></td>
<td>0.003*</td>
</tr>
<tr>
<td>Epidural</td>
<td>35 (45.5%)</td>
<td>42</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Spinal</td>
<td>5 (33.3%)</td>
<td>10</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>36 (23.4%)</td>
<td>118</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>Epidural duration (days)</td>
<td>2±2</td>
<td>3±1.3</td>
<td>3±1</td>
<td>0.579</td>
</tr>
<tr>
<td>Surgeon</td>
<td></td>
<td></td>
<td></td>
<td>0.039*</td>
</tr>
<tr>
<td>A</td>
<td>19 (19.4%)</td>
<td>79</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>5 (25%)</td>
<td>15</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>20 (44.4%)</td>
<td>25</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>22 (28.6%)</td>
<td>55</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>22 (25.3%)</td>
<td>65</td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at p<0.05. **Significant at p<0.01.

Table 8-1 (Continued).
<table>
<thead>
<tr>
<th></th>
<th>PPOI n=88 (26.9%)</th>
<th>Non-PPOI n=239</th>
<th>All n=327</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative Duration (mins)</td>
<td>198±127</td>
<td>167±140</td>
<td>180±137.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Wound size (cm)‡</td>
<td>18±10</td>
<td>12±12</td>
<td>15±11</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Bowel resection Length (cm)‡</td>
<td>29±25</td>
<td>21±24.2</td>
<td>23±25</td>
<td>0.005*</td>
</tr>
<tr>
<td>Operative Difficulty</td>
<td>7±3</td>
<td>5±3</td>
<td>6±4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Operative Bowel Handling</td>
<td>6±3</td>
<td>4 (3)</td>
<td>5 (4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Estimated Blood Loss (mls)</td>
<td>100±170</td>
<td>40±100</td>
<td>50±150</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Operative Contamination</td>
<td></td>
<td></td>
<td>0.374</td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>81 (26.4%)</td>
<td>226</td>
<td>307</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>6 (42.9%)</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (20%)</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Intravenous Fluid (total)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid (L)</td>
<td>6.1±3.2</td>
<td>3.2±2.2</td>
<td>4.0±2.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Colloid (L)</td>
<td>0.49±0.97</td>
<td>0.27±0.81</td>
<td>0.33±0.86</td>
<td>0.001*</td>
</tr>
<tr>
<td>Red cells (units)</td>
<td>0.50±1.2</td>
<td>0.26±0.9</td>
<td>0.32±1.0</td>
<td>0.042*</td>
</tr>
<tr>
<td>Peri-operative Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction Agent (Propofol)</td>
<td>110±70</td>
<td>120±73</td>
<td>120±80</td>
<td>0.851</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>11±2</td>
<td>11±3</td>
<td>11±2</td>
<td>0.021*</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0±0.2</td>
<td>0±0.3</td>
<td>0±0.25</td>
<td>0.322</td>
</tr>
<tr>
<td>MEDD Opioid</td>
<td>30.5±34.0</td>
<td>27±26.4</td>
<td>27.6±28.6</td>
<td>0.100</td>
</tr>
<tr>
<td><strong>Bloods (Day 1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin†</td>
<td>111.1±18.1</td>
<td>114.1±16.9</td>
<td>113.2±17.3</td>
<td>0.410</td>
</tr>
<tr>
<td>White count</td>
<td>10.5±4.3</td>
<td>10.5±3.4</td>
<td>10.5±3.7</td>
<td>0.586</td>
</tr>
<tr>
<td>Creatinine</td>
<td>81±39</td>
<td>70±31</td>
<td>72.5±33</td>
<td>0.006*</td>
</tr>
<tr>
<td>Albumin†</td>
<td>34.3±4.3</td>
<td>34.8±4.4</td>
<td>34.6±4.4</td>
<td>0.491</td>
</tr>
<tr>
<td>Sodium</td>
<td>138±3</td>
<td>137±3</td>
<td>137±3</td>
<td>0.428</td>
</tr>
<tr>
<td>Potassium†</td>
<td>4.1±0.4</td>
<td>4.1±0.4</td>
<td>4.1±0.4</td>
<td>0.747</td>
</tr>
<tr>
<td>Calcium‡</td>
<td>2.2±0.1</td>
<td>2.2±0.1</td>
<td>2.2±0.1</td>
<td>0.073</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.83±0.14</td>
<td>0.84±0.12</td>
<td>0.84±0.12</td>
<td>0.390</td>
</tr>
<tr>
<td><strong>Bloods (Day 3)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin†</td>
<td>112.7±18.2</td>
<td>116.0±17.8</td>
<td>114.9±17.9</td>
<td>0.313</td>
</tr>
<tr>
<td>White count</td>
<td>8.3±4.6</td>
<td>8.1±3.7</td>
<td>8.2±4.1</td>
<td>0.867</td>
</tr>
<tr>
<td>Creatinine</td>
<td>74±35</td>
<td>71±27.5</td>
<td>72±24.2</td>
<td>0.017*</td>
</tr>
<tr>
<td>Sodium</td>
<td>137±4</td>
<td>137±3</td>
<td>137±3.2</td>
<td>0.023*</td>
</tr>
<tr>
<td>Potassium</td>
<td>4±0.5</td>
<td>4±0.5</td>
<td>4±0.5</td>
<td>0.037*</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.3±0.1</td>
<td>2.3±0.1</td>
<td>2.3±0.1</td>
<td>0.950</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.79±0.1</td>
<td>0.78±0.1</td>
<td>0.78±0.1</td>
<td>0.424</td>
</tr>
<tr>
<td>Haemoglobin drop across surgery†</td>
<td>16.5±14.1</td>
<td>14.9±12.4</td>
<td>15.4±13.0</td>
<td>0.323</td>
</tr>
<tr>
<td>Creatinine drop across surgery</td>
<td>-1±18</td>
<td>1±13</td>
<td>0±13</td>
<td>0.064</td>
</tr>
<tr>
<td>Albumin drop across surgery†</td>
<td>6.8±4.8</td>
<td>7.2±5.2</td>
<td>7.1±4.7</td>
<td>0.475</td>
</tr>
<tr>
<td>Day of first mobilisation</td>
<td>2±3</td>
<td>1±1</td>
<td>1±1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>ERAS‡</td>
<td>23 (24.7%)</td>
<td>68</td>
<td>93</td>
<td>0.288</td>
</tr>
</tbody>
</table>

*Table 8-1 (Continued).*
also noted to have a higher creatinine on Day 1 and Day 3 post-operatively. Day of first mobilisation occurred later in those who developed PPOI (Day 2 vs Day 1; p<0.001). There was no significant difference in the incidence of PPOI in the ERAS group (24.7%) vs. those who underwent standard multimodal care (27.5%) (p=0.288).

8.4.4 Independent Predictors of PPOI

Logistic regression analyses identified a number of independent predictors for PPOI as displayed in Table 8-2. Pre-operative predictors included male gender (OR 3.01 [vs. female]), and decreasing pre-operative albumin (OR 1.11 [per g/L unit change]). Intra-operative predictors of PPOI included open or converted technique (OR 6.37 [vs. laparoscopic technique]), increasing wound size (OR 1.09 [per cm]), surgeon-assessed operative difficulty (OR 1.28 [per unit on 10-point Likert scale]) and surgeon-assessed bowel handling (OR 1.38 [per unit on 10-point Likert scale]). To avoid correction of related variables separate regression models were created for operative technique and wound size, and operative difficulty and bowel handling. All ‘reversal of loop ileostomy’ cases were likewise excluded from regression when evaluating operative technique and wound size to avoid skewing of effect estimate. Post-operative predictors of PPOI were increasing intravenous crystalloid administration (OR 1.55 [per litre]), increasing red cell transfusion (OR 1.84 [per unit]), and later day of first mobilisation (OR 1.39 [per day]).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (vs. female)</td>
<td>3.01</td>
<td>1.25</td>
<td>7.27</td>
</tr>
<tr>
<td>Decreasing pre-operative albumin (per g/L unit)</td>
<td>1.11</td>
<td>1.02</td>
<td>1.22</td>
</tr>
<tr>
<td>Open/converted technique (vs. laparoscopic)</td>
<td>6.37</td>
<td>1.68</td>
<td>24.39</td>
</tr>
<tr>
<td>Increasing wound size (per cm)</td>
<td>1.09</td>
<td>1.02</td>
<td>1.16</td>
</tr>
<tr>
<td>Operative difficulty (per unit)</td>
<td>1.28</td>
<td>1.03</td>
<td>1.59</td>
</tr>
<tr>
<td>Operative bowel handling (per unit)</td>
<td>1.38</td>
<td>1.08</td>
<td>1.76</td>
</tr>
<tr>
<td>Total IV crystalloid (per litre)</td>
<td>1.55</td>
<td>1.24</td>
<td>1.93</td>
</tr>
<tr>
<td>Red cell transfusion (per unit)</td>
<td>1.84</td>
<td>1.06</td>
<td>3.22</td>
</tr>
<tr>
<td>First mobilisation (per day)</td>
<td>1.39</td>
<td>1.13</td>
<td>1.71</td>
</tr>
</tbody>
</table>

Table 8-2 Results of logistic regression.
8.4.5 Risk Stratification System for PPOI

8.4.5.1 System Construction

The I-Score 1 and I-Score 2 risk stratification systems were constructed using the results of logistic regression. Surgeon-assessed operative difficulty and bowel handling were found to confer a similar predictive effect on ROC analysis in all scoring system iterations whether input independently or in tandem; operative difficulty was therefore used exclusively for simplicity. Both operative technique and wound size were included in models because their relation to each other was not evident; for example, 50/126 laparoscopic cases had wound sizes >10cm and 7/120 open/converted cases had wound sizes <10cm. Laparoscopic wounds >10cm were most often related to extended umbilical port wounds or Pfannenstiel incisions for specimen delivery. For both scoring systems ‘reversal of loop ileostomy’ was considered an open procedure. Uniform single-point scoring was used for identified variables as it was found that weighted scoring for variables with higher odds ratios did not confer a predictive advantage on ROC analyses.

8.4.5.2 I-Score 1

The I-Score 1 incorporated independent predictors of PPOI from the pre-, intra-, and immediate post-operative periods to generate a score out of 8 (Table 8-3). Data point breaks for continuous variables were selected as follows: albumin (<34g/L), operative difficulty (≥8/10 on a Likert scale), wound size (>10cm), and intravenous crystalloid administration (>5L). These values were chosen for each variable as they provided a balance between optimising discriminative capacity and enhancing clinical utility. Retroactive application of this scoring system to the source dataset showed distinct cut-offs in PPOI incidence between scores of ≤1 vs. 2-3 vs. ≥4 (p<0.001). ROC analyses demonstrated the I-Score 1 to have ‘fair’ discriminative capacity (AUC 0.791, 95%CI 0.738-0.844; Figure 8-2).

8.4.5.3 I-Score 2

The I-Score 1 was revised to include only pre- and intra-operative independent predictors of PPOI. This led to the development of the I-Score 2 which excluded day of first mobilisation and intravenous crystalloid consumption to generate a score out of 6 (Table 8-4). Dataset cut-offs were discerned to occur at scores of ≤1 vs. 2 vs. ≥3 (p<0.001) with a 7-fold increase in risk from low to high-risk strata. The I-Score 2 was found to have a marginally lower predictive capability than the I-Score 1 on ROC analyses but retained ‘fair’ discrimination with respect to PPOI risk (AUC 0.742, 95%CI 0.684-0.799; Figure 8-2).
Male gender 1
Pre-operative albumin <34g/L 1
Operative difficulty ≥8/10 1
Open/converted technique 1
Wound size >10cm 1
RBC transfusion 1
IV crystalloid >5L 1
First mobilisation after Day 1 1

8

<table>
<thead>
<tr>
<th>I-Score 1</th>
<th>PPOI</th>
<th>Total</th>
<th>Incidence of PPOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>0-1</td>
<td>3</td>
<td>87</td>
</tr>
<tr>
<td>Moderate-risk</td>
<td>2-3</td>
<td>26</td>
<td>135</td>
</tr>
<tr>
<td>High-risk</td>
<td>≥4</td>
<td>59</td>
<td>105</td>
</tr>
</tbody>
</table>

Table 8-3 I-Score 1 risk stratification system.

Male gender 1
Pre-operative albumin <34g/L 1
Operative difficulty ≥8/10 1
Open/converted technique 1
Wound size >10cm 1
Red cell transfusion 1

6

<table>
<thead>
<tr>
<th>I-Score 2</th>
<th>PPOI</th>
<th>Total</th>
<th>Incidence of PPOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>0-1</td>
<td>7</td>
<td>106</td>
</tr>
<tr>
<td>Moderate-risk</td>
<td>2</td>
<td>31</td>
<td>118</td>
</tr>
<tr>
<td>High-risk</td>
<td>≥3</td>
<td>50</td>
<td>103</td>
</tr>
</tbody>
</table>

Table 8-4 I-Score 2 risk stratification system.
8.4.5.4 Risk scoring without ‘reversal of loop ileostomy’

ROC analyses were repeated with ‘reversal of loop ileostomy’ cases excluded from the data set to ensure these procedures had not skewed results. Adjusted AUCs for the I-Score 1 and I-Score 2 were 0.786 (95%CI 0.728-0.843) and 0.746 (95%CI 0.684-0.808) respectively.
8.5 Discussion

Many of the independent predictors of PPOI identified in this study’s logistic regression model are concordant with those previously described in the literature. Recurring predictors of prolonged ileus after colorectal surgery in other risk factor analyses include male gender[46, 121] and RBC transfusion (or estimated blood loss);[111, 121] lower pre-operative albumin was correlated with PPOI in two of these analyses but this association did not persist on regression.[45, 46] Although it is difficult in a clinical setting to individually interrogate each of the identified variables, many can be linked to the likely aetiology of PPOI. Operative blood loss may translate to relative ischaemia at the level of the bowel wall with subsequent myocyte dysfunction.[13] Low albumin is likely to precipitate PPOI by causing intestinal oncotic oedema but also reflects poor systemic nutritional reserves.[316] Recovery of gastrointestinal function after abdominal surgery has been shown to occur an average of 2 days later in patients who undergo open vs. laparoscopic surgery.[48] While this applies to ‘normal’ ileus there is ostensibly a degree of overlap with the occurrence of prolonged ileus, and therefore represents a finding consistent with those described in this study. Intravenous crystalloid has been identified as a major risk factor for developing PPOI, with a 1.5-fold increase in risk for each litre administered. Overzealous peri-operative fluid delivery has been strongly associated with impaired gastrointestinal function, and it is postulated that this may occur by either causing gut wall oedema or local electrolyte disturbances.[10, 11]

It was noted with interest that surgeon-assessed operative difficulty and degree of bowel handling were independent predictors for PPOI. This for the first time objectively quantifies the surgeon’s anecdotal ability to identify patients at risk of experiencing a delay to resumption of normal gut function. Operative difficulty and bowel handling are parameters closely related to one another, and may reflect challenges inherent to other identified variables such as operating within a narrower male pelvis and in procedures requiring conversion to open or red cell transfusion for bleeding.

The impact of opioid analgesia on gastrointestinal function has been well elucidated. Impaired gut motility occurs as a result of activation of peripheral μ–opioid receptors located within the myenteric plexus which in turn inhibit release of acetylcholine and decrease smooth muscle tone.[74, 81, 83] Narcotic-related dysmotility is thought to play a central role in post-operative gut dysfunction and this is strongly corroborated by the success of Alvimopan, a μ–opioid receptor antagonist, in shortening the duration of ‘normal’ ileus.[84] The absence of peri-operative opioid consumption as an independent predictor for PPOI in
the present study therefore represents an important negative finding. Review of the literature shows an identical result in all risk factor analyses examining this parameter including that described in Chapter 3,[45, 46, 111] and suggests that mechanisms unrelated to narcotic analgesia are more critical to the pathogenesis of prolonged ileus.

PPOI occurs in a significant subset of those undergoing colorectal surgery and its clinical impact extends to both patient and hospital. Although many attempts have been made to identify the aetiologic mechanisms of PPOI and deliver targeted therapy, to date there is no effective treatment to shorten its duration. There are however a number of measures thought to be of preventive benefit. These include the use of thoracic epidurals with local anaesthetic infusion, restrictive intravenous fluid regimens, gum chewing, rigorous monitoring and correction of electrolytes, and early mobilisation.[317, 318] Multimodal ERAS programs integrate many of these elements with the prevention of ileus having been cited as a ‘key objective’ in a recent consensus review.[125] In the absence of the universal application of all these techniques, there exists a niche for a system capable of predicting those at risk of developing PPOI and alerting the clinician to focus attention on the early institution of preventive measures.

The present study has developed two scoring systems and has demonstrated an 16-fold and 7-fold increase in risk of PPOI between low and high-risk strata for the I-Score 1 and I-Score 2 systems respectively. Although the I-Score 1 shows improved discriminative capacity on ROC analysis when compared to the I-Score 2, the application of the latter tool at the conclusion of surgery offers a simple and timely method of appraising risk. Patients falling into the ‘high-risk’ bracket may be candidates for a dedicated pathway incorporating elements such as enforced mobilisation on Day 0 or Day 1, gum-chewing, early oral feeding, and vigilant monitoring of restrictive fluid prescription. Additionally, it may be possible in select cases to predict those at ‘high-risk’ during pre-operative work-up (for example, males with low albumin presenting for an open procedure with an anticipated wound size greater than 10cm). Such patients have close to a 50% risk of developing PPOI after surgery and may therefore be candidates for pre-operative counselling of the condition and in particular its association with prolonged hospital stay.

A number of risk scoring systems have been previously created for predicting outcomes after surgery.[319] Apart from the efficacy of such systems, important considerations include their ease of application and clinical utility. Models which incorporate readily available variables are easier to use, less liable to having missing entries, and therefore typically more accurately compiled than their counterparts which require input of non-routine variables. This may however come at the expense of reduced discriminative capacity. Furthermore,
stratification systems capable of predicting outcomes before the occurrence of an event not only allow the timely institution of preventive measures but may also serve as an audit tool comparing outcomes between surgical cohorts.[319, 320] A key objective in the creation of the present study’s prediction models was simplicity and the ability to implement it at a clinically opportune time. The I-Score 2 collates six easily assessable parameters and may be executed at the end of surgery to estimate risk of developing PPOI. It is hoped that, in line with other scoring systems,[321, 322] continued iterations of this model will improve its discriminative capacity and translate its applicability to other surgical populations.

An important limitation of the present study is the lack of internal and external validation of the I-Score. The sample size of this cohort did not permit split-sampling cross-validation, and the rigorous definition of PPOI utilised meant validation could not be undertaken retrospectively. It is therefore yet to be determined whether the proposed scoring systems will retain their predictive capability in an independent data set. These concerns may be addressed by further prospective appraisal.
8.6 Conclusion

The incidence of PPOI in this cohort was 26.9%. Independent predictors for the development of PPOI included male gender, decreasing pre-operative albumin, open/converted surgical technique, increasing wound size, surgeon-assessed operative difficulty and bowel handling, total intravenous crystalloid, red cell transfusion, and day of first mobilisation. Peri-operative opioid consumption was neither a correlate or predictor of PPOI. Results of logistic regression were used to construct two novel risk stratification systems for the occurrence of PPOI. Both demonstrated ‘fair’ predictive capability on ROC analyses, with the second model utilising only pre- and intra-operative variables and showing a 7-fold increase in risk from low to high-risk strata. Further prospective evaluation is required to adequately validate these scoring systems.
9.1 Background

The peri-operative period is associated with profound disturbances to normal gastrointestinal function. This is thought to stem from a combination of inflammatory cell activation, electrolyte imbalance, autonomic dysfunction, and activation of peripheral opioid-receptors – all features associated with surgical trauma and the ensuing post-operative recovery, and clinically manifest as the ileus syndrome. However, the mechanism by which pathogenic disturbances at the level of the gut translate to clinical symptoms is not well understood. It is presumed that the missing intermediary step relates to aberrations of normal intestinal contractility. Dysfunction may result from gastrointestinal hypomotility, dysmotility, or the complete absence of motility.[73, 92, 101, 102] It is therefore valuable to characterise the fundamental changes in intestinal contractility which underpin post-operative ileus. This in turn may identify new therapeutic targets and also has the potential to serve as an objective and quantifiable baseline against which the efficacy of future interventions to treat ileus can be measured.

To date, two major obstacles have hindered the ability to accurately characterise in vivo motility changes in POI. The first relates to the ethical concerns which arise with accessing a segment of the gastrointestinal tract during the peri-operative period. A manometry device which measures gastric and/or small bowel pressure changes will require pre-operative placement (and connection to an acquisition unit) via the oesophagus and oro- or naso-pharynx. This may directly interfere with anaesthetic pre-oxygenation and endotracheal intubation, and has the potential to be easily removed by a patient emerging from anaesthesia. A second option is intra-luminal placement of a recording device via visceral incision at the time of surgery, but this is unethical in a human cohort. A final consideration is siting of a manometry tool within the large bowel via the anus. Although this placement may provide a feasible means of acquiring peri-operative motility data, it is important particularly in the context of colorectal resection that such a device does not interfere with the formation or healing of a new anastomosis.

A second barrier to defining in vivo motility is the inability to reliably and reproducibly record and present data on pressure movement within the bowel. Literature attempting to characterise in vivo contractility have traditionally used isolated barometric or ‘low resolution’ manometric recording devices capable of obtaining pressure readings at discrete intervals of 7-15cm.[58-60] This has been significantly mitigated recently with the development of a High Resolution Manometry (HRM) catheter – a novel tool designed to record in vivo spatiotemporal luminal pressure readings at 1cm intervals thereby providing information on actual pressure wave propagation.[323, 324] The HRM device has greatly improved the
sensitivity and detail of recordings without compromising the flexibility or safety of the catheter itself.[104]

It is proposed that colorectal surgical cases form an ideal cohort within which to investigate ileus-related motility changes. Procedures typically involve substantial bowel handling and entail the formation of an enteric anastomosis. Both of these features have been previously correlated with post-operative gastrointestinal dysfunction of increased severity.[2, 17, 22, 47] Furthermore, when compared to the upper gut, coordinated colorectal function is more dependent on extrinsic innervation than intrinsic myenteric activity.[21, 55-57] An accurate characterisation of peri-operative distal propagating activity in a colorectal surgical cohort therefore stands to shed light not only on the actual changes in motility but, via comparison with healthy controls, may also facilitate insight into whether clinical recovery is attributable to a return of ‘normal’ extrinsically regulated and patterned motor activity.

9.2 Study Objective

The aim of this study was to characterise changes in distal colorectal motility through the pre-operative, intra-operative and immediate post-operative periods in human patients undergoing elective right hemicolecotomy using an in vivo high resolution manometry catheter.
9.3 Methods

9.3.1 Ethics Approval

Ethical approval was obtained from the Ministry of Health’s National Ethics Committee (NTX12/06/049) and Auckland District Health Board's Multidisciplinary Research Review Committee (A+5601) prior to study commencement.

9.3.2 Study Population

The source population included all New Zealand citizens and permanent residents living within the catchment area of ADHB. All patients scheduled to undergo elective intra-abdominal colorectal surgery for any indication between August 2013 and September 2014 were screened for eligibility. Inclusion criteria for this study were patients between 18 and 75 years of age coming forward for elective standard, limited or extended right hemicolectomy. This was to be performed by the Colorectal Unit at Auckland City Hospital using laparoscopic or open technique. Exclusion criteria were all patients with a current or previous functional gastrointestinal motility disorder; presence of a co-existing medical illness known to affect colorectal motility; ASA of 4 or greater; those anticipated on anaesthetic pre-assessment to require High-Dependency Unit (HDU) or ICU support; those requiring epidural placement; current pregnancy; and those who had previously undergone gastrointestinal surgery.

9.3.3 Recruitment and Consent

Potential patients were approached on an individual basis pre-operatively by the study investigator (Ryash Vather) and provided with verbal information on research rationale and protocol. Patients were also given a Participant Information Sheet which included investigator contact details (Appendix D). If initially agreeable to involvement, contact was made with members of the clinical, research, and administrative teams to ensure the planned right hemicolectomy could be scheduled at a time conducive to study execution. Written informed consent was obtained from participants prior to HRM catheter placement and surgery.

9.3.4 High Resolution Manometry

Distal colonic and rectal intraluminal pressure was recorded in vivo using a solid-state high resolution manometry catheter containing 36 individual pressure sensors spaced at one centimetre intervals (Figure 9-1).[325, 326] This catheter utilises fibre-optic technology and was developed, designed and custom-built for the purposes of this study by the
Commonwealth Scientific and Industrial Research Organisation (CSIRO), New South Wales, Australia.

9.3.4.1 Catheter Development, Design and Function

HRM catheter development, design, and validation for clinical use has been previously described in detail by Arkwright et al.[325, 326] Briefly, the device contains multiple fibre-optic strain gauges which, via Wave Division Multiplexing technology, are all interrogated by a single fibre.[325] Each strain gauge consists of a fibre Bragg grating (FBG) enclosed in a rigid metal casing containing a single polarised window with a flexible diaphragm. These units form the sensory component of the catheter and are arranged in series at one centimetre intervals. The entire device is encased in a silicone rubber jacket sealed at its furthest sensory end with a watertight rubber plug and bored plastic head. Its other end is fitted with an optical connector for attachment to a spectral interrogator acquisition unit (FBG-scan 804; FOS&S, Geel, Belgium). The acquisition unit is in turn connected to a laptop computer running a custom-written LabVIEW program (National Instruments, Austin, Texas, USA) displaying pressure changes across all sensors in real time. The sensory portion of the catheter spans 36 cm (1 sensor per cm) in length and has a girth of 3mm.

Variations in intraluminal pressure cause the flexible diaphragms within each strain gauge to flex inward against their specific FBG. This causes changes in the spectral peak of the reflected broadband optical wavelength within each sensor. Spectral peaks are separated by a wavelength of 1.3nm thereby allowing simultaneous recording of multiple sensors in real time across the single fibre.[325-327] HRM devices have been shown to record intra-luminal pressure activity with at least the same consistency and reliability as their solid-state and water-perfused predecessors.[327-329] However, notable advantages of the fibre-optic tool over these devices are improved flexibility, smaller cross-sectional diameter, and the absence of bulky external perfusion pumps or transducers for recording.[325, 326, 329]

9.3.4.2 Acquisition of Equipment (Funding Sources)

The following grants were awarded by their respective bodies via competitive application and were used to purchase the HRM catheter and associated equipment:

- Colorectal Surgical Society of Australia and New Zealand project grant (2012-2014).
- Auckland Medical Research Foundation project grant (2012-2014).
- Maurice and Phyllis Paykel Trust project grant (2012-2014).
Figure 9-1 *Ex vivo* photograph of the high resolution manometry fibre-optic catheter. The catheter tip is located in the upper right corner of the photograph, with the sensor region adjacent. The green arrows point to coloured markings on the sensor region of the catheter (Sensor 10 = black, Sensor 20 = red, Sensor 30 = green), and black markings at 10cm intervals on the non-sensory portion.
9.3.4.3 Catheter Preparation

In vitro calibration of the device was undertaken a day prior to each case. This involved placement of the HRM catheter within a sealed cylindrical tube. Pressures within the sealed system were then manually raised and lowered cyclically between 0-100mmHg using an analogue pressure transducer. Readings were compared to those electronically acquired from the fibre-optic device with information pertaining to a successful calibration being saved as a calibration file on the acquisition system.

Prior to each case, the HRM catheter’s external rubber jacket was labelled at defined points with coloured permanent marker (Sensor 10 – black; Sensor 20 – red; Sensor 30 – green) to allow investigators to endoscopically approximate the intraluminal location of the sensors. Black permanent markings were also made at 10cm intervals from the sensor furthest from the tip, thereby allowing distance of the last sensor from the anal verge to be determined by direct visualisation (Figure 9-1). A 10cm rubber overtube was then placed over the catheter. The internal diameter of this overtube was marginally larger than the external diameter of the catheter. Its function was to reduce the risk of kinking and catheter breakage by allowing free sliding movement within the anal canal. A single loop of nylon was then threaded through the bored notch within the catheter’s plastic head and secured to itself with a double overhand knot. The knot was placed next to the tip and wrapped in multiple layers of stretched Parafilm (Sigma-Aldrich, St. Louis, Missouri, USA) to ensure it did not cause discomfort to the patient upon device insertion or removal.

9.3.4.4 Catheter Placement

Placement of the HRM catheter within the distal colorectum was facilitated by colonoscopy. All colonoscopies were performed by a consultant gastroenterologist or surgeon using either light sedation with midazolam or no sedation, and either low dose intravenous opioid or no analgesia. The antimuscarinic, anticholinergic agent butylscopolamine was not used for any procedure.

Patients were positioned in the left lateral position and lubricant applied to the anal canal. A metal snare (Olympus, Centre Valley, Pennsylvania, USA) was advanced through the endoscope and tightened around the nylon thread at the tip of the HRM catheter. Both scope and catheter were then inserted and advanced per rectally with ample lubrication. The catheter was handled independently of the colonoscope to ensure it did not kink with scope movement and instead advanced or regressed linearly. After reaching a point approximately
Figure 9-2 Endoscopic photograph of HRM catheter attachment.
Figure 9-3 *In situ* radiograph of HRM catheter.
The numbered opaque sensory units show a full-length HRM catheter threaded through the entire large bowel. Use of a full-length HRM catheter was not feasible in the present cohort given participants were to undergo segmental colorectal resection. The red line shows the approximate *in situ* location of the 36-sensor HRM catheter used (*photo courtesy of A/Prof Phil Dinning*).
35-50cm from the anorectal junction (thereby ensuring the entire 36cm sensory portion of the catheter was intraluminal), the catheter was released from the snare with the nylon loop at its tip kept in view. A single endoclip (Olympus, Centre Valley, Pennsylvania, USA) was then advanced through the scope and deployed across the nylon loop, affixing it to colonic mucosa (Figure 9-2 & Figure 9-3). The scope was then gently removed ensuring minimal displacement of the catheter. Participants were turned on the bed to the supine position and the catheter was secured to the inner thigh via Tegaderm (3M, St. Paul, Minnesota, USA). Care was taken to ensure the overtube remained in place across the whole length of the anal canal.

9.3.4.5 Data Recording

Participants were then taken to the endoscopy recovery area in the supine position. The head of the bed was inclined to approximately 30 degrees, and participants were asked to restrict body movement as much as possible. The optical connector of the catheter was attached to the acquisition unit. The previously saved calibration file was loaded and recording commenced. Data was saved in real-time as .txt files. Recording was undertaken in 2-hour periods to minimise risk of corrupting all data in the event of acquisition failure. The position of the HRM catheter was assessed at regular intervals to ensure it had not displaced or dislodged.

9.3.4.6 Catheter Removal

The HRM device was removed upon study completion by disconnecting it from the acquisition unit and applying gentle traction to its ex situ end. A distinct ‘giving-way’ sensation was noted by the investigator as the endoclip detached from colonic mucosa, and catheter and overtube slipped out. This process was painless for the patient.

9.3.4.7 Catheter Sterilisation

The catheter was transported to Auckland City Hospital’s Sterile Services Unit (SSU). Parafilm and nylon were removed from its tip using scissors. SSU staff then sterilised the catheter using standard high level disinfection protocol. Care was taken to ensure the optical connector end of the catheter was hand cleaned and not submerged in disinfection solution. The sterilised catheter was then returned to locked storage.

9.3.4.8 HRM Data Analysis

Each manometric recording was examined for the presence of individual-sensor phasic pressure excursions using PlotHRM – a purpose-built program written in Matlab© (The
Manometric events were defined as pressure excursions of at least 5mmHg occurring in sequence across four or more adjacent sensors (i.e. $\geq 4\text{cm}$), with the upstroke in one channel commencing after the upstroke and before the downstroke in the previous channel. If a pressure excursion returned to baseline before its counterpart in the adjacent channel had started, then the two were not considered part of the same manometric event. Direction of event movement was termed antegrade if moving anally, retrograde if moving orally, and synchronous if stationary. Variables recorded included event frequency, amplitude (mmHg), velocity (cm/s) and extent (cm). To achieve unbiased samples, an in-built ‘random point generator’ in PlotHRM placed a random mark on a random channel. Investigators then observed the next pressure event to the right of the mark. This technique was used where more than twenty events of a particular motor pattern were observed in a given recording period and is consistent with previously performed analyses.[330]

9.3.4.9 ‘Normal’ Colorectal Motility

When recordings are viewed across multiple channels, manometric events form recognizable propagating motor patterns. Dinning et al. have previously characterised colorectal motor patterns in detail by performing pancolonic high resolution manometry in a series of 10 healthy human controls.[330] An important feature of these controls were that all described normal bowel habit with no symptoms of upper gastrointestinal or evacuatory dysfunction. They were also screened to ensure they did not have a history of metabolic, neurogenic or endocrine disorders known to cause constipation or incontinence; did not have a history of abdominal surgery other than appendicectomy; and were not taking regular medications (including laxatives). Propagating motor patterns were described as follows:

- **Cyclic motor patterns** – repetitive pressure events with cyclic frequency of 2-6/min moving retrograde, antegrade, or less frequently synchronously across four or more adjacent sensors. The majority of these events occur in the sigmoid colon where they are the dominant pattern.

- **Short single motor patterns** – isolated propagating pressure events spanning approximately 6-9cm, and separated from other patterns by an interval of more than one minute. These events are characterised as retrograde or antegrade.

- **Long single motor patterns** – isolated propagating pressure events spanning an average of 40cm, and separated from other patterns by an interval of more than one minute. These events occur predominantly in the proximal colon, and are rare compared to cyclic and short single motor patterns.
An important biomarker of normal motility is the motor response of the large bowel to meal ingestion, and has been termed the gastrocolic reflex.[331-335] This was defined by Dinning et al. in the same cohort of human controls using high resolution manometry.[330] Consumption of a high-caloric meal causes an increase in the frequency of propagating motor patterns (occurring within 20 minutes of consumption and lasting at least 2 hours); an increase in the frequency and extent of retrograde cyclic motor patterns, particularly in the sigmoid colon; and an increase in the average amplitude (mmHg) of pressure events compared to those pre-meal.

9.3.5 **Surgery**

It was arranged with clerical and clinical staff for study patients’ right hemicolecotomies to be electively scheduled to occur in the early afternoon. This would provide sufficient time in the morning to place the HRM catheter via limited colonoscopy and obtain baseline recordings before transfer to the operating room. All right hemicolecotomies were performed either by, or under the direct supervision of, a consultant colorectal surgeon at Auckland City Hospital. All patients were placed in the supine position for the duration of surgery. Technical aspects of the procedure were left to the discretion of the surgeon. Briefly, abdominal access was gained via an open (midline or transverse laparotomy) or laparoscopic approach. This was followed by dissection lateral to the caecum and ascending colon with mobilisation of viscera and mesentery towards the midline. Avascular mesenteric windows on either side of the ileocolic pedicle were opened and the vessels skeletonised, ligated and divided. When the bowel was sufficiently mobilised to allow exteriorisation, extracorporeal resection of the involved segment was undertaken with primary stapled enteric anastomosis. The bowel was then returned to the abdominal cavity. The fascia and skin were then closed.

9.3.6 **Manometry Protocol**

9.3.6.1 **Pre-operatively**

Participants were asked to present to Auckland City Hospital’s Endoscopy Suite at 7.30am on the day of their scheduled right hemicolecotomy. In accordance with standard institutional protocol for limited colonoscopy, two fleet enemas were administered rectally with subsequent evacuation of faeces from the distal colorectum. The catheter was then endoscopically sited within the distal large bowel as described above and participants were returned to the recovery area. Recording was commenced with a minimum three-hour period of baseline manometric data being obtained. In accordance with pre-operative protocol, no food or drink was given to participants during this period and all were fitted with antithromboembolic compression stockings.
9.3.6.2 Intra-operatively

Participants were transferred to the Pre-operative Assessment Unit in the late morning shortly before proceeding to the operating room. Care was taken on transfer from bed to operating table and vice versa to ensure the catheter was not inadvertently dislodged. Anaesthetic protocol was left to the discretion of the anaesthetist. Briefly, pre-operative medication included intravenously administered cefoxitin, benzodiazepine (midazolam), short-acting opioid (morphine or fentanyl), and a muscle relaxant (suxamethonium or atracurium). Induction was achieved with intravenous propofol and maintained with an inhaled volatile anaesthetic agent (isoflurane or sevoflurane). Anaesthetic emergence was facilitated by intravenous administration of an anticholinesterase (neostigmine) in combination with a muscarinic antagonist (glycopyrrolate). Manometric recording began prior to induction, and continued uninterrupted through all stages of right hemicolectomy until anaesthetic emergence.

9.3.6.3 Post-operatively

Post-operatively patients were transferred to the Anaesthetic Recovery unit, and then, after full emergence, to the surgical ward. Acquisition of manometric data continued throughout this period with interruptions in recording occurring only when participants were physically transferred between units. The HRM catheter was removed before midday on Day 1 post-operatively thereby allowing approximately 16 hours of post-operative recording. Convalescence on the surgical ward conformed to a protocolised multimodal ERAS rehabilitation programme which mandated stepwise analgesia progression, restrictive post-operative maintenance intravenous fluid therapy, subcutaneous thromboprophylaxis, and early post-operative feeding. The timings at which any solid or semi-solid meals were consumed was noted. Participants were mobilised by nursing staff soon after catheter removal in keeping with ERAS protocol. The remainder of post-operative patient care continued at the discretion of the overseeing clinical team.

9.3.7 Sample Size

It has been previously demonstrated that it is possible to differentiate colonic motility in healthy controls from patients with severe constipation in a sample of 8 subjects per arm.[336] However, in vivo characterisation of peri-operative large bowel motility using high resolution manometry has not been performed previously and presents its own set of ethical and logistical challenges. These include prolonged duration of recording compared to control studies; suitability of and frequency with which patients are placed on the surgical waitlist for right hemicolectomy; anticipated difficulties in obtaining patient consent; and inadequate
understanding of the potential adverse events of *in situ* peri-operative catheter placement. A sample size of between 5-8 patients was therefore deemed clinically, ethically and scientifically appropriate to investigate this study’s hypothesis.

### 9.3.8 Primary Outcome

The primary outcome for this study was the occurrence of propagating motor patterns (as defined above). Motor patterns were quantified by their direction, frequency, amplitude, velocity, and extent.

### 9.3.9 Analysis

All manometric traces were de-identified after recording and manually analysed using PlotHRM. In each manometric recording, obvious artefact and simultaneous pressure events that spanned all recording channels were digitally removed as previously described by Wiklendt et al.[337] Analysis was undertaken independently by two investigators (Ryash Vather, Phil Dinning), with any discrepancies in trace findings being resolved by discussion and consensus.

Although the HRM-defined colonic meal response has been previously used to characterise normal colorectal motility,[330, 338] its utility in the present cohort is limited. Participants were not permitted to commence oral feeding until they reached the ward post-operatively. No meal-induced colonic motor activity would therefore be expected to occur pre- or intra-operatively. Meals consumed on the surgical ward post-operatively were low-caloric, not standardised between patients, and subject to each individual’s ability to tolerate an oral diet. Colonic meal responses were therefore not qualified or quantified in this cohort.

Frequency, amplitude, extent and speed of propagating events were determined for the pre-, intra-, and post-operative periods with data presented as mean ± standard deviation. Comparison of data across the three recording periods were made using one-way analysis of variance (ANOVA). The total time within each period that cyclic motor events formed the predominant pattern was calculated and expressed as a percentage. Average amplitude of pressure events in pre-, intra-, and post-operative periods were calculated characterising pressure at every point, across all channels. This was summed and divided by the number of samples at a data acquisition rate of 10Hz, and compared to the other time periods using one-way ANOVA. All statistics were performed using Prism 5 (GraphPad Software, La Jolla, California, USA). Results were considered statistically significant if p<0.05.
9.4 Results

9.4.1 Patient Flow

Between August 2013 and September 2014, 22 patients were assessed for eligibility. Nine patients declined consent and a further patient was unable to provide informed consent because of mild dementia. Four patients met exclusion criteria of being anticipated to require post-operative HDU/ICU support (n=2), being scheduled for pre-operative siting of an epidural (n=1), and having the anticipated procedure changed to right hemicolecction or subtotal colectomy depending on intra-operative findings (n=1). A further three patients were excluded because of being unable to coordinate endoscopic placement with surgical booking (n=2) or consultant surgeon overseeing patient care declining involvement (n=1).

9.4.2 Baseline Characteristics

*In vivo* high resolution manometry was performed on 5 patients (4 males and 1 female) of median age 58 (range 25-72) years. The original indication for surgery was either neoplasia (n=4) or inflammatory bowel disease (n=1). The mean duration of *in vivo* recording was 316 (range 190-432) minutes pre-operatively; 157.5 (range 88-207) minutes intra-operatively; and 1080 (range 1004-1299) minutes post-operatively.

Participant 2 was noted on catheter placement to have colonic mucosal bridges – consistent with his known Crohn’s disease – approximately 45cm from the anorectal junction. It was unclear if this segment of the gut would be involved in resection and the catheter was therefore secured 10-12cm distal to this lesion. This meant the bottom 6 sensors of the catheter protruded from the anus and did not record manometric data. The sensory portion of the catheter was sited within the distal large bowel in its entirety for all other patients. Participant 1 had a pre-operative diagnosis of caecal adenocarcinoma and was found upon surgery to have advanced locally infiltrative disease. After extensive mobilisation and handling of the right colon (lasting approximately 60 minutes) the procedure was abandoned without formation of an ileocolic anastomosis. All other patients underwent right hemicolecction as planned.

9.4.3 Clinical Correlates

None of the 5 patients passed flatus or stool during the post-operative recording period as determined by self-reporting and nursing observation. In accordance with standard ERAS protocol, all patients were offered breakfast on Day 1 post-operatively of whom two had a light meal. This consisted of a single slice of toast and 2-3 tablespoons of cereal for one patient, and a small serving of fruit salad for the second patient.
Figure 9-4 Summary of contractile activity in the distal colorectum of Patient 4.
Each blue bar provides an overview of distal colorectal contractile activity over a single recording. Blue areas signify periods of colonic quiescence while yellow, green, and red areas signify the presence of and progressive amplitude increase in contractile activity. Cyclic motor events emerged towards the end of the intra-operative period and became the dominant pattern during the first post-operative recording (32 minutes in Anaesthetic Recovery Area).
Figure 9-5 Manometric data acquired over a 10 minute window in a post-operative recording of Patient 4. The blue bar at the top of the figure is an overview of contractile activity within the distal colorectum over a 2 hour recording. The shaded yellow box is a 10 minute window taken from this period. The series of traces below corresponds to recordings taken from each of the 36 sensors on the HRM catheter over this window. Cyclic motor patterns are observed here at a frequency of 2.8 events/minute.
Figure 9-6 Percentage (95% CI) of each recording allotment occupied by cyclic motor events.
9.4.4 Peri-operative Changes in Motility

Observed changes in peri-operative motility were consistent across all five patients; Figure 9-4 and Figure 9-5 provide a sample overview of distal colonic and rectal contractile activity in a single participant (Patient 4). Cyclical motor patterns occurred pre-, intra-, and post-operatively in all patients with a frequency of 2.5-4 cycles/minute. The percentage of each recording period occupied by cyclic motor patterns increased steadily through the peri-operative period (p<0.001) (Figure 9-6). Cyclic events were initially observed for an average of 19.7% of the pre-operative recording time period. This increased steadily through the intra-operative period from before incision (17.2%), through surgery (47.4%), to after abdominal closure (88.2%). Post-operatively, cyclic motor activity occupied between 81-98% of each manometric recording period (overall mean 89.1%). Velocity of random-point identified cyclic motor events did not differ across these recording periods for antegrade (p=0.332) and retrograde (p=0.409) patterns; however, differences were observed for extent (p<0.001) and amplitude (p<0.001) with an increase in both after commencement of surgery (Table 9-1).

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<th>Intra-operative</th>
<th>Post-operative</th>
<th>p-value</th>
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<td><strong>Velocity (cm/s)</strong></td>
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<td>1.78±1.98</td>
<td>1.52±1.05</td>
<td>0.332</td>
</tr>
<tr>
<td><strong>Extent (cm)</strong></td>
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<td>6.94±1.95</td>
<td>7.29±2.64</td>
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<td><strong>Amplitude (mmHg)</strong></td>
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<td>43.96±30.96</td>
<td>32.23±21.75</td>
<td>&lt;0.001*</td>
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<tr>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Velocity (cm/s)</strong></td>
<td>0.409</td>
</tr>
<tr>
<td><strong>Extent (cm)</strong></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Amplitude (mmHg)</strong></td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Table 9-1 Cyclic motor pattern descriptors

A total of 65 retrograde and 44 antegrade short single motor patterns were observed across all recordings. These occurred pre-operatively in all 5 patients at 3.12±4.16 events/hour; intra-operatively in 2 patients at 3.59±2.69 events/hour; and post-operatively in 3 patients at 0.40±0.58 events/hour. Five long single motor patterns were observed in one post-operative recording of a single participant. The percentage of each period occupied by short and long single motor patterns has not been expressed as their occurrence was sporadic and irregular across all three peri-operative recording periods. A significant difference in extent (p=0.002) and amplitude (p<0.001) of antegrade short single motor events; and velocity
(p<0.001) and amplitude (p<0.001) of retrograde short single motor events was identified between recording periods (Table 9-2 & Table 9-3).

### Table 9-2 Short single motor pattern descriptors

<table>
<thead>
<tr>
<th></th>
<th>Pre-operative</th>
<th>Intra-operative</th>
<th>Post-operative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antegrade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity (cm/s)</td>
<td>1.11±0.52</td>
<td>1.33±0.50</td>
<td>0.95±0.92</td>
<td>0.654</td>
</tr>
<tr>
<td>Extent (cm)</td>
<td>3.66±0.57</td>
<td>8±2.45</td>
<td>5±1.73</td>
<td>0.002*</td>
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<tr>
<td>Amplitude (mmHg)</td>
<td>19.12±10.11</td>
<td>36.96±24.81</td>
<td>29.20±19.76</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

|                  |               |                 |                |         |
| **Retrograde**   |               |                 |                |         |
| Velocity (cm/s)  | 0.70±0.94     | 3.19±1.86       | 1.43±0.91      | <0.001* |
| Extent (cm)      | 5.57±2.11     | 7.5±0.58        | 6.33±3.35      | 0.180   |
| Amplitude (mmHg) | 24.41±15.31   | 28.26±11.18     | 22.06±24.82    | <0.001* |

### Table 9-3 Long single motor pattern descriptors

Mean pressure amplitudes were calculated for the three recording periods. The average amplitude increased from 3.13±1.65mmHg pre-operatively to 5.68±3.64mmHg intra-operatively and 5.01±2.67mmHg post-operatively; however, these differences were not statistically significant (p=0.274). When considering the post-operative period exclusively, mean pressure was found to be significantly higher in the anaesthetic recovery area immediately after surgery (8.66±3.12mmHg) than on the ward (average 1.71-6.87mmHg) (p<0.001).
9.5 Discussion

Prior to interpreting this study’s findings, it is valuable to consider the changes that occur to colorectal motility in humans in various states of health and disease. It was demonstrated that colonic contractile activity is reduced during sleep but is markedly enhanced on early morning waking.\[98-100\] Patients with spinal cord injury have been observed to have increasing resting colonic tone and motility.\[339-341\] This was also characterised by Aaronson et al. in terms of colonic myoelectric activity and it was found that patients with spinal cord injury had higher basal activity than their healthy control counterparts.\[342\] Barometric analysis of the colon following distal colorectal resection has shown that patients have an increased resting tone after surgery.\[58\] It was demonstrated by Brown et al. that patients with rectal prolapse (and ostensibly traction on the visceral nerve supply to the rectum) had greater colonic contractility than healthy controls.\[343\] Although one must be careful to account for the variable and interchangeable definitions used for ‘contractility’, ‘motility’, and ‘tone’ in these studies, it may still be observed that a feature common to all states of health and disease is the apparent influence of autonomic modulation.

It is helpful to supplement understanding of human motility with findings from animal studies. Gastrointestinal motor activity has long been hypothesised to be underpinned by a ‘pacemaker’ within the bowel wall.\[344, 345\] It has been shown in experimental ultrastructural and knock-out studies that spontaneously depolarising interstitial cells of Cajal (ICC), arranged in continuous enteric networks, are responsible for intestinal slow wave pacemaker activity.\[346-348\] Stomach, small bowel, and large bowel have all been demonstrated to possess ICC networks, although in contrast to the upper gut, intrinsic enteric pacemaking within the colorectum appeared to be functionally more susceptible to extrinsic neural input.\[21, 53-57, 349\] A series of laboratory studies were undertaken to qualify this more concisely, but results were equivocal with often contradictory conclusions.\[350-354\] It was subsequently observed that lidocaine or tetrodotoxin-mediated neural blockade did not abolish cyclic motor activity;\[355\] conversely, high amplitude propulsive motor events were effectively inhibited by this neural blockade but resumed with stimulation by a cholinergic agonist.\[57, 355, 356\] It was surmised by Huizinga et al. that this "strongly suggests that under control conditions the nervous system supplies the stimulus [for propulsive events] but is not the mechanism creating rhythmicity".\[57\]

These findings provide a framework within which to interpret the present study’s results. As outlined in Chapter 1, a sentinel pathophysiologic event in ileus is autonomic dysfunction with increased sympathetic and decreased parasympathetic outflow. Both mechanisms serve to diminish the release of acetylcholine within the gut wall.\[24, 31, 35-38\] In line with
the above human and animal studies, it is suggested that surgically-induced autonomic shift ‘unmasks’ omnipresent slow wave activity originating from within the colorectal wall. This may be manifest on HRM recording as cyclic motor patterns, and is corroborated by noting that the frequency of these events (approximately 3 cycles/min) is consistent with previously described myogenic pacemaker activity.[330, 357-359] It is further speculated that this occurs concomitantly with an absence of high amplitude propagating sequences (HAPS). These infrequent propulsive events originate in the proximal colon, are responsible for mass movement of intraluminal colonic content, and are believed to be primarily under cholinergic neural control.[330, 355, 356, 360-363] Although it was not methodologically possible to appraise the occurrence of HAPS in the present study, it is postulated that ileus may be characterised by the occurrence of persistent cyclic motor activity in the absence of propulsive motor activity, both of which are underpinned by autonomic shift favouring sympathetic over parasympathetic outflow.

An important caveat to this hypothesis relates to Dinning et al.’s recent work in healthy human subjects which demonstrated a post-prandial increase in retrograde cyclic motor patterns in the sigmoid colon.[330] Feeding is associated with parasympathetic activation,[21, 363, 364] and these findings are therefore inconsistent with those described above. A potential explanation may relate to Dinning et al.’s conclusion that “it seems possible that there is a dominant pacemaker site in the human sigmoid colon, which can be activated after a meal”.[330] This pacemaker may therefore be distinct from another which is responsible for the observed post-operative cyclic motor predominance. Strong evidence for dual colonic pacemakers exists in animal models where it has been demonstrated that ICC are arranged in two anatomical networks – one within the myenteric plexus (ICC-MY) and another at the junction of submucosa and circular muscle (ICC-SM).[346, 349, 365] ICC-MY and ICC-SM networks are also thought to function autonomously in the animal colon.[57, 355] Although not yet translated to humans, this provides a possible explanation for the occurrence of cyclic motor events in post-prandial controls and post-surgical patients.

Little inference can be made on the significance of short and long single motor patterns in ileus given the scarcity with which these events were observed (109 short single and 5 long single motor events over a cumulative total of 129 hours of recording). It is speculated that these motor patterns share the same slow wave based myogenic mechanism as cyclic motor events but respond differently to autonomic dysfunction. This may pertain to the longitudinal extent of motor patterns, with short and long single events being expectedly more dependent on neural pathways than their shorter extent cyclic counterparts.[330]
An alternate potential explanation for the observed results relate to segmental resection and formation of a new anastomosis. Visceral transection has been shown to impair downstream motility and cause acute disruptions in slow wave activity and phasic contractions.[47, 50] However, this is an unlikely cause for the cyclic motor pattern predominance seen for two reasons. First, the distal colorectum investigated by the HRM catheter was anatomically separated from the site of resection by 60-90cm of intact bowel. It is implausible that the rectosigmoid region, so far removed from the caecal region, would be so swiftly and profoundly influenced by upstream enteric discontinuity. Second, cyclic activity was observed without attenuation in Patient 1, who underwent significant bowel handling without resection. It is therefore proposed that motility changes are the result of the surgical insult and systemic response as outlined above, rather than the creation of a direct barrier to neuro-mechanical coupling.

It is postulated that an intervention capable of stimulating parasympathetic outflow may be effective in accelerating resolution of ileus. This may take the form of a medication such as neostigmine (reversible acetylcholinesterase inhibitor) which has already shown success in colonic pseudo-obstruction[366, 367] and in enhancing colonic motility following surgery.[368] Two previous trials investigating the effects of neostigmine vs. placebo on POI exhibited methodologic and reporting deficiencies.[152, 369] It is important to note that although neostigmine was used during anaesthetic emergence in the present cohort, its use was coupled with the muscarinic antagonist glycopyrrolate. Post-ganglionic cholinergic outflow to the gut end-organ is mediated by muscarinic receptors,[362, 363, 370] and the actions of neostigmine would have therefore been blocked. Thorough prospective appraisal of neostigmine in ileus is therefore warranted. An alternative intervention is percutaneous tibial nerve stimulation (PTNS). This involves percutaneous placement of a small calibre needle 4-8cm cephalad to the medial malleolus with intermittent low-voltage electrical stimulation.[371] Although PTNS is used primarily for faecal and urinary incontinence,[372] a recent pilot study has shown promising results in those with constipation.[373] PTNS may readily be administered in the post-operative setting and merits prospective evaluation in the post-surgical cohort.

An important limitation of this study was its small sample size. As outlined above, this primarily reflected difficulty in obtaining patient consent because of the invasiveness and duration of catheter placement. However, data from all five patients were complete and strongly concordant, and results may therefore be interpreted reliably. A second limitation relates to the lack of data describing motility changes in other parts of the gastrointestinal tract. Varying ultrastructure and physiological mechanisms in stomach and small bowel are
likely to yield different peri-operative motility patterns than those observed in the large bowel, and remain to be characterised in future work. Thirdly, this study has focused on colorectal motor activity in the peri-operative period (i.e. ‘normal’ post-operative ileus). This may not necessarily be translatable to prolonged ileus, and manometric appraisal of this clinically distinct syndrome is required. Finally, whether aberrations in peri-operative motility ever return to ‘baseline’ remains to be qualified, and HRM assessment is therefore warranted in the long-term follow-up of a post-surgical cohort.
9.6 Conclusion

Patients undergoing right hemicolecotony were found to have a progressive increase in distal colorectal cyclic motor activity through the intra-operative period. Cyclic motor patterns occupied the vast majority of post-operative recordings. Short and long single motor patterns were observed infrequently or were entirely absent. Post-operative ileus is therefore characterised by ubiquitous cyclic motor activity occurring in the relative absence of short and long single motor patterns. This may be due to ‘unmasking’ of myogenic pacemaker activity precipitated by surgically-induced autonomic shift favouring sympathetic over parasympathetic outflow.
CHAPTER 10:

IN VIVO HIGH RESOLUTION MANOMETRY –
COLORECTAL MOTILITY AFTER PREVIOUS SEGMENTAL RESECTION
10.1 Background

It was demonstrated in Chapter 9 that there are profound disturbances to colorectal motility during and immediately after major abdominal surgery. These changes may be underpinned by aberrations in extrinsic autonomic input. It was surmised that clinical features which signal ongoing ileus (such as absence of flatus and stool) may occur not as a result of hypomotility or atony, but rather the relative absence of propulsive motor patterns in the presence of ubiquitous cyclic motor activity. An important limitation of this work however is the lack of information pertaining to whether colorectal motility returns to ‘baseline’ in patients who have undergone segmental resection. While it is postulated that the changes in motility precipitated by surgery are short-lived, this has yet to be qualified by evidence demonstrating normal motor activity in the long-term follow-up of a post-surgical cohort.

Performance of high resolution manometry in patients who have previously undergone colorectal resection also provides the opportunity to appraise the effect of healed anastomoses on motility. Anterior resection entails segmental resection of the rectum with the formation of a new colorectal anastomosis. It is proposed that the distal location of this join makes it ideal for interrogation with the 36-sensor HRM catheter. Coordinated motor activity traversing a healed anastomosis may be attributed to either distension-induced peristalsis, contiguous extrinsic autonomic patterning, or true neural regeneration at this site. The former two mechanisms may be reasonably discounted in those who have undergone segmental resection and currently have bowel devoid of luminal content; the latter therefore becomes the most feasible pathway, and is strongly corroborated by animal models which have demonstrated the myenteric plexus is endowed with considerable neuroplasticity and regenerative potential.[49, 374-376] Observation of coordinated trans-anastomotic motor activity in an appropriate surgical cohort would therefore not only support a hypothesis of neural regeneration at this site, but also provide preliminary evidence that, although new joins are associated with greater post-operative gut dysfunction than non-anastomotic procedures of similar severity,[47, 48] there are ostensibly no lasting effects on colorectal motility.

A final consideration is the development of functional defaecatory disorders following large bowel surgery.[377] Factors implicated in evacuatory dysfunction include iatrogenic visceral or somatic nerve injury during surgery, direct damage to the anal sphincter complex, or failure of neurons to re-establish and communicate across sites of anastomosis.[370, 378-381] It has been proposed that retrograde propagating activity in the sigmoid colon may play a pivotal role in maintaining bowel continence.[330] This concept is corroborated by a study
which showed sacral nerve stimulation significantly increased the frequency of these events in faecally incontinent patients.[382] Retrograde propagating events have been temporally associated with retrograde flow,[383] and it was therefore postulated that such motor patterns may act as a physiologic ‘brake’ preventing premature rectal filling.[382] An increase in the frequency of these motor patterns have also been observed in the healthy colon in response to a high caloric meal, and may hence be considered a component of normal colorectal motility.[330] In patients who have undergone distal colorectal resection, the enteric and extrinsic neural pathways which underpin retrograde motor activity may be compromised by creation of a direct physical barrier to neuromuscular activity at the site of anastomosis or by interference with the generation of coordinated propulsive activity. This in turn may play a role in the symptomatology of post-colectomy evacuatory disorders. It is hypothesised that patients who have preserved normal bowel function following segmental resection should demonstrate normal distal colorectal motility.

10.2 Study Objective

The purpose of this study was to utilise in vivo high resolution manometry to define distal colorectal motor patterns in patients who had previously undergone anterior resection and preserved normal bowel function. Specific aims were to determine whether these patients exhibited a normal colonic meal response and to establish whether propagating motor patterns traversed the anastomoses.
10.3 Methods

10.3.1 Ethics Approval

Ethical approval was obtained from the Ministry of Health’s National Ethics Committee (NTX12/06/049) and Auckland District Health Board’s Multidisciplinary Research Review Committee (A+5601) prior to study commencement.

10.3.2 Study Population

The source population included all New Zealand citizens and permanent residents living within the catchment area of ADHB. All patients on the gastroenterology out-patient colonoscopy waitlist between January and June 2013 were screened for eligibility. Inclusion criteria were patients aged between 18 and 75 who had undergone anterior resection at least 12 months prior, and were now presenting for routine follow-up or surveillance colonoscopy. All index procedures were to have involved primary end-to-end large bowel anastomosis with or without covering loop ileostomy. The anastomosis was to be sited a minimum of 5cm above the anorectal ring to ensure sufficient manometric data could be acquired from below this point. Exclusion criteria were patients who had a current or previous functional gastrointestinal motility disorder; post-operative anastomotic leak; any co-existing medical illness known to affect colorectal motility; received pre- or post-operative radiotherapy; and current pregnancy. All remaining participants were screened for ‘normal’ bowel function using the Comprehensive Faecal Incontinence Questionnaire (CFIQ). The CFIQ is a reliability-tested survey which systematically defines patterns of bowel movement, frequency and severity of symptoms, risk factors for evacuatory dysfunction, and use of pharmaceutical agents to assist defaecation.[384] Its use has been previously validated in a New Zealand population.[385] Those with evidence of faecal urgency, incontinence, constipation or obstructed defecation, and those using laxatives or anti-diarrhoeal medication to assist with bowel control were excluded.

10.3.3 Recruitment and Consent

Eligible patients were contacted via telephone on an individual basis by the study investigator (Ryash Vather) and provided with verbal information on study rationale and protocol. If initially agreeable to involvement, a Participant Information Sheet was mailed out (Appendix E) and followed-up by phone call a few days later to obtain verbal consent. Contact was then made with the gastroenterology booking clerk to schedule a date suitable
for patient, research staff and clinical personnel. Written informed consent was obtained from participants prior to colonoscopy and HRM catheter placement.

10.3.4 High Resolution Manometry

Distal colonic and rectal intraluminal pressure was recorded in vivo using the same custom-built 36-sensor HRM catheter described in Chapter 9.[325, 326] Information pertaining to HRM catheter function, siting, and sterilisation; manometric recording and analysis; and ‘normal’ colorectal motility are analogous to those detailed in Section 9.3.4.

10.3.5 Colonoscopy

In accordance with institutional protocol, all participants were asked to begin a low-residue diet two days prior to colonoscopy. Bowel preparation was commenced a day prior with 3 x 70g sachets of Glycoprep-C (Fresenius Kabi, New South Wales, Australia) made to 3L of solution, and was followed by consumption of water until bowel movements were observed to run clear. Participants were fasted for at least 12 hours prior to the procedure. Manometry catheters have been shown to record propagating activity effectively in the empty colon.[330, 386] Colonoscopies were performed by a consultant surgeon or gastroenterologist using either light sedation with midazolam or no sedation, and either low dose intravenous opioid (fentanyl) or no analgesia. The antimuscarinic, anticholinergic agent butylscopolamine was not used for any procedure. Initial surveillance colonoscopy was undertaken at the discretion of the endoscopist, with any luminal pathology being either biopsied or removed.

10.3.6 Manometry Protocol

10.3.6.1 Catheter Siting

Following completion of the surveillance colonoscopy, the HRM catheter was threaded per rectally alongside the colonoscope and secured to the transverse/descending colon as described in Section 9.3.4.4. Care was taken during placement to ensure that at least 5 sensors were located below the anastomosis. The colour indicators on the catheter were used to identify the sensor overlying the anastomosis on scope removal (Figure 10-1), and note was made of the distance between black markings on the ex situ portion of the catheter to the anal verge.
Figure 10-1 Endoscopic photograph of HRM catheter traversing the colorectal anastomosis.
A red rectangle outlines Sensor 20 (coloured with red permanent marker). Sensor 18, lying 2 sensors above this marking, overlies the distal colorectal anastomosis.
10.3.6.2 Data Recording

Recordings were commenced within 10 minutes of arrival to the endoscopy recovery area. Participants were asked to remain in the supine position, with the bed inclined 30 degrees, and to restrict body movement for the duration of the study. After a two-hour period of basal manometric recording participants were given a standardised 700kCal meal (24% protein, 43% fat, 33% carbohydrate) consisting of a chicken sandwich and high-caloric Nepro nutritional drink (Abbott Nutrition, Columbus, Ohio, USA). A further two hours of post-prandial recording was then performed prior to catheter removal. This protocol was analogous to that used by Dinning et al. in their study of 10 healthy human controls.[330]

10.3.6.3 Assessment of Catheter Displacement

In order to confidently characterise trans-anastomotic activity it was imperative that the intraluminal location of HRM sensors relative to the adjacent bowel remained constant over the duration of the trace. Three methods were used to determine occurrence and degree of HRM catheter movement. Firstly, the location of black markings on the non-sensory portion of the catheter relative to anal verge was noted at the time of placement and again upon removal, with a displacement of <2cm being considered acceptable. Secondly, all catheters were removed by applying gentle traction as outlined in Section 9.3.4.6 and care was taken to note the sensation of ‘giving way’ upon detachment of endoclip from colonic mucosa. Finally, manometric traces were evaluated for evidence of slippage, as demonstrated by a sharp upstroke in all sensors followed by uniform displacement of all 36 channels.

10.3.7 Sample Size

A total of 10 controls were used by Dinning et al. to define ‘normal’ colorectal motility,[330] and a previous study was able to differentiate colonic motility in healthy controls from patients with severe constipation using 8 subjects in each arm.[336] A sample size of 10 was therefore proposed to be sufficient to determine the occurrence of normal motility in this patient cohort. However, a second key objective of this study was the accurate characterisation of trans-anastomotic motor activity. This required the HRM catheter to remain relatively fixed for the full duration of the 4 hour trace. It was conservatively estimated that an unacceptable degree of catheter displacement may occur in 1 out of 3 patients. A sample size of 15 patients was therefore deemed appropriate to investigate this study’s hypotheses with a factored margin of error.
10.3.8 **Primary Outcome**

The primary outcome for this study was the occurrence of propagating motor patterns. Motor patterns were quantified by their direction, frequency, amplitude, velocity, and extent. This was to be considered with respect to a colonic meal response and coordinated trans-anastomotic motor activity.

10.3.9 **Analysis**

All manometric traces were de-identified after recording and manually analysed using PlotHRM. In each manometric recording, obvious artefact and simultaneous pressure events that spanned all recording channels were digitally removed as previously described by Wiklendt et al.[337] Analysis was undertaken independently by two investigators (Ryash Vather, Phil Dinning) in a blinded fashion, with neither investigator having knowledge of the location of the anastomosis until completion of analysis. Any discrepancies in trace findings were resolved by discussion and consensus.

The colonic meal response was characterised as described in Section 9.3.4.9. Average amplitude of pressure events was calculated by splitting pre- and post-meal recordings into twelve 10-minute intervals each. Pressure at every point, across all channels, was summed and divided by the number of samples at a data acquisition rate of 10Hz. Average amplitude in the post-prandial period was then compared to that of the basal period. Difference in the absolute frequency of post- and pre-prandial events was expressed as the delta (‘Δ’) value. All data were then compared to those previously acquired from Dinning et al.’s healthy control population.[330]

The sensor overlying the anastomosis was revealed on completion of analysis, and the occurrence of coordinated motor activity traversing the join was qualified and quantified. In order for a manometric event to be classified as involving the anastomosis, pressure excursions were to involve at least one channel above it and one channel below it.

Frequency, amplitude, velocity, and extent of propagating events were expressed as mean ± standard deviation. The Wilcoxon signed-rank test was used to compare these characteristics and mean pressure between the two time periods. Statistical comparison of data between study patients and healthy controls were made using the student t-test. All statistics were calculated using Prism 5 (GraphPad Software, Inc., La Jolla, CA, USA). Results were considered statistically significant if p<0.05.
10.4 Results

10.4.1 Patient Flow

Between January and June 2014, 38 patients were assessed for eligibility. Seventeen patients were excluded through the screening process for having symptoms of evacuatory dysfunction as described in clinic letters (n=10), receiving peri-operative radiotherapy (n=5), and having post-operative leak (n=2). In total, 21 patients were approached for study inclusion of whom two declined consent. A further four patients were excluded for disclosing symptoms of evacuatory dysfunction upon assessment with the CFIQ.

10.4.2 Baseline Characteristics

Patient and procedure characteristics are shown in Table 10-1. High resolution manometry was performed on 15 patients (6 males and 9 females) of median age 68 (range 47-75) years. Index anterior resections were undertaken a median of 8 (range 1-17) years prior to study involvement. The original indication for surgery was either neoplasia (n=14) or diverticular disease (n=1). Median stool frequency as surveyed in the CFIQ was 2 (range 1-4) bowel motions/day. Mean duration of in vivo recording was 260 (range 246-280) minutes.

10.4.3 Catheter Displacement

Catheter displacement occurred in 3 patients. In Patient 6, displacement was complete and occurred before receiving the high-caloric meal; data from this patient was excluded from all further analysis. In Patients 3 and 12, catheter movement of 5cm and 7cm respectively occurred over the duration of trace. The position of the anastomosis relative to the moving catheter was unclear, and therefore no inference of propagating activity across the join was made. However, it was still possible to quantify a meal response in both of these patients.

10.4.4 Meal Response

Data from Patient 6 was excluded prior to this subset of analysis. A response to the standardised 700kCal meal was observed in 13 of the remaining 14 participants.

10.4.4.1 Mean pressure

All recordings were split into 10 minute allotments and mean pressures calculated for each of these. A significant increase in pre- to post-meal mean pressures was observed in 13 participants (p<0.05), with a single participant showing no difference between periods.
<table>
<thead>
<tr>
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<th>Sex</th>
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<th>Years since surgery</th>
<th>Post-operative chemotherapy</th>
<th>Other bowel procedures</th>
<th>Bowel motions/ day</th>
<th>Evacuatory dysfunction</th>
<th>Distance of join from anorectal ring (cm)</th>
<th>Sensor overlying join</th>
<th>Catheter displacement</th>
<th>Duration of recording (mins)</th>
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<td>14</td>
<td>F</td>
<td>65</td>
<td>17</td>
<td></td>
<td></td>
<td>1</td>
<td>nil</td>
<td>22</td>
<td>21</td>
<td>nil</td>
<td>248</td>
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<tr>
<td>15</td>
<td>M</td>
<td>71</td>
<td>3</td>
<td></td>
<td></td>
<td>4</td>
<td>nil</td>
<td>12</td>
<td>31</td>
<td>nil</td>
<td>247</td>
</tr>
</tbody>
</table>

Table 10-1 Patient baseline characteristics.
Figure 10-2 Mean pressure for all patients (95% CI) in 10 minute pre-meal and post-meal allotments.
Figure 10-3 Sample of manometric data acquired over a 5 minute post-prandial window.
The blue bar at the top of this figure is an overview of contractile activity within the distal colorectum over the pre- and post-prandial period. The shaded yellow box is a 5 minute window taken from the post-prandial period. The series of traces below corresponds to recordings taken from each of the 36 sensors on the HRM catheter over this window. Cyclic motor patterns are observed in the top half of this recording; two short single motor patterns are observed in the bottom half.
When considering the whole cohort (Figure 10-2), mean pressures during the 2-hour basal period remained relatively constant at 1.54 – 2.12mmHg. This increased to 3.04±1.72mmHg within 10 minutes of meal consumption, and peaked at 4.27±2.05mmHg over the following 10 minutes. The range of mean pressures during the post-prandial period was 2.81 – 4.27mmHg. Combined mean pressures for all participants’ recordings increased from 1.78±0.17mmHg pre-meal to 3.33±0.40mmHg post-meal (p<0.001).

10.4.4.2 Propagating Motor Patterns

There was a significant increase in pre- to post-meal motor activity with respect to the frequency of retrograde (Δ30.5±30.4 events; p<0.001) and antegrade (Δ13.4±12.3 events; p<0.001) cyclic motor patterns. No significant delta values were noted for either retrograde (Δ-0.6±4.1 events; p=0.811) or antegrade (Δ0.2±0.43 events; p=0.253) short single motor patterns. All long single motor patterns occurred after meal consumption and no inference was therefore made on differences between pre- and post-prandial periods. No differences were observed in velocity, extent or amplitude of any event type between basal and post-prandial periods.

Cyclic contractile activity formed the predominant motor pattern (Figure 10-3) and was found to occur in 13 of the 14 included patients. The average frequency was 34.8±27.1 retrograde and 15.7±11.9 antegrade cyclic motor events per patient (Table 10-2).

<table>
<thead>
<tr>
<th>Antegrade</th>
<th>Pre-meal</th>
<th>Post-Meal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (cm/s)</td>
<td>2.35±2.31</td>
<td>1.23±0.85</td>
<td>0.521</td>
</tr>
<tr>
<td>Extent (cm)</td>
<td>3.77±0.60</td>
<td>4.6±1.70</td>
<td>0.611</td>
</tr>
<tr>
<td>Amplitude (mmHg)</td>
<td>22.15±9.48</td>
<td>37.75±29.74</td>
<td>0.364</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retrograde</th>
<th>Pre-meal</th>
<th>Post-Meal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (cm/s)</td>
<td>0.69±0.84</td>
<td>0.98±0.58</td>
<td>0.056</td>
</tr>
<tr>
<td>Extent (cm)</td>
<td>3.8±1.5</td>
<td>4.85±2.10</td>
<td>0.275</td>
</tr>
<tr>
<td>Amplitude (mmHg)</td>
<td>28.01±17.81</td>
<td>37.59±26.49</td>
<td>0.393</td>
</tr>
</tbody>
</table>

Table 10-2 Cyclic motor pattern descriptors.
Short single motor patterns were noted in 8 patients with an average of 4.6±5.3 retrograde and 1.4±0.5 antegrade events over the duration of the trace (Table 10-3).

<table>
<thead>
<tr>
<th>Antegrade</th>
<th>Pre-meal</th>
<th>Post-Meal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (cm/s)</td>
<td>2.64±3.33</td>
<td>1.92±1.83</td>
<td>1.000</td>
</tr>
<tr>
<td>Extent (cm)</td>
<td>5±2.83</td>
<td>8.5±3.04</td>
<td>0.400</td>
</tr>
<tr>
<td>Amplitude (mmHg)</td>
<td>66.61±55.55</td>
<td>43.07±15.20</td>
<td>1.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retrograde</th>
<th>Pre-meal</th>
<th>Post-Meal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (cm/s)</td>
<td>2.85±1.17</td>
<td>3.63±1.50</td>
<td>0.486</td>
</tr>
<tr>
<td>Extent (cm)</td>
<td>4.83±1.73</td>
<td>6.88±0.63</td>
<td>0.114</td>
</tr>
<tr>
<td>Amplitude (mmHg)</td>
<td>38.78±22.12</td>
<td>50.38±21.20</td>
<td>0.486</td>
</tr>
</tbody>
</table>

Table 10-3 Short single motor pattern descriptors.

Long single motor patterns were observed only post-meal in 3 patients (1 having antegrade only; and 2 having both antegrade and retrograde events), with an average of 2.67±1.15 antegrade and 0.67±0.58 retrograde events (Table 10-4).

<table>
<thead>
<tr>
<th>Antegrade</th>
<th>Post-meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (cm/s)</td>
<td>1.18±0.58</td>
</tr>
<tr>
<td>Extent (cm)</td>
<td>27.80±8.64</td>
</tr>
<tr>
<td>Amplitude (mmHg)</td>
<td>20.91±29.40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retrograde</th>
<th>Post-meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (cm/s)</td>
<td>0.90±2.08</td>
</tr>
<tr>
<td>Extent (cm)</td>
<td>27.38±8.43</td>
</tr>
<tr>
<td>Amplitude (mmHg)</td>
<td>26.50±31.64</td>
</tr>
</tbody>
</table>

Table 10-4 Long single motor pattern descriptors
Figure 10-4 Sample short single motor pattern traversing the anastomosis.

The blue bar at the top of this figure is an overview of contractile activity within the distal colorectum and the shaded yellow box a 5 minute window from the post-prandial period. The site of anastomosis in the series of 36 manometric traces has been identified by the blue line. A retrograde short single motor pattern traverses this anastomosis.
10.4.4.3 Comparison to Healthy Controls

The observed meal response with respect to change in mean pressures from basal to post-prandial periods did not significantly differ between study patients and healthy controls \((p=0.780)\). Likewise, comparison of delta values between patients and controls showed no significant differences with respect to retrograde \((\Delta 30.5 \text{ vs. } 50.3 \text{ events}; p=0.347)\) and antegrade \((\Delta 13.4 \text{ vs. } 9.8 \text{ events}; p=0.131)\) cyclic motor patterns; and retrograde \((\Delta -0.6 \text{ vs. } -0.4 \text{ events}; p=0.781)\) and antegrade \((\Delta 0.2 \text{ vs. } 0.2 \text{ events}; p=0.432)\) short single motor patterns. The absolute frequency of specified motor patterns during basal and post-prandial periods was then compared between cohorts. It was found that there was a significant difference in the absolute number of pre-meal antegrade cyclic motor patterns \((2.1 \text{ [study patients]} \text{ vs. } 8.3 \text{ [healthy controls] events}; p=0.038)\). There were however no significant differences between cohorts with respect to post-meal antegrade \((p=0.48)\), and pre- \((p=0.13)\) or post-meal \((p=0.18)\) retrograde cyclic motor patterns; and antegrade or retrograde short single motor patterns at any period. Data cumulatively indicate that the meal response recorded in study patients did not significantly differ from that previously observed in healthy controls.

10.4.5 Trans-anastomotic Motor Activity

Data from patients 3, 6 and 12 were excluded prior to performance of the following analysis. All anastomoses were directly visualised at the time of colonoscopy, and were located a median of 14.5cm (range 7-22cm) from the anorectal ring. In total, 9 of the 12 included participants were found to have coordinated motor activity traversing the anastomosis.

There were 85 trans-anastomotic events in total, with 74 cyclic, 5 short single, and 6 long single motor patterns. Cyclic events crossing the join were observed in 8 patients, with 63.5% of these being retrograde in direction. The average frequency of cyclic motor patterns was 9.3±7.3 events per patient, with an average velocity of 1.9±2.1cm/s, extent of 4.07±1.9 cm, and amplitude of 31.1±32.8 mmHg. Short single motor patterns traversed the anastomosis in 1 participant. There were 5 retrograde events in this patient with an average velocity of 5.57±4.28 cm/s, extent of 8.49±2.11cm and amplitude of 50.5±36.0mmHg. Trans-anastomotic long single motor patterns were observed in 3 participants (Figure 10-4). The average frequency was 2±0.71 events per patient with 83.3% being antegrade in direction. The average velocity of events was 1.56±0.52cm/s, with an extent of 32.7±4.52cm and amplitude of 48.20±46.10mmHg.
10.5 Discussion

It has been demonstrated in the long-term follow-up of patients who have previously undergone anterior resection that there is a colonic meal response comparable to that of healthy controls, and that in most patients there are coordinated motor events traversing the anastomosis. These data suggest that there is a return to ‘baseline’ colorectal motility following major segmental resection and that the changes in peri-operative motor activity observed in Chapter 9 are acute and do not persist after tissue healing is complete. An important feature of the cohort investigated in the present study however was that all participants reported normal bowel habit following surgery, and consequently the extent to which preservation of evacuatory function post-resection is related to restitution of normal motility is unclear. It is hence valuable to consider the potential mechanisms which underpin colorectal motility and defaecation following en-bloc large bowel resection and anastomosis.

Normal intestinal motility is believed to be a result of interplay between the enteric nervous system, interstitial cells of Cajal and extrinsic autonomic innervation. The ENS is a dense neural network anatomically organised in two intramural ganglia – the myenteric plexus and submucosal plexus – and comprised of sensory neurons, motor neurons (excitatory and inhibitory) and interneurons arranged in local reflex arcs,[21] while colonic ICC establish a pacemaker network as previously detailed.[54, 57, 349]

Transection and re-anastomosis of the gut therefore imparts a physical barrier to neural and electromechanical coupling within the gut wall. It is proposed that the appearance of coordinated trans-anastomotic motor activity, as observed in the present study, may in part be explained by restoration of myenteric plexus continuity across an anastomosis. This hypothesis was initially investigated in a guinea pig model which showed migration of the myoelectric complex across intestinal joins in 80% of animals 60 days after surgery,[375] and was subsequently corroborated by two animal studies which found histological evidence of neural regeneration across healed colorectal anastomoses.[49, 374] Evidence of myenteric neuro-regenerative potential was further provided in a murine study by Hanani et al. who demonstrated neurogenesis in a chemically ablated colonic myenteric plexus.[376] These data cumulatively provide indirect evidence for the presence of enteric neural stem cells capable of migration, differentiation, and connection to other neurons. However, the translational and functional significance of this apparent regenerative potential to bowel motility has not previously been elucidated. The present study noted the occurrence of coordinated cyclic, short single, and long single motor patterns traversing the anastomosis in humans who had previously undergone resection. All participants underwent bowel preparation and the colorectum was devoid of intraluminal content. It is therefore postulated...
that trans-anastomotic motor activity is unlikely to be related to bolus distension but rather, in line with previous work, is reflective of neural regeneration and myenterically-modulated myocyte contraction.

Defaecation is believed to be a carefully regulated process involving coordinated colorectal motility occurring in tandem with a localised, wholly intramural recto-anal reflex.[93, 387-389] Repetitive phasic motor patterns have been reported to occur in the rectum (termed 'rectal motor complexes') and are proposed to act as an autonomous physiologic 'brake' preventing premature flow of colonic content into the rectum.[359] This hypothesis has recently been corroborated through high resolution manometry which has shown that rectal motor complexes are characterised by a series of retrograde short single motor patterns.[382] These specialised motor patterns appear to be an integral component of normal colorectal motility and bowel control, and are particularly prevalent after a high-caloric meal.[330]

In light of this, it is postulated that the mechanisms by which distal colorectal segmental resection precipitates prolonged disturbances in defaecation are twofold. First, extrinsic and/or intramural resection-related nerve injury may impair motor patterns which normally prevent premature rectal filling. Increased stool frequency could potentially be effected by a motor pattern shift favouring propulsive antegrade over retrograde activity, or an isolated reduction in frequency of retrograde events. It is plausible that an inverse relationship exists between frequency of retrograde activity and degree of faecal dysfunction,[382, 390, 391] and may partly explain the variable severity of patient-reported symptoms.[378, 392] Second, transection of the rectum may impair the recto-anal reflex. For either of these scenarios, a return to normal defaecation is theoretically contingent on neural regeneration across the anastomosis in the absence of physiologic compensatory measures preventing dysfunction. This hypothesis may also explain the higher incidence of evacuatory symptoms following sigmoid or rectal resection when compared to right-sided colectomy.[377, 380, 381]

An important limitation of this study was the distal placement of the fibre-optic catheter within the large bowel, which did not allow interrogation of meal-related contractile activity in the more proximal regions of the colon. However, the distal colon and rectum were the regions of pathophysiologic interest and focus was hence shifted here. Secondly, catheter displacement occurred in 3 out of 15 participants. Although propagation across the join was therefore only appraisable in 12 participants, a meal response could still be quantified in 14 participants. Finally, study patients were older than healthy controls (median age 68 vs 53 years) and it is known that both ENS and ICC networks show degeneration with normal ageing.[365, 393] It might be expected that the frequency of motor events in study patients
may be reduced, but a test of statistical significance demonstrated no difference between cohorts.
10.6 Conclusion

Patients who had previously undergone anterior resection and preserved normal bowel function, demonstrated a normal colonic meal response that did not differ significantly from healthy controls. Motor patterns traversed the colorectal anastomosis in coordination in a majority of participants. Data collectively indicate that normal colorectal motility is eventually restored in patients following surgery, and provide functional evidence in humans for anastomotic nerve regeneration.
SUMMARY OF RESULTS
This thesis endeavoured to answer the following five questions:

1. How should ileus be classified and clinically defined?
2. What are best-practice recommendations for the conservative management of prolonged ileus?
3. Is Gastrografin useful in shortening an established episode of prolonged ileus?
4. Which clinical factors predict the development of prolonged ileus?
5. How does intestinal motor activity change during the peri-operative period, and does motility ever return to ‘normal’ after visceral resection?

In a review of current concepts (presented in the Introduction) the aetiology of post-operative ileus was described, with a focus on its clinical correlates and therapeutic approaches to management. Gastrointestinal dysfunction following abdominal surgery is believed to occur as a result of inflammatory cell activation, autonomic dysfunction with sympathetic shift, disruption of enteric continuity, activation of gut opioid-receptors, and electrolyte and gastrointestinal neuropeptide disturbances. A final common pathway for these effectors is gut wall oedema, relative hypoxia, and impaired motility. The clinical features which characterise ileus are nebulous and transitory, and no clear definitions exist for the syndrome. This has led to a poor understanding of its incidence and risk factors, and has compromised the external validity of clinical trials appraising interventions to shorten its duration. Ileus is associated with poorer patient outcomes following surgery and confers a resource-intensive burden on healthcare systems. No therapies effective in attenuating or aborting an episode of prolonged ileus have as of yet been identified.

The first study was a retrospective review of those who underwent elective colorectal surgery at ADHB over 2011. The aim of this work was to obtain baseline local data thereby ensuring future prospective research was methodologically robust. In total, 255 consecutive patients underwent elective intra-abdominal surgery by the Colorectal Unit in 2011, of whom 50 (19.6%) developed prolonged ileus. The mean duration of ileus was 4.54 days. Increasing age and increasing haemoglobin drop across surgery were independent predictors for developing prolonged ileus. Procedure, morphine equivalent daily dose, pre-operative creatinine, highest post-operative white cell count, lowest post-operative sodium, and Clavien-Dindo complication grade were all significant associations, but were not found to be independent predictors on logistic regression. The veracity of these results was however limited by retrospective design and lack of uniform endpoint reporting. Two important potential pitfalls were identified – first, the absence of a transparent definition for ileus will limit applicability and reproducibility of any prospective work; second, prolonged
ileus is managed at the discretion of overseeing clinicians without reference to any best-practice guidelines.

The second study described a systematic review and global survey undertaken to clarify the terminology of ileus and propose concise, clinically quantifiable definitions. A high-sensitivity, low precision systematic literature search was conducted through the Ovid MEDLINE, EMBASE, CINAHL, Cochrane Collaboration and National Guideline databases between January 1996 and December 2011 using keywords and database-specific indexed subject headings. A total of 3,234 publications were initially identified with data being finally extracted from 52 clinical trials. A global survey was then executed by asking all authors who had published in the field over the preceding ten years to complete a short online questionnaire. Of the 118 authors approached, 45 responded with 44 completing the survey in its entirety. Data from the systematic review and global survey were amalgamated to provide the following definitions. “Post-operative ileus (POI)” – interval from surgery until passage of flatus/stool AND tolerance of an oral diet; “prolonged post-operative ileus (PPOI)” – two or more of nausea/vomiting, inability to tolerate oral diet, absence of flatus and stool, distension, radiologic confirmation – occurring on or after Day 4 post-operatively without prior resolution of POI; “recurrent post-operative ileus” – two or more of nausea/vomiting, inability to tolerate oral diet, absence of flatus and stool, distension, radiologic confirmation – occurring after apparent resolution of POI. The definition proposed for PPOI was 80% concordant with the responses from the global survey, and that of recurrent POI 75% concordant.

The third study was a narrative review of contemporary literature aiming to identify conservative management strategies which may aid resolution of PPOI. A high sensitivity, low precision literature search was conducted through the Ovid MEDLINE, EMBASE, Google Scholar and Cochrane Collaboration databases from inception to July 2012 using keywords and database-specific indexed subject headings. Recommendations for management were accompanied by Strength of Recommendation Taxonomy gradings of A, B or C as follows – i) patients with PPOI warrant regular review and correction of the following electrolytes: sodium, potassium, magnesium and calcium (Grade B); ii) patients with PPOI require review of their analgesic prescription within weaning of narcotic pain relief and sequential substitution with regular paracetamol, regular non-steroidal anti-inflammatory drugs (if not contraindicated), regular or as-required Tramadol, and as-required opiate for breakthrough pain (Grade A); iii) patients who develop PPOI with nausea or vomiting as a prominent feature will benefit from nasogastric decompression (Grade C); iv) isotonic dextrose-saline crystalloid solution administered within a restrictive regimen (1-1.25ml/kg/hr).
is the post-operative maintenance fluid of choice (Grade B); v) nasogastric losses or vomiting as a result of fluid sequestration in PPOI should be replaced in approximately equivalent volume with normal saline or balanced isotonic crystalloid solution containing supplemental potassium (Grade C); vi) it is advisable for patients who develop PPOI to ambulate regularly, with assistance as necessary (Grade C); vii) parenteral nutrition should be commenced in patients who are unable to tolerate an adequate oral intake due to PPOI for more than 7 days post-operatively (Grade A); viii) upon resolution of PPOI and resumption of an oral diet, parenteral nutrition may be ceased without weaning (Grade A); ix) suspicion of sepsis or early post-operative small bowel obstruction warrant investigation and exclusion using clinical assessment and appropriate imaging (Grade C).

Hyperosmotic, orally-administered, water-soluble contrast media such as Gastrografin are theoretically capable of mitigating the gut wall oedema which underpins ileus. An important consideration in the design of a trial investigating Gastrografin for this indication is to ensure that medication re-packaged during the blinding process and placed in storage remains stable. A laboratory study was therefore conducted using rapid reverse phase High Performance Liquid Chromatography (HPLC) to assay the active diatrizoate salt component of re-packaged Gastrografin in various storage conditions. The HPLC method was validated for specificity (no elution peak with placebo), linearity ($r^2=0.999$), accuracy ($\leq5\%$) and precision ($\leq3\%$). Gastrografin exposed to the anticipated storage conditions of $25^{\circ}C$, $60\%$ relative humidity, and no light remained stable for 30 days with no physical change to the solution. Gastrografin stored under identical conditions but exposed to 1.2 million lux hours of light remained stable for 7 days. Gastrografin stored at $4^{\circ}C$, minimal humidity ($<10\%$), and no light underwent crystallisation; this was readily reversed by agitation and had no discernible effect on drug stability at 30 days.

A double-blinded, placebo-controlled, randomised trial was then conducted evaluating the therapeutic efficacy of enterally-administered Gastrografin in those who developed PPOI following elective colorectal surgery. Patients were uniformly assessed for the occurrence of PPOI using the previously formulated definition. Those who met diagnostic criteria for PPOI were allocated study medication and assessed 12-hourly for its resolution. Other aspects of clinical management were standardised according to the evidence-based recommendations described above. The primary outcome was the duration of PPOI. In total, 80 patients were randomised equally to receive 100ml of Gastrografin (Exposure Group) or flavoured distilled water (Control Group) with five in the Exposure Group and four in the Control Group being excluded from analysis. The remaining participants were evenly matched at baseline. Mean duration of PPOI did not differ between Exposure and Control Groups (83.7 vs. 101.3 hours;
p=0.191). When considering individual markers of PPOI resolution, Gastrografin did not affect time to resolution of nausea and vomiting (64.5 vs. 74.3 hours; p=0.404) or consumption of oral diet (75.8 vs. 90.0 hours; p=0.297). However, it accelerated time to flatus or stool (18.9 vs 32.7 hours; p=0.047) and time to resolution of abdominal distension (52.8 vs 77.7 hours; p=0.013). There were no significant differences between groups in nasogastric output; analgesia, antiemetic or fluid requirement; complications; or length of stay.

A prospective cohort study was conducted in tandem with the above clinical trial to determine peri-operative risk factors associated with the development of PPOI following elective colorectal surgery and to create a risk stratification system capable of predicting its occurrence. In total, 92 peri-operative variables were recorded for each enrolled patient prior to their assessment for PPOI using the standardised definition above. PPOI occurred in 88 of 327 patients (26.9%). Independent predictors of PPOI were male gender (OR 3.01), decreasing pre-operative albumin (OR 1.11 [per g/L unit]), open or converted technique (OR 6.37 [vs. laparoscopic]), increasing wound size (OR 1.09 [per cm]), surgeon-assessed operative difficulty (OR 1.28 [per unit on 10-point Likert scale]), surgeon-assessed operative bowel handling (OR 1.38 [per unit on 10-point Likert scale]), red cell transfusion (OR 1.84 [per unit]), intravenous crystalloid administration (OR 1.55 [per litre]), and delayed first mobilisation (OR 1.39 [per day]). The I-Score 1 risk stratification model assimilated predictors to generate a score out of 8 with fair discriminative capacity (AUC 0.791, 95%CI 0.738-0.844). The I-Score 2 included only pre- and intra-operative variables to generate a score out of 16 with a 7-fold increase in risk from low to high-risk strata and fair predictive capacity (AUC 0.742, 95%CI 0.684-0.799). ROC analyses were repeated with ‘reversal of loop ileostomy’ cases excluded from the data set and adjusted AUCs for the I-Score 1 and I-Score 2 were found to be 0.786 (95%CI 0.728-0.843) and 0.746 (95%CI 0.684-0.808) respectively.

The changes in intestinal contractility which accompany major abdominal surgery were then characterised using High Resolution Manometry (HRM). A 36-sensor fibre-optic HRM catheter was endoscopically placed within the distal colorectum of patients scheduled to undergo right hemicolectomy with recordings made through the pre-, intra-, and post-operative periods. Five patients were enrolled of whom four underwent standard resection; one patient had their procedure abandoned because of advanced locally infiltrative disease. At least 3 hours of recording was undertaken pre-operatively and 16 hours post-operatively. Cyclical motor patterns occurred pre-, intra-, and post-operatively in all patients with a frequency of 2.5-4 cycles/minute. The mean percentage of each recording period occupied
by cyclic events increased steadily through the peri-operative period \( (p<0.001) \) as follows: 19.7% pre-operatively; 17.2% during anaesthetic induction, 47.2% through surgery, and 88.2% during anaesthetic emergence; and 89.1% post-operatively. Short single motor patterns were comparatively scarce, occurring pre-operatively in all 5 patients at 3.12±4.16 events/hour; intra-operatively in 2 patients at 3.59±2.69 events/hour; and post-operatively in 3 patients at 0.40±0.58 events/hour. Five long single motor patterns were observed in one post-operative recording of a single participant. Mean pressures for all events increased from 3.13±1.65mmHg pre-operatively to 5.68±3.64mmHg intra-operatively and 5.01±2.67mmHg post-operatively, although this was not statistically significant \( (p=0.274) \).

The results of this HRM work must be qualified by establishing whether motility ever returns to ‘baseline’ in those who have undergone segmental resection. It is also possible in the long-term follow-up of a post-surgical cohort to evaluate the effect of enteric anastomoses on gut function. In a final study, the 36-sensor HRM catheter was sited within the distal colorectum of patients who had previously undergone anterior resection and were now presenting for surveillance colonoscopy. The colonic meal response and the presence of coordinated trans-anastomotic motor activity were the outcomes of interest. A total of 15 patients were enrolled of whom one had total catheter displacement and two had partial catheter displacement. A significant increase in pre- to post-meal mean pressures was observed in 13 of the 14 included participants \( (p<0.05) \). Combined mean pressures for all participants’ recordings increased from 1.78±0.17mmHg pre-meal to 3.33±0.40mmHg post-meal \( (p<0.001) \). Cyclic contractile activity formed the predominant motor pattern with an average frequency of 34.8±27.1 retrograde and 15.7±11.9 antegrade motor events per patient. The observed meal response did not significantly differ between study patients and healthy controls with respect to change in mean pressures from basal to post-prandial periods \( (p=0.780) \), or delta values for retrograde \( (p=0.347) \) and antegrade \( (p=0.131) \) cyclic motor patterns; and retrograde \( (p=0.781) \) and antegrade \( (p=0.432) \) short single motor patterns. Coordinated motor activity traversing the anastomosis was observed to occur in 9 of the 12 included participants and were in total comprised of 74 cyclic, 5 short single, and 6 long single motor patterns.
The following conclusions can be made based on the research presented in this thesis.

There is considerable heterogeneity with which terminology and definitions of post-operative ileus are used in the literature, and there is a clear requirement for their standardisation. Based on academic opinion, three classes can be broadly defined – post-operative ileus (POI), prolonged post-operative ileus (PPOI), and recurrent post-operative ileus.

Best-practice recommendations for the conservative management of PPOI may serve to standardise and optimise in-patient care, although many recommendations have an inconsistent evidence base and require validation.

Gastrografin is not clinically useful in shortening an episode of PPOI characterised by upper and lower gastrointestinal symptoms. It may however be of therapeutic benefit in the subset of PPOI patients who display lower gastrointestinal symptoms exclusively.

Independent predictors for the development of PPOI following elective colorectal surgery include male gender, decreasing pre-operative albumin, open/converted technique, increasing wound size, operative difficulty and bowel handling, total intravenous crystalloid, red cell transfusion, and day of first mobilisation. Two novel risk prediction tools were constructed incorporating these variables and were shown to have fair discriminative value.

Post-operative ileus is characterised at the enteric level by ubiquitous cyclic motor activity occurring in the relative absence of short and long single motor patterns. Cyclic motor activity progressively increases through the intra-operative period and occupies the vast majority of the immediate post-operative period. This may be due to ‘unmasking’ of myogenic pacemaker activity precipitated by surgically-induced autonomic shift favouring sympathetic over parasympathetic outflow.

Patients who have preserved bowel function following anterior resection demonstrate a normal colonic meal response with a majority exhibiting coordinated trans-anastomotic motor activity. Data collectively indicate that normal colorectal motility is eventually restored in patients following surgery, and provide functional evidence for anastomotic nerve regeneration.
FUTURE DIRECTIONS FOR RESEARCH
This thesis has attempted to better characterise ileus on both a clinical and pathophysiologic front. Results and conclusions have however brought to light important avenues for future research which merit consideration.

Gastrografin was shown to accelerate resolution of lower gastrointestinal symptoms in patients with PPOI without any significant effect on upper gastrointestinal symptoms. This is ostensibly related to its mechanical action whereby it promoted wall-to-lumen fluid shift in the small and large bowel tubes, but lacked an equivalent effect in the cavernous, non-cylindrical stomach. It is therefore proposed that Gastrografin administered in combination with a prokinetic/gastric-emptying agent may serve to effectively address both PPOI symptom clusters. Assessment of this intervention should take the form of a randomised, double-blinded trial utilising the same standardised definition of ileus and ideally involving three study arms (prokinetic and Gastrografin; prokinetic alone; and placebo).

The I-Score 1 and I-Score 2 have not been adequately validated. An avenue for future research is to therefore appraise the discriminative capacity of this score in a local colorectal cohort followed by an independent data set. An important proviso to this work is that it must be undertaken prospectively given that the definition of PPOI used cannot be viably applied retrospectively. It is anticipated that continued application and revision of these scoring systems will hone their predictive accuracy by better informing understanding of risk factors for PPOI.

Peri-operative high resolution manometry of the distal colorectum has shed light on the motility changes which accompany ileus. Future research should focus on translating findings to other segments of the gastrointestinal tract perhaps by siting the HRM catheter within a newly constructed ileostomy or by inserting it nasally after endotracheal intubation so that it lies in the stomach. There is also functional evidence for a myogenic colorectal pacemaker, and an attempt to define it anatomically in humans may be made by serial histologic sectioning of cadaveric or freshly-resected specimens. Two interventions that are postulated to be of use in attenuating ileus, based on this HRM work, are unopposed post-operative neostigmine administration and percutaneous tibial nerve stimulation. Both interventions may prove useful in correcting the autonomic shift favouring sympathetic outflow which accompanies surgery. The application of HRM in a cohort of patients who have previously undergone anterior resection but not preserved normal bowel function may shed light on the importance of trans-anastomotic motor integrity in long-term evacuatory function. Finally, there is merit in correlating changes in motility with slow wave activity of the bowel. This may be effected by intra-luminal placement of both an HRM catheter and surface electrodes assessing neuroelectric activity.
APPENDIX A
ONLINE GLOBAL SURVEY
Dear Dr. [insert name],

I have recently begun a PhD at the University of Auckland (New Zealand) looking at Postoperative Ileus, and my research group would greatly appreciate your opinion regarding the terminology and clinical criteria you use when defining this.

We note that you have authored an important publication in the field of postoperative ileus recently, and your input as an expert via the performance of a short survey would be really valued. This survey should take less than 2 minutes, and can be found at http://www.surveymonkey.com/s/ileus

It is our hope that a collation of expert opinions regarding the terminology and clinical definitions in use will help better clarify this for future studies. We plan for the results of this survey to be part of a publication in the peer-reviewed literature.

Thank you very much for your time. Please do not hesitate to contact us if you have any questions or comments.

Sincerely,

Dr. Ryash Vather
Research Fellow to Assoc. Prof. Ian Bissett
Department of Surgery
The University of Auckland
Work: +64 9 373 7599 ext 89790
Mobile: +64 21 210 2024
Email: r.vather@gmail.com
Dear Dr. [insert name],

This is just a friendly reminder about our survey on the terminology and clinical criteria used when defining postoperative ileus. We have not received a response from you yet, and would greatly value your opinion on this topic.

The survey should take less than 2 minutes, and can be found at http://www.surveymonkey.com/s/ileus

Attached below is the original email sent out two weeks ago. Please feel free to get in touch with us if you have any concerns, and thank you again for your time.

Sincerely,

Dr. Ryash Vather
Research Fellow to Assoc. Prof. Ian Bissett
Department of Surgery
The University of Auckland
Work: +64 9 373 7599 ext 89790
Mobile: +64 21 210 2024
Email: r.vather@gmail.com
Thank you for choosing to participate in this survey. Please note that the term 'post-operative ileus' has been abbreviated to ‘POI’.

Please write your name: [FREE TEXT]

Please list your specialty (e.g. colorectal surgery): [FREE TEXT]

Please identify the country in which you practice: [FREE TEXT]
After intra-abdominal surgery almost all patients have a period of physiologic gastrointestinal (GI) dysfunction.

1. Do you have a specific term for this? Y/N
   a. If YES, what do you call it: [SELECT ONE]
      i. Normal POI
      ii. Physiologic POI
      iii. Obligatory POI
      iv. POI [not further specified]
      v. Pseudo-obstruction
      vi. Adynamic ileus
      vii. Other (please specify) [FREE TEXT]

2. Which essential criteria must be met in order for you to define a resolution of this gut dysfunction? Please tick as many boxes as necessary [SELECT ONE OR MORE]
   a. Passage of flatus
   b. Passage of stool
   c. Tolerance of an oral diet
   d. Presence of bowel sounds
   e. Absence of nausea or vomiting
   f. Absence of abdominal pain
   g. Absence of abdominal distension
   h. Radiologic evidence
   i. Removal of NG tube
   j. Other (please specify) [FREE TEXT]
In some cases, post-operative GI dysfunction can extend past the expected timeframe.

1. Do you have a specific term for this? Y/N
   a. If yes, what do you call it: [SELECT ONE]
      i. Prolonged POI
      ii. Paralytic POI
      iii. Pathologic POI
      iv. Severe POI
      v. POI [not further specified]
      vi. Adynamic ileus
      vii. Other (please specify) [FREE TEXT]

2. What is your expected timeframe (in days) for physiologic post-operative GI tract dysfunction? (i.e. at what time point does this ongoing gut dysfunction stop being physiologic?) If in your opinion this varies with procedure, please list the maximum duration.
   a. 1 day
   b. 2 days
   c. 3 days
   d. 4 days
   e. 5 days
   f. 6 days
   g. 7 days
   h. Other (please specify) [FREE TEXT]

3. Which essential criteria must be met in order for you to define this as ongoing post-operative GI dysfunction, which has not yet resolved? Please tick as many boxes as necessary [SELECT ONE OR MORE]
   a. Absence of flatus
   b. Absence of stool
   c. Inability to tolerate of an oral diet
   d. Absence of bowel sounds
   e. Ongoing nausea or vomiting
   f. Ongoing abdominal pain
   g. Ongoing abdominal distension
   h. Radiologic evidence
   i. Need for NG tube insertion
   j. Other (please specify) [FREE TEXT]
A final scenario is where post-operative GI dysfunction appears to resolve, only for there to be a reoccurrence of the symptoms & signs indicating GI dysfunction.

1. Do you have a specific term for this? Y/N
   a. If yes, what do you call it: [SELECT ONE]
      i. Recurrent POI
      ii. Paralytic POI
      iii. Pathologic POI
      iv. Severe POI
      v. POI [not further specified]
      vi. Adynamic ileus
      vii. Other (please specify) [FREE TEXT]

2. Which essential criteria must be met in order for you to define this as a reoccurrence of post-operative GI dysfunction? Please tick as many boxes as necessary [SELECT ONE OR MORE]
   a. Absence of passage of flatus
   b. Absence of passage of stool
   c. Inability to tolerate of an oral diet
   d. Absence of bowel sounds
   e. Nausea or vomiting
   f. Abdominal pain
   g. Abdominal distension
   h. Radiologic evidence
   i. Need for NG tube insertion
   j. Other (please specify) [FREE TEXT]
Please feel free to list any final comments on the content or design of this survey: [FREE TEXT]
APPENDIX B
RANDOMISED CONTROLLED TRIAL:
(PATIENT INFORMATION SHEET & CONSENT FORM)
Gastrografin in Postoperative Ileus

Study Investigators:
Dr. Ryash Vather
PhD candidate & Research Fellow
Department of Surgery
The University of Auckland
Ph: 021 210 2024

A/Prof Ian Bissett
Head of Department
Department of Surgery
The University of Auckland
Ph: 09 373 7599 ext: 89821

You are invited to take part in a research study looking at a new way to improve gut recovery after surgery.

Please take your time to think about this and decide whether you wish to take part in it. Taking part is completely voluntary and if you decide you do not wish to, it will not affect your continuing healthcare in any way.

What is it all about?
After abdominal surgery there is a period of unavoidable loss of gut function. During this time, patients are unable to eat and drink, do not pass wind or stool, and may also experience nausea and vomiting. Though this resolves within 2-3 days for most patients, around 25% continue to experience these symptoms. The clinical term for this is ‘prolonged postoperative ileus’.

Prolonged postoperative ileus has been shown to slow recovery after surgery, increase the risk of developing other complications, and increase the length of hospital stay. Patients with it consistently have worse outcomes after surgery when compared to their counterparts. Prolonged postoperative ileus is therefore a major problem in the surgical setting, but despite this there are no readily available effective treatments for it. Current management involves giving intravenous fluids, pain relief and anti-vomiting medication, and waiting for the condition to resolve by itself.

The scientific basis for an ileus is not fully understood, and this has contributed to the inability to find an adequate treatment. However, it is believed that the development revolves around three key factors: bowel wall swelling, use of narcotic pain relief, and abnormalities in activity at nerve receptors.

The clinical trial in which we hope to involve you aims to assess whether a medication known as ‘gastrografin’ can effectively shorten the duration of a postoperative ileus. Gastrografin is commonly used by doctors to assess and treat small bowel obstruction (a condition similar to ileus). It is safe, well-tolerated, and has the ability to draw fluid out of the bowel wall. Given that bowel wall swelling is thought to be a key factor in a developing ileus, it is predicted that gastrografin will be an effective treatment.

Gastrografin in Postoperative Ileus
Version 2 (19 June 2012)
R Vather, IP Bissett
Why are you being asked?
You are scheduled to undergo elective abdominal surgery at Auckland City Hospital, and are therefore an ideal candidate for our trial. You have a 1 in 4 chance of developing a prolonged postoperative ileus. Based on earlier studies, this is expected to last between 4-5 days. We would like to investigate whether gastrografin is effective in shortening the duration of this ileus, and would therefore like to administer either gastrografin or placebo to you if you are diagnosed. If you do not develop a postoperative ileus there will be no difference in your postoperative care.

Participation will not have any effect on your waiting list time, or the operation itself. However, if you do go on to develop a postoperative ileus, you stand to gain from a faster recovery, shorter length of hospital stay and improved outcome by enrolment in this trial.

If you choose not to participate, there will be no difference in the quality of the care you receive at any point.

Participant selection
Inclusion criteria for this study are patients over 18 years of age who have undergone elective laparoscopic or open abdominal surgery for any indication at Auckland Hospital, and are diagnosed with prolonged postoperative ileus.

Exclusion criteria for this study will be patients who are pregnant, have previously had an allergic reaction to gastrografin or iodinated contrast agents, have a high anaesthetic risk (ASA ≥ 4), or have manifest hyperthyroidism.

It is anticipated that this study will take place over a period of 1.5 years, through which time 350 patients will be screened and around 100 participants recruited.

What happens during the study?
All aspects of your care before, during, and for the first 4 days after your surgery will occur routinely as decided by your surgical team.

On Day 4 after your surgery you will be visited by Dr. Vather, a study investigator. He will perform a brief assessment (lasting about 3-4 minutes) to gauge whether you have developed a prolonged postoperative ileus. If you do not, you will continue your recovery as per the surgical team, and be assessed again on a daily basis. If you do have an ileus, you will be enrolled in the trial.

Upon enrolment, you will be randomly assigned to receive either gastrografin or a placebo (a medication with no effect) within 6 hours. This whole process will be blinded, meaning neither you nor us will know what you have received. This ensures that scientific integrity is maintained during assessment and analysis of results. You will follow a standardised ‘best practice’ protocol during your postoperative ileus (in addition to your study medication) to make certain you receive the best quality of care. Dr. Vather will review you every 12 hours, to assess whether your ileus has resolved and to ensure there are no concerns. Upon resolution of the ileus, you will be visited daily until discharge. No further follow-up will be needed after this from the clinical trial perspective.

We strongly encourage you to contact study investigators at any point if you have any questions or concerns. Our contact details can be found at the top of this leaflet.
Risks & benefits
There are no major risks associate with this study.
Gastrografin is a safe drug which is very well-tolerated. It is the main initial treatment for bowel obstruction, a condition similar to ileus. Commonly quoted risks include aspiration (inhaling the medication by mistake), dehydration or allergic reactions (these may include skin rashes or nausea, and rarely angioedema [facial swelling] or bronchospasm [difficulty breathing]). However, the chances of any of these occurring and leading to a serious adverse event are exceptionally small.

The benefit to participating in this study is a potentially faster recovery and earlier discharge. We predict that gastrografin will draw fluid out of the bowel, allowing it to begin working properly again. Therefore, these patients may have a shorter duration of ileus, and stand to benefit from an earlier discharge. This in turn is likely to reduce the risk of developing other complications and improving overall health outcomes after surgery.

Confidentiality & Protection of Privacy
This study will form part of Dr. Vather's PhD, and is therefore a supervised study. No material which could personally identify you will be used in any reports of this study.

Study participants be allocated a participant number, with all relevant pieces of clinical information being attached to this number. Identifying patient information (i.e. name and NHI) will be recorded on a single password protected computer, and will only be able to be accessed by a single investigator (Dr. Vather).

Confidentiality will be maintained through analysis and presentation of results, without any reference to patient identifiable data.

Records from this study will be kept for 10 years after study completion on the investigators' password-protected computers at the University of Auckland as is routine protocol. Upon reaching this time point all electronic and paper copies of this information will be destroyed.

ACC compensation
In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, please contact your nearest ACC office or a study investigator.

Medical Insurance
Involvement with this trial is unlikely to affect any medical insurance you may have. However, if you are concerned about this, we encourage you to check with your insurance provider.
Financial considerations
There is no cost and no incentive payment for your participation in this trial.

Ethical Approval
This study has received ethical approval from the Northern X Regional Ethics Committee.

General Information
We are happy to send you a copy of the results of this study upon its completion. It is expected results will be published as a journal article, and presented at various international conferences.

Please take all the time you need to think about this study. We ask that you let us know whether you would like to be involved on the day before your colonoscopy at the latest.

You are welcome to have friends or whanau support you through the duration of this study if you wish.

If you would like more detailed scientific information on this study please contact the study investigators.

If you have any questions or concerns about your rights as a participant in a research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Their phone number is 0800 555 050 and their email is advocacy@mdc.org.nz.

Thank you for making the time to read about, and consider taking part in this study. Please feel free to contact us (details at the start of the leaflet) if you have any questions about this study.
Gastrografin in Postoperative Ileus

REQUEST FOR INTERPRETER

<table>
<thead>
<tr>
<th>Language</th>
<th>I wish to have an interpreter.</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaf</td>
<td>I wish to have a NZ sign language interpreter.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maori</td>
<td>E hiaha ana ahau ki tetahi kawhakamaoni/ kaiwhaka pakeha korero.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook Island Maori</td>
<td>Ka inangaro au ki tetahi tangata uri reo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fijian</td>
<td>Au gadrava me du e vakadewa vosa vai au</td>
<td>Io</td>
<td>Saga</td>
</tr>
<tr>
<td>Niuean</td>
<td>Fia manako au ke fakaaoga e taha tagata fakahokotoko kupu.</td>
<td>E</td>
<td>Naked</td>
</tr>
<tr>
<td>Samoan</td>
<td>Ou te mana o ia i ai se fa'amataa upu.</td>
<td>Io</td>
<td>Leai</td>
</tr>
<tr>
<td>Tokelauan</td>
<td>Ko ou e fofou ki he tino ke fakaliiku te gagana Peletania ki na gagana o na motu o te Parihika.</td>
<td>Io</td>
<td>Leai</td>
</tr>
<tr>
<td>Tongan</td>
<td>Oku ou fiema'u ha fakatonea.</td>
<td>Io</td>
<td>Ikai</td>
</tr>
</tbody>
</table>

- I have read and I understand the information sheet dated 19 June 2012 for volunteers taking part in the study to investigate the therapeutic value of gastrografin in prolonged postoperative ileus. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
- I have had the opportunity to use family/whānau support or a friend to help me ask questions and understand the study.
- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my ongoing health care.
- I have had this project explained to me in detail by a study investigator.
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
- I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.
- I understand the compensation provisions for this study.
- I have had time to consider whether to take part in this study.
- I know who to contact if I have any side effects to the study.
- I understand that my GP will be informed of all clinically significant abnormal results.
- I know who to contact if I have questions about the intervention used in this study or about the study in general.
I wish to receive a copy of the results

☐ Yes    ☐ No

Please note, there will be a delay between data collection and publication of results.

I _______________________________ hereby consent to take part in this study.

(full name)

Signature ___________________________ Date ___________________________

Investigator name ________________________________

Investigator Signature ________________________________

Investigator contact details

Dr. Ryash Vather          A/Prof. Ian Bissett
021 210 2024              09 373 7599  ext 89821

Interpreter (if required)

I _______________________________ translated the project to the participant.

Signature ___________________________ Date ___________________________
APPENDIX C
RANDOMISED CONTROLLED TRIAL:
(DATA COLLECTION FORM)
# Gastrografin in Postoperative Ileus

## OT date:

<table>
<thead>
<tr>
<th>Diagnosis (daily)</th>
<th>Criteria</th>
<th>s=2 criteria?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>Postop Day</td>
<td>A</td>
</tr>
</tbody>
</table>

**Diagnosis**

A. Nausea OR Vomit
   - within last 12 hours
   - nausea: nil/mild/mod/sea

B. Inability to tolerate oral diet
   - For 2 previous meal times
   - <25% of pre-op meal quantity

C. No flatus AND stool over last 24 hours

D. Distension
   - nil/mild/mod/sev

E. Radiologic confirmation
   - within last 24 hours
   - AXR with dilated SB > 3cm
   - CT Abdo with report stating POI

<2 - cont. daily review
≥2 - assess resolution after 12 hours

---

### Day 4 – other measures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Total wound size (cm):</th>
<th>Day 0-4 total: Panadol</th>
<th>Other opiate</th>
<th>NSAIDs</th>
<th>Antiemetic -Ondansetron -Cyclizine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 0-4 total colloid (L):</td>
<td></td>
<td>PCA</td>
<td>Tramadol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 0-4 total crystalloid (L):</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Day of first:**

- Mobilisation
- Flatus
- Stool

---

Ryash Vather 021 210 2024
Ian Bissetti 021 347 442

237
### Resolution (12-hourly)

<table>
<thead>
<tr>
<th>Date</th>
<th>Post-op Day: am/pm</th>
<th>Criteria</th>
<th>All 4?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>W</td>
<td>X</td>
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</tbody>
</table>

**W.** No vomiting for 12 hours with NG spigotted or removed AND nausea: nil / mild / mod / sev

**X.** Able to tolerate oral diet for last meal:
- Lite or full diet
- Solid or semi-solid (not fluid)
- >25% of pre-op meal quantity

**Y.** Passage of flatus OR stool within last 24 hours

**Z.** Distension: nil / mild / mod / sev

All 4 – back to daily review <4 – cont. 12-hour assessment

---

### NGT

<table>
<thead>
<tr>
<th>Y / N</th>
</tr>
</thead>
</table>

- Time of insertion
- Time of spigot
- Time of removal
- Total output

### TPN

<table>
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<tr>
<th>Y / N</th>
</tr>
</thead>
</table>

- Time commenced
- Time stopped

---

### Total over PPOI course:

- Panadol
- NSAIDs
- PCA
- Tramadol

### Other opiate

- Antiemetic
  - Ondansetron
  - Cyclizine

### Total crystalloid (L):

### Total colloid (L):
APPENDIX D

IN VIVO HIGH RESOLUTION MANOMETRY:
PERI-OPERATIVE COLORECTAL MOTILITY
(PATIENT INFORMATION SHEET & CONSENT FORM)
Peri-operative large bowel pressure wave propagation

Study Investigators:  
Dr. Ryash Vather  
PhD candidate & Research Fellow  
Department of Surgery  
The University of Auckland  
Ph: 021 210 2624  
A/Prof Ian Bissett  
Head of Department  
Department of Surgery  
The University of Auckland  
Ph: 09 373 7599 ext 89821

You are invited to take part in a research study about pressure wave movement in the large intestine, around the time of surgery.

Please take your time to think about this and decide whether you wish to take part in it. Taking part is completely voluntary and if you decide you do not wish to take part, it will not affect your continuing healthcare in any way.

What is it all about?  
Pressure waves in the gastrointestinal tract help break down and move food through its different parts, aiding in digestion and absorption of nutrients. After major abdominal surgery, this pressure wave movement does not work properly for a few days and this usually means patients have difficulty eating, drinking, passing wind/stool and may possibly experience abdominal swelling.

It has been shown scientifically that pressure wave movement occurs first in the small intestine, then the stomach, and finally the large intestine (pictured to the right). This is why patients are so frequently asked if they have passed wind and stool after an operation – it tells us whether the pressure waves in the gastrointestinal tract have fully returned.

However, despite this knowledge, the actual strength, frequency, direction and timing with which pressure waves re-appear is not known. Being able to understand how this actually works will greatly increase our scientific knowledge, and is very likely to be a stepping stone to speeding up recovery after operations.

The study we hope to involve you with will look at the way large bowel pressure waves change around the time of an operation. We hope to do this by placing a catheter within the large intestine prior to your surgery, and having it record information before, during and after the operation. We plan to include a total of 12-15 patients in this study. Patients such as yourself will be approached if they are over the age of 18, and scheduled to have an elective R. hemicolecotomy at Auckland City Hospital.
Why are you being asked?
You have seen a colorectal surgeon at Auckland DHB and have been placed on the waiting list for an elective R. hemicolectomy. This makes you an eligible candidate for our planned study should you wish to participate (please see full details below).

Please note that if you do choose to participate in this study it will not have any effect on the operation, your recovery or the time you spend in hospital. It is purely observational, and you are free to withdraw from this study at any point.

Likewise, if you don’t choose to participate, there will be no difference in the quality of the care you receive.

Participant selection
Inclusion criteria for this study are patients over 18 years of age, scheduled to undergo elective R. hemicolectomy for any indication at Auckland Hospital using a laparoscopic or open technique.

Exclusion criteria for this study will be patients who are pregnant, have previously undergone colorectal surgery, have a high anaesthetic risk (ASA ≥ 4), or have past/active functional motility disorders.

What happens during the study?
On the morning of your planned operation, we will ask that you come in to hospital at 7:30am. We will meet you at this time and take you through to the Endoscopy Suite. You will be given a Fleet enema to clear your large bowel of any faeces (please note, this is routinely done before R. hemicolectomy at Auckland Hospital), and then undergo a flexible sigmoidoscopy.

A flexible sigmoidoscopy is similar to a colonoscopy, except the scope is only passed for about 1/5th the distance. Therefore, this procedure is usually very well tolerated, safe, and requires no pain relief or sedation. Once the scope has reached the descending/sigmoid colon, we will attach the pressure catheter to the inside of the bowel wall. This too has been shown to be safe and painless. The entire procedure should not take more than 5-10 minutes.

The catheter is attached to an ‘acquisition box’ by a cable. This cable can easily be disconnected and reconnected, allowing you to move around freely. We will show both you and the nursing staff how this is done, and we encourage you to contact us if you are unsure of anything.

Your operation will take place in the afternoon, giving us a few hours to record ‘baseline’ readings from the catheter. The operation itself and postoperative recovery will progress as normal, with all decisions being made by the surgical team overseeing your care. We ask that you note the times at which you eat, drink, and pass wind/stool. A study investigator (Dr. Vather) will visit you twice a day while you are in hospital to make sure there are no concerns – if there are this study will be stopped immediately.

The catheter will be removed before Day 2 postoperatively or at the time of your first bowel motion, whichever occurs earlier. This is done by gently pulling on it, and is safe and not painful. There will be no further appointments or follow-up needed from our side of things.

We strongly encourage you to contact study investigators at any point if you have any questions or concerns. Our contact details can be found at the top of this leaflet.

Post-operative large bowel pressure wave propagation
Version 2 (15 June 2012)
R Vather, IP Basett
Risks & benefits
There will be no direct benefit to you by participating in this study. However, the information we obtain from this study will benefit scientific knowledge greatly, and will likely form the basis for trialling new treatments aimed at improving postoperative recovery.

There are no major risks associated with this study. However, this study will require a flexible sigmoidoscopy which is an additional procedure. This is very safe (with the risk of bleeding, perforation or diverticulitis being less than 1 in 10,000), requires no sedation, and is tolerated very well. A possible inconvenience of this study is the catheter’s limit to free mobilisation. However, it can be easily disconnected and reconnected, either by you, the nursing staff or a study investigator.

There will be no change to the length of your hospital stay, your postoperative recovery or the quality of care you receive whether you choose to participate or not.

Confidentiality & Protection of Privacy
No material which could personally identify you will be used in any reports of this study.

Study participants be allocated a participant number, with all relevant pieces of clinical information being attached to this number. Identifying patient information (i.e. name and NHII) will be recorded on a single password protected computer, and will only be able to be accessed by a single investigator (Dr. Vather).

Confidentiality will be maintained through analysis and presentation of results, without any reference to patient identifiable data.

Records from this study will be kept for 10 years after study completion on the investigators’ password-protected computers at the University of Auckland as is routine protocol. Upon reaching this time point all electronic and paper copies of this information will be destroyed.

ACC compensation
In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, please contact your nearest ACC office or a study investigator.

Ethical Approval
This study has received ethical approval from the Northern X Regional Ethics Committee.

Pen-operative large bowel pressure wave propagation
Version 2 (19 June 2012)
R Vather, IP Bassett
General Information
We are happy to send you a copy of the results of this study upon its completion. It is expected that these results will be published as a journal article, and presented at various international conferences.

Please take all the time you need to think about this study. We ask that you let us know whether you would like to be involved on the day before your surgery at the latest.

You are welcome to have friends or whanau support you through the duration of this study if you wish.

If you would like more detailed scientific information on this study please contact the study investigators.

If you have any questions or concerns about your rights as a participant in a research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Their phone number is 0800 555 050 and their email is advocacy@hdc.org.nz.

Thank you for making the time to read about, and consider taking part in this study. Please feel free to contact us (details at the start of the leaflet) if you have any questions about this study.

Peri-operative large bowel pressure wave propagation
Version 2 (19 June 2012)
R Vatter, IF Blissett
Consent Form

Peri-operative large bowel pressure wave propagation

REQUEST FOR INTERPRETER

<table>
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<tr>
<th>Language</th>
<th>Statement</th>
<th>Yes</th>
<th>No</th>
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<td>Deaf</td>
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<tr>
<td>Maori</td>
<td>E hāna ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.</td>
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<td>Cook Islands Maori</td>
<td>Ka inangaro au i tetai tangata un rec.</td>
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<tr>
<td>Fijian</td>
<td>Au qadrova me dua e vakadews vosa vei au</td>
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<tr>
<td>Niucaen</td>
<td>Fa manako au ke fakaaoa e taha tagata fakahokohoko kupu.</td>
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<tr>
<td>Samoan</td>
<td>Otu te mana’o ia i ai se fa’amatala upe.</td>
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<tr>
<td>Tokelaun</td>
<td>Ko au e fofoi ki he tino ke fakatili te gagana Peletania ki na gagana o na motu o te Pakefika</td>
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<tr>
<td>Tongan</td>
<td>Oku ou fiema’u ha faletono’u’a.</td>
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</table>

- I have read and I understand the information sheet dated 19 June 2012 for volunteers taking part in the study designed to assess pressure wave movement in the peri-operative setting. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
- I have had the opportunity to use family/whānau support or a friend to help me ask questions and understand the study.
- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my ongoing health care.
- I have had this project explained to me in detail by a study investigator.
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
- I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.
- I understand the compensation provisions for this study.
- I have had time to consider whether to take part in this study.
- I know who to contact if I have any side effects to the study.
- I know who to contact if I have questions about the intervention used in this study or about the study in general.
I wish to receive a copy of the results

☐ Yes  ☐ No

I ___________________________________________ hereby consent to take part in this study.

(full name)

Signature_________________________  Date_________________________

Investigator name____________________________

Investigator Signature________________________

Investigator contact details  Dr. Ryash Vather  AvProf. Ian Bissett
021 210 2024  09 373 7599  ext 89821

________________________________________

Interpreter (if required)

I __________________________________________ translated the project to the participant.

Signature_________________________  Date_________________________
APPENDIX E

IN VIVO HIGH RESOLUTION MANOMETRY:
COLORECTAL MOTILITY AFTER PREVIOUS SEGMENTAL RESECTION
(PATIENT INFORMATION SHEET, CONSENT FORM &
COMPREHENSIVE FAECAL INCONTINENCE QUESTIONNAIRE)
Pressure wave propagation across healed large bowel anastomoses

Study Investigators: Dr. Ryash Vather
PhD candidate & Research Fellow
Department of Surgery
The University of Auckland
Ph: 021 210 2024

A/Prof Ian Bissett
Head of Department
Department of Surgery
The University of Auckland
Ph: 09 373 7599 ext 89821

You are invited to take part in a research study looking at pressure wave movement across healed large intestine joins.

Please take your time to think about this and decide whether you wish to take part in it. Taking part is completely voluntary and if you decide you do not wish to, it will not affect your continuing healthcare in any way.

What is it all about?
Pressure waves in the gastrointestinal tract help break down and move food through its different parts, aiding in digestion and absorption of nutrients. After colorectal surgery is performed, there is usually a segment of the large intestine (pictured here) which is removed. The ends of the remaining parts of large intestine are then joined together at what is known as an ‘anastomosis’. This join heals with time, and soon the large bowel forms a single tube in continuity without the diseased part being present.

Most patients who have undergone this type of operation recover without any long-term problems. However, a small but significant number go on to develop major problems with constipation or incontinence. The consequences of this are severe, with this group of patients often having a reduced quality of life, being restricted socially and developing psychological disorders.

The scientific cause for postoperative constipation or incontinence is thought to be related to nerve injury at the time of surgery, or a failure of the bowel wall to adequately heal at the actual site of the join. It is not clear if there is pressure wave movement across anastomoses.

Being able to understand whether pressure waves move across anastomoses (and if so, their strength, frequency and direction) will greatly increase our scientific knowledge of functional healing at these joins. It will also serve as a platform for future studies looking at new treatments for the severe constipation and incontinence which may affect patients after large bowel surgery.

Pressure wave propagation across healed large bowel anastomoses
Version 2 (19 June 2012)
R Vather, IP Bissett
The study we hope to involve you with will look at the way pressure waves move across large bowel joins. We hope to do this by placing a catheter within the large intestine at the time of your scheduled colonoscopy, and recording information from it for 6-8 hours after the procedure. We plan to include a total of 12-15 patients in this study. Patients such as yourself will be approached if they are over the age of 18, and have previously had surgery to the lower part of their large bowel.

Why are you being asked?
You have previously had a segment of your lower large bowel removed during surgery, with the two free ends being joined together. It is now time for your scheduled surveillance colonoscopy, and this makes you an eligible candidate for our planned study should you wish to participate (please see full details below).

Please note that if you do choose to participate in this study it will not have any effect on your colonoscopy or future follow-up. However, it will require you to stay for 6-8 hours after the procedure (rather than 1-2 hours which is the norm). The study is purely observational, and you are free to withdraw from it at any point.

Likewise, if you don’t choose to participate, there will be no difference in the quality of care you receive.

Participant selection
Inclusion criteria for this study are patients over 18 years of age who have previously undergone anterior resection or sigmoid colectomy with primary anastomosis for any indication at least 6 months prior, and are now presenting to Auckland Hospital for routine surveillance colonoscopy.

Exclusion criteria for this study will be patients who are pregnant, have previously undergone colorectal surgery, have an anastomosis ≤10cm from the anal verge, or have past/active functional motility disorders.

What happens during the study?
On the day of your planned colonoscopy, we will ask that you arrive at Auckland City Hospital at 8am. We will meet you at this time and take you through to the Endoscopy Suite, where we would have scheduled your colonoscopy to occur first on the morning list.

The colonoscopy will take place as normal, with sedation and pain relief being given as required. At the end of this procedure, while the scope is being removed, the pressure-recording catheter will be attached to the inside of the bowel wall, and run across the anastomosis. This is safe and painless, and will take only a few seconds to perform.

The catheter is attached to an ‘acquisition box’ by a cable. This cable can easily be disconnected and reconnected, allowing you to move around freely. We will show both you and the nursing staff how this is done, and encourage you to contact us if you are unsure of anything.

We estimate that your colonoscopy will be finished by around 9am, and ask that you stay in hospital until around 4pm in the afternoon. During this time we will obtain recordings from the catheter, and ask that you note the time at which you eat, drink, and pass wind/stool. A study investigator (Dr. Vather) will visit you 4 times through the day while you are in hospital to ensure there are no concerns – if there are the study will be stopped immediately.

*Pressure wave propagation across healed large bowel anastomoses*
*Version 2 (19 June 2012)*
*R Vather, IP Bissett*
The catheter will be removed in the afternoon, prior to your discharge home. This is done by gently pulling on it, and is safe and not painful. There will be no further appointments or follow-up needed from the research side of things.

We strongly encourage you to contact study investigators at any point if you have any questions or concerns. Our contact details can be found at the top of this leaflet.

**Risks & benefits**

There will be no direct benefit to you by participating in this study. However, the information we obtain from this study will benefit scientific knowledge greatly, and will likely form the basis for new treatments aimed at improving outcomes in those who suffer from constipation or incontinence following surgery.

There are no major risks associated with this study. However, this study will require that you stay in hospital for 6-8 hours after the colonoscopy (rather than 1-2 hours). A second inconvenience of this study is the catheter’s limit to free mobilisation. However, it can be easily disconnected and reconnected, either by you, the nursing staff or a study investigator.

There will be no change to the colonoscopic technique (and findings) or the quality of care you receive whether you choose to participate or not.

**Confidentiality & Protection of Privacy**

No material which could personally identify you will be used in any reports of this study.

Study participants are allocated a participant number, with all relevant pieces of clinical information being attached to this number. Identifying patient information (i.e. name and NHI) will be recorded on a single password protected computer, and will only be able to be accessed by a single investigator (Dr. Vather).

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*Pressure wave propagation across healed large bowel anastomoses*

*Version 2 (19 June 2012)*

*R Vather, IP Bizette*
Ethical Approval
This study has received ethical approval from the Northern X Regional Ethics Committee.

General Information
We are happy to send you a copy of the results of this study upon its completion. It is expected results will be published as a journal article, and presented at various international conferences.

Please take all the time you need to think about this study. We ask that you let us know whether you would like to be involved on the day before your colonoscopy at the latest.

You are welcome to have friends or whanau support you through the duration of this study if you wish.

If you would like more detailed scientific information on this study please contact the study investigators.

If you have any questions or concerns about your rights as a participant in a research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Their phone number is 0800 555 050 and their email is advocacy@hdic.org.nz.

Thank you for making the time to read about, and consider taking part in this study. Please feel free to contact us (details at the start of the leaflet) if you have any questions about this study.
Peri-operative large bowel pressure wave propagation

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<td>Ka inangaro au i totai tangata uri reo.</td>
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<td>Island Māori</td>
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<td>Fijian</td>
<td>Au gadreva me dua e vakadewa vosa vel au</td>
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<tr>
<td>Niuean</td>
<td>Fia manako au ke fakaaoga e taha taqata</td>
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<td></td>
<td>fakahokohoko kupu</td>
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<tr>
<td>Samoan</td>
<td>Ou to mana'oa ia i ai se fo'amatala upu.</td>
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<tr>
<td>Tokelau</td>
<td>Ko au e lofo ki he tino ke fakatilii te gagana</td>
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<td></td>
<td>Peletania ki na gagana o na motu o te Patherika</td>
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<tr>
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- I have read and I understand the information sheet dated 10 June 2012 for volunteers taking part in the study designed to assess pressure wave movement in the peri-operative setting. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
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- I understand the compensation provisions for this study.
- I have had time to consider whether to take part in this study.
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Peri-operative large bowel pressure wave propagation
Version 1 (27 April 2012)
R Vather, IP Bisett
Page 1 of 2
I wish to receive a copy of the results

☐ Yes  ☐ No

I __________________________ hereby consent to take part in this study.

(full name)

Signature____________________ Date___________________

Investigator name______________________________

Investigator Signature____________________________

Investigator contact details  Dr. Ryash Vather  A/Prof. Ian Bissett
021 210 2024  09 373 7599  ext. 89621

_____________________________________________________________________________________

Interpreter (if required)

I __________________________ translated the project to the participant.

Signature____________________ Date___________________

Peri-operative large bowel pressure wave propagation
Version 1 (27 April 2012)
R Vather, IP Bissett
COMPREHENSIVE FAECAL INCONTINENCE QUESTIONNAIRE

General Information

1. What is your gender?
   - Female
   - Male

2. What is your age in years?

3. Which ethnic group do you belong to?
   (Please tick the box or boxes that apply to you)
   - NZ European
   - Maori
   - Samoan
   - Cook Island Maori
   - Tongan
   - Niuean
   - Chinese
   - Indian
   - Other
   (such as Dutch, Tokelauan, Japanese)
   Please state:

   [Blank space for answer]
**Pattern of Bowel Movements**

6. Do you feel you have a problem with bowel control?
   - [ ] Yes
   - [ ] No

The following questions relate to your usual pattern of bowel movements in the last 3 months

7. On average, in the past 3 months, how often did you pass a bowel motion?
   (Please tick one)
   - [ ] More than 3 times per day
   - [ ] 2 to 3 times per day
   - [ ] Once per day
   - [ ] 2 to 3 times per week
   - [ ] Once per week
   - [ ] Less than once per week

The next question relates to any difficulty you may have had passing a bowel motion in the past 3 months

8. In the past 3 months, have you experienced any of the following?
   (Please tick all that apply to you)
   - [ ] Straining (having to push hard) on more than 1 out of every 4 bowel motions
   - [ ] Feeling that your bowel motion is incomplete more than a quarter of the time
   - [ ] Feeling of blockage during bowel motions more than a quarter of the time
   - [ ] Need to use fingers or hands to help with passing a bowel motion more than a quarter of the time
   - [ ] None of the above statements apply to me
9. **In the past 3 months** have you used medications regularly, including laxatives or medication for diarrhoea, to help you pass a bowel motion?

- [ ] Yes
- [ ] No

---

The following section relates to **any amount of bowel leakage (ACCIDENTAL loss of gas, mucus or stool/faeces/tiko/siko) you may have had in the last month**

10. For each of the following, please mark on average how often **in the past month** you experienced **any amount of bowel leakage**.

Please tick one box in each row.

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>1 to 3 times a month</th>
<th>Once a week</th>
<th>2 or more times a week</th>
<th>Once a day</th>
<th>2 or more times a day</th>
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<tr>
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<td>(farting, tete)</td>
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<tr>
<td>Leakage of Mucus</td>
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<td>(yellow discharge)</td>
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<tr>
<td>Leakeage of Liquid</td>
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<td>Stool (poo, tikotiko, teke, siko)</td>
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<tr>
<td>Leakage of Solid</td>
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<td>Stool (puru tutae, tiko, siko)</td>
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</table>
11. How often in the past month did you wear a pad because of bowel leakage?
   □ Never
   □ 1 to 3 times a month
   □ Once a week
   □ 2 or more times a week
   □ Once a day
   □ 2 or more times a day

12. In the past month, did you have any warning or feeling when you needed to pass a bowel motion?
   □ Yes
   □ No (Go to question 13)

   If Yes, did you have to rush/hurry to reach the toilet as soon as you felt the need to pass a bowel motion?
   □ Yes
   □ No

13. In the past month, did you ever have bowel leakage shortly after emptying your bowels or passing a bowel motion?
   □ Yes
   □ No

The following question relates to your bladder control in the past month.

14. In the past month have you experienced loss of control of your bladder

   (a) on coughing, laughing, sneezing or other physical activity?
   □ Yes
   □ No

   (b) when feeling an urgent need to pass water (urinate/mimi), but not making it to the toilet in time?
   □ Yes
   □ No
If you are male
The next questions are only for WOMEN

15. How many children have you given birth to?

16. Thinking back on these births, what type of delivery did you have?
   - [ ] Normal
   - [ ] Caesarian

17. In your longest labour, how long did you push for (second stage)?
   (Please tick one)
   - [ ] Less than 1 hour
   - [ ] 1 to 2 hours
   - [ ] More than 2 hours

18. Thinking back on all your labours, were any of the following required?
   - [ ] Forceps
   - [ ] Other instruments
   - [ ] No birthing aid required

19. Thinking back on all your labours, did you ever have a tear or episiotomy involving the muscles of your anus (back passage)?
   - [ ] Yes
   - [ ] No

20. What was the weight of your largest baby?
   
   [ ] kg
   [ ] lbs

21. Have you ever had a hysterectomy (operation to remove your womb/whare tangata)?
   - [ ] Yes    If yes, was it → [ ] Abdominal
   - [ ] Other
   - [ ] No
The following questions are for everyone

22 Have you ever had any of the following types of surgery to your bowels or anus (back passage)?
(Please tick all that apply to you)

☐ Removal and rejoining of part of your bowel
☐ Anal fistula surgery
☐ Operation on anal muscles
☐ Operation for haemorrhoids or piles
☐ Major prostate operation
☐ None of the above

23 Do you have a stoma (bag) for emptying your bowels?

☐ Yes
☐ No

24 Have you ever injured your anus (back passage), not including during childbirth?

☐ Yes
☐ No

25 Do you suffer from any of the following medical problems?
(Please tick all that apply to you)

☐ Inflammatory bowel disease  *(Eg Crohns disease or ulcerative colitis)*
☐ Irritable bowel syndrome
☐ Rectal prolapse
☐ Diabetes
☐ Stroke
☐ Other neurological condition
☐ Decreased mobility
☐ Haemorrhoids or Piles
☐ None of the above apply


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146. Groudine SB, Fisher HA, Kaufman RP, Jr., Patel MK, Wilkins LJ, Mehta SA, et al. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens...


238. Sim R, Cheong DM, Wong KS, Lee BMK, Liew QY. Prospective randomized, double-blind, placebo-controlled study of pre- and postoperative administration of a COX-2-specific


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