Non-invasive vagus nerve stimulation to reduce postoperative ileus: Feasibility study

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Declarations

The candidate confirms that the work submitted is his, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 5 contains materials from:

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Abstract

Background

Postoperative ileus is a debilitating complication after abdominal surgery. Numerous treatments to curtail its impact on patients and healthcare systems have been explored but few have led to clinically meaningful improvements in care. Electrical stimulation of the vagus nerve using a non-invasive and self-administered device has emerged as a new candidate treatment. This work aimed to explore the feasibility of a definitive randomised evaluation in patients undergoing major colorectal surgery.

Method

Firstly, a scoping review was performed, exploring the role of the vagus nerve in maintaining intestinal homeostasis and its role in reducing ileus in pre-clinical and early clinical studies. Secondly, a randomised, sham-controlled, feasibility trial was undertaken, examining the feasibility of recruitment, treatment compliance, participant blinding, and data completeness for a future trial. This was supplemented by semi-structured interviews with patients and healthcare professionals, exploring barriers and enablers of feasibility. Finally, a core outcome set for postoperative ileus was developed through international, multi-stakeholder consensus.

Findings

In existing pre-clinical studies, vagus nerve stimulation was shown to suppress intestinal inflammation and attenuate postoperative intestinal dysfunction via a cholinergic anti-inflammatory reflex. Early clinical studies showed that this was directly translatable to humans. The feasibility trial showed that participant recruitment, compliance to self-administration, and the collection of clinically-relevant endpoint data were readily feasible. In contrast, unblinding of participants was common, mainly due to expectations regarding the sensation and user-experience of the device. The interview findings identified a lack of confidence and a steep learning curve as modifiable barriers to fidelity. A core outcome set comprising twenty outcomes was ratified for use in future research.

Conclusion

A definitive randomised evaluation of non-invasive, vagus nerve stimulation may be feasible after modification. Targets for change include refinement to participant blinding procedures and confirmation of the fidelity of self-administration. A dedicated assessment of clinical efficacy is required prior to progressing to definitive assessments of clinical and cost effectiveness.

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List of abbreviations

AChR	Acetylcholine receptor
ACPGBI	Association of Coloproctology in Great Britain & Ireland
AF	Atrial fibrillation
AHP	Allied healthcare professional
ARR	Adjusted relative risk
ASA	American Society of Anesthesiologists
AV	Atrio-ventricular
BMI	Body mass index
BRI	Bradford Royal Infirmary
CE	Conformité Européene
ChAT	Choline acetyltransferase
CI	Confidence Intervals
COMET	The Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COREQ	Consolidated Criteria for Reporting Qualitative Research
COS	Core outcome set
COSMIN	Consensus-based Standards for Selection of Health Measurement Instruments
COS-STAD	Core Outcome Set-STAndards for Development framework
COS-STAR	Core Outcome Set-Standards for Reporting
COVID	Coronavirus disease 2019
COX-2	Cyclooxygenase-2
CQC	Care quality commission

CRF	Case report form
CTB	Cholera toxin-b
DC	Direct Current
DMV	Dorsal motor nucleus of the vagus
EGFR	Estimated glomerular filtration rate
ERAS	Enhanced Recovery After Surgery
FDA	Food and Drug Administration
FD70	Fluorescein isothiocyanate-labelled dextran
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
HRA	Health Research Authority
IC	Immunochemistry
IHI	Institute for Healthcare Improvement
IL	Interleukin
IP	Intraperitoneal
ITT	Intention to treat
IQR	Interquartile range
JAK2/STAT	Janus kinase 2/signal transducer and activator of transcription 3
MPO	Myeloperoxidase
MS	Millisecond
NANC	Non-adrenergic noncholinergic
NGT	Nasogastric tube
NGT	Nominal Group Technique
NHS	National Health System
NICE	National Institute for Health and Care Excellence

NIHR	National Institute of Health and Care Research
NRS	Numerical rating scale
NSTEMI	Non-ST-elevated myocardial infarction
NTS	Nucleus of the solitary tract
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OMERACT	Outcome Measures in Rheumatology Framework
OR	Odds ratio
PAF	Population attributable fractions
PVD	Peripheral vascular disease
POD	Postoperative day
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROM	Patient-reported outcome measure
RCT	Randomised controlled trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture Platform
SD	Standard deviation
SJUH	St. James's University Hospital
SMD	Standardised mean difference
STEMI	ST-elevated myocardial infarction
TFA	Theoretical Framework of Acceptability
TIDieR	Template for Intervention Description and Replication
TNFα	Tumour necrosis factor alpha
TRH	Thyrotropin-releasing hormone

UK	United Kingdom
US	United States
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WHO	World Health Organisation
$5HT_4$	5-hydroxytryptamine 4

Chapter 1

An introduction to postoperative ileus

Preface

Postoperative ileus is a common complication after surgery, with profound implications for both patients and healthcare systems. Whilst numerous clinical interventions have been evaluated to reduce ileus, its incidence remains high, as does the need for further research into new and innovative treatments. In this chapter, a description of aetiologies underpinning postoperative ileus is presented. The incidence and burden on healthcare users and providers are examined. As well, a detailed exploration of previous treatments used to reduce ileus are explored. The chapter ends with a roadmap describing the overall aim and objectives of this thesis.

1.1. Postoperative ileus in clinical practice

1.1.1. Summary of the clinical challenge

Postoperative ileus is a temporary cessation of coordinated intestinal motility after surgery. It is characterised clinically as a disruption of normal bowel function which becomes apparent one to two days after surgery and may persist in excess of 10 days (1). The symptoms of ileus comprise nausea and vomiting, abdominal distension, and constipation (2). Vomiting is typically persistent and high-volume, often requiring the use of a nasogastric tube to decompress the stomach and reduce the risk of pulmonary aspiration. Abdominal distension may be associated with pain but not usually with peritonism unless associated with other intra-abdominal complications. Constipation is absolute, with absence of flatus and stool which return at varying timepoints during the postoperative period. Other symptoms include nausea, acid reflux, and anorexia.

In 2014, a patient-professional consensus process facilitated by the Association of Coloproctology in Great Britain & Ireland (ACPGBI) identified postoperative ileus as an unmet clinical challenge (3). It was agreed through consensus that efforts to reduce ileus should be considered as being amongst the highest research priorities in the field of colorectal surgery. Existing guidelines developed by the Enhanced Recovery After Surgery (ERAS) Society echo this by identifying ileus as a key objective for improving patient recovery after colorectal surgery (4). The same is recommended by ERAS guidelines applicable to other fields of abdominal and pelvic surgery, such as gynae-oncology and radical cystectomy (5, 6). Whilst all of these guidelines recommend the use of multi-modal strategies to prevent ileus, the strength of evidence for most individual clinical interventions remains weak.

1.1.2. Aetiology

Normal intestinal motility is coordinated by the enteric nervous system, comprising of neural circuits that control motor function, mucosal secretions, and immune functions in the gut (7). The neural circuits are composed of enteric neurones arranged in networks of ganglia within myenteric and submucosal plexuses. They produce patterns of excitation and inhibition of intestinal smooth muscle, ultimately leading to waves of coordinated and propulsive peristaltic movements. Extrinsic spinal and vagal neurones regulate these activities. Afferent (sensory) pathways transmit information about chemical and mechanical changes in gut homeostasis to the central nervous system, triggering conscious sensations, such as pain and nausea. They also modulate efferent (motor) pathways travelling from the central nervous system to the gut, which in turn play a role in maintaining intestinal homeostasis (8).

Postoperative ileus disrupts the normal pattern of intestinal motility. It is considered to comprise two distinct phases: an early neurogenic phase and a later inflammatory phase (9). During the early phase, stimuli from the initial incision stimulate spinal afferents which activate an inhibitory feedback pathway in the spinal cord. Further stimuli elicited by handling the gut activate a series of supra-spinal pathways that are mediated by the brainstem. Both of these abolish motility across the intestinal tract in the early hours after surgery but the effects are transient and self-limiting (9). During the later phase (typically from 3-4 hours after surgery), intestinal handling activates peritoneal mast cells. Through the release of histamine and other vasoactive mediators, intestinal permeability is increased, allowing translocation of luminal bacteria and subsequent activation of intestinal macrophages that reside in the gut muscularis. The activated macrophages release pro-inflammatory cytokines and chemokines, attracting large numbers of nitric oxide- and prostaglandin-releasing leucocytes. It is the action of

these and their metabolites which impair the contractility of intestinal smooth muscle in the handled region of gut. The generalised pattern of ileus occurring in distant and unhandled areas develops due to further activation of inhibitory neural pathways stimulated by the accumulating inflammatory infiltrate. This leads to a longer period of smooth muscle impairment, affecting the entire intestinal tract (9).

Whilst much work has been done to understand the mechanisms underpinning ileus, less is known about how these translate into its typical clinical symptoms. For many years, the development of postoperative intestinal dysfunction was considered to arise exclusively from gut paralysis or atony. That is to say that the usual pattern of propulsive peristalsis was considered to be slower or absent after surgery, leading to ineffective transit of intestinal contents (10). The return of motility occurs differentially, first in the small bowel (<24 hours), next in the stomach (24-48 hours), and finally in the colon (>48 hours) (11). Other work has challenged this idea, arguing instead that intestinal dysfunction arises as a result of dysregulated motility throughout the gut. In 1986, it was observed by Condon and colleagues that electromechanical activity becomes abnormal in the postoperative period but is not entirely absent as might be expected during a state of intestinal paralysis. Using low-resolution manometry, they showed that colonic slow waves were present throughout the entire postoperative period, with the resolution of ileus marked by a shift from low to high frequency slow waves (12). Later in 2018, Vather and colleagues used high-resolution manometry to evaluate motility in the distal colon of eight patients undergoing right hemicolectomy. Here, they demonstrated the presence of a cyclic motor pattern in the sigmoid colon which was markedly hyperactive and persisted for the duration of their assessment up to 16 hours after surgery. It was postulated that this may represent an inhibitory mechanism, disrupting the normal mechanism of colonic transit and giving rise to the

clinical features of postoperative ileus (13). These findings were corroborated by Wells and colleagues in 2023 during their assessment of seven other patients undergoing right hemicolectomy. As well as confirming the presence of hyperactive cyclic motor activity in the distal colon of all patients, they showed that this peaked at 12 hours after surgery and declined over 2-4 days. Of note, none of the participants achieved a bowel motion in the postoperative period until after the pattern of hyperactivity returned to a preoperative baseline (14). This area of investigation provides a novel insight into the possible mechanism of gut dysfunction and its sequalae. Whether the true basis of dysfunction rests with hypomotility, dysmotility, or a complex combination of both, there is wide community consensus that ileus exists broadly as a temporary inhibition of effective motility after surgery (15).

1.1.3. Definition

The definition of postoperative ileus used in previous research is widely variable, which is challenging for the rigorous evaluation of new treatments. Common terminologies include “postoperative ileus” and “prolonged postoperative ileus”, which are used to delineate patterns of intestinal symptoms occurring over different timeframes. Prolonged postoperative ileus describes a pattern of symptoms (such as vomiting, constipation, and abdominal distension) which persists for more than four days whereas ileus that is not prolonged describes a shorter period of symptoms that may be transient and less profound (16). Other terminologies such as “primary” and “secondary” ileus describe the underlying cause of intestinal dysfunction, which may be due to intestinal handling during surgery or the effect of intra-abdominal infection or inflammation. Each of these definitions can be defined differently and thus may lead to significant clinical and statistical heterogeneity when considered in systematic reviews and meta-analyses of existing evidence. A review by Wolthuis and

colleagues, for instance, identified five different definitions for prolonged postoperative ileus across 54 studies (16). At present there is little agreement on the most appropriate way to define postoperative ileus and this is problematic for the efficient and productive use of finite research resources (17).

1.1.4. Incidence

Postoperative ileus is common after colorectal surgery. In a large study by Scarborough and colleagues, 3140 of 26,682 (11.8%) patients developed ileus after undergoing elective colonic resection. This was the most frequently observed complication in this study, with others such as bleeding (n=2032; 7.6%) and surgical site infection (n=1873; 7.0%) occurring less often (18). Notably, some variation in the observed incidence of ileus exists across different populations of patients. For instance, in a randomised controlled trial of chewing gum to reduce ileus after open colorectal surgery, a total of 43 out of 112 (38.3%) patients developed ileus (19). In a cohort study of patients undergoing laparoscopic colorectal surgery, however, only 37 out of 820 (4.5%) patients went on to develop ileus during their recovery (20). The definitions of ileus across these studies were variable, possibly accounting in part for some of the variation. Nevertheless, the incidence of ileus across most studies remains high, with a comprehensive review by Wolthuis and colleagues demonstrating an overall incidence of prolonged postoperative ileus of 10.2% (95% CI 5.6 to 17.8) in randomised controlled trials (RCTs) and 10.3% (95% CI 8.4 to 12.5) in non-RCTs (16).

1.2. Risk factors for postoperative ileus

1.2.1. Baseline risk factors

A number of baseline risk factors for postoperative ileus have been identified in previous

literature. Male sex is one of the most commonly observed factors, with one study reporting an increased odds ratio (OR) of 1.6 (95% CI: 1.3 to 2.1) compared to females and another study reporting an OR as high as 3.01 (95% CI 1.25 to 7.27) (21, 22). Several other cardiorespiratory and metabolic co-morbidities have also been associated with increased rates of ileus. These include chronic obstructive pulmonary disease (COPD) (OR 1.99, 95% CI 1.25 to 3.17), peripheral vascular disease (OR 1.80, 95% CI 1.20 to 2.70), and increased body mass index (BMI) (OR 2.52, 95% CI 1.23 to 5.20) (22, 23). A history of previous abdominal surgery (OR 2.41, 95% CI 1.14 to 5.12) is strongly associated with ileus, as are factors such as pre-operative hypoalbuminaemia (OR 1.11, 95% CI 1.02 to 2.22) and pre-operative use of opioid analgesia (OR 3.17, 95% CI 1.21 to 8.34) (21, 24). Some of these, such as BMI, are modifiable since they can be optimised within programmes of prehabilitation prior to surgery. Others such as peripheral vascular disease are not modifiable but can be controlled in the pre-operative period to mitigate the risk of ileus and other complications.

1.2.2. Operative risk factors

Open surgery is a key risk factor for ileus, which can be modified through the use of minimally invasive surgical techniques. Previous studies report an OR of 3.74 (95% CI 1.56 to 11.12) when compared to laparoscopic surgery (25). This is likely due to a higher degree of surgical stress, intestinal handling, and peritoneal exposure during open surgery, which are known to increase intestinal inflammation and lead to increased intestinal smooth muscle dysfunction (26). Other intra-operative risk factors include the need for perioperative transfusion (OR 1.90, 95% CI 1.50 to 2.50), larger volumes of intravenous fluids (OR 1.55, 95% CI 1.24 to 1.93), formation of an intestinal stoma (OR 1.40, 95% CI 1.1 to 1.8), larger wound size (OR 1.09, 95% CI 1.02 to 1.16), and longer operative times, particularly if exceeding 3 hours or

more (OR 1.60, 95% CI 1.2- to 2.2) (21, 24). Resection of bowel as an emergency procedure is also a risk factor (OR 2.2, 95% CI 1.4 to 3.5), independent of the type of surgical approach (i.e. open or laparoscopic) or the formation of a stoma (22).

1.2.3. Postoperative risk factors

The use of postoperative opioid analgesia is a commonly reported risk factor for ileus. In a study by Barletta and colleagues, the dose (OR 9.9, 95% CI 1.2 to 82.2) and duration (OR 1.5, 95% CI 1.2 to 2) of opioids were found to be independently associated with ileus after colorectal surgery (27). In a study by Artinyan and colleagues, the total opioid dose was found to be an independent predictor for the duration of ileus, with larger doses leading to a more protracted period of intestinal dysfunction (28). The mechanism of opioid-induced gut dysfunction is a result of activated peripheral μ-opioid receptors located within the gut myenteric plexus. When agonised, these inhibit the release of acetylcholine which increases intestinal smooth muscle tone and reduces propulsive activity (29). Other postoperative independent risk factors include inflammatory complications such as anastomotic leak (OR 2.50, 95% CI 1.93 to 3.24), increased intravenous fluids (OR 1.55, 95% CI 1.24 to 1.93), and delayed mobilisation (OR 1.39, 95% CI 1.13 to 1.71) (21, 30).

1.3. Impact and burden of postoperative ileus

1.3.1. Impact and burden for patients

Postoperative ileus is a major burden for patients and delays their recovery after surgery. A study by Scarborough and colleagues showed that ileus was significantly associated with the onset of multiple other postoperative adverse events within 30 days of surgery, including end-organ dysfunction (adjusted relative risk (ARR): 3.80,

95% CI 3.23 to 4.45), mortality (ARR 2.57, 95% CI 1.94 to 3.41), and prolonged hospitalisation (ARR 3.58, 95% CI 3.43 to 3.74). Using population attributable fractions (PAF), it was estimated that ileus had the largest overall effect on 30-day mortality (PAF 22.6%, 95% CI 14.5 to 30.0) and prolonged hospital stay (PAF 25.6%, 95% CI 24.5 to 26.7) compared to any other major complication such as anastomotic leak, surgical site infection, and postoperative pneumonia. That is to say that if it was possible to entirely prevent ileus in this population of patients, the incidence of 30-day mortality and prolonged hospitalisation would decrease by 22.6% and 25.6%, respectively (18). This is hypothetical, however, as to achieve it would require the elimination of other causes of secondary postoperative intestinal dysfunction, such as major intra-abdominal infections. In another study of 32,392 patients undergoing elective colorectal resection, the development of ileus alone did not increase mortality in the postoperative period. Instead, the simultaneous occurrence of other complications, including anastomotic, pulmonary, cardiovascular, renal, and septic events, led to dramatic increases in mortality, with the greatest rate reported for patients with ileus and pulmonary complications (22%) (31).

1.3.2 Impact and burden for healthcare systems

The economic and logistical impact of postoperative ileus on international healthcare systems is also highly burdensome. In the early 2000s, two studies from the United States (US) quantified the financial cost of surgery for patients with and without ileus. In one study, the average inpatient cost of treatment after colectomy was $25,089 (Standard Deviation (SD): $35,386) for patients with ileus and $16,907 (SD: $29,320) for those without (32). In a similar study, the average inpatient cost was estimated at $18,877 and $9,460 respectively, with the overall cost attributed to managing ileus across the US estimated to be as high as $1.46 billion per annum (33). More

recently, data from single institutions in Australia and New Zealand have described in detail the specific expenditures which lead to increased costs for patients with ileus after colorectal surgery. In both studies, the average overall cost of treatment was significantly higher for patients who developed ileus compared to those who did not (AU$37,690 vs. AU$29,822, *P*< 0.001; and NZ$27,981 vs. NZ$16,317, *P*<0.005, respectively). Increased expenditure was observed in multiple domains of healthcare, including medical and nursing care, radiology and diagnostics, pharmacy, laboratory costs, and allied healthcare services. Many of these were attributed to an increased length of hospital stay and more frequent occurrence of other postoperative complications during the course of their extended recovery (34, 35).

1.4. Interventions to prevent or reduce postoperative ileus

1.4.1. Minimally invasive surgery

Minimally invasive surgery (such as laparoscopy or robotic surgery) is one of the corner stones of enhanced recovery after surgery, as recommended by enhanced recovery guidelines (4). In principle, minimally invasive surgery leads to less traumatic tissue handling, reduced peritoneal air exposure, and better preservation of abdominal temperature. All of these contribute to reduced intestinal inflammation and reduced smooth muscle dysfunction, leading to greater preservation of intestinal motility (26). In a Cochrane review published in 2005, 17 RCTs (1991-2004) reported on the duration of ileus with respect to first passage of flatus (n=8; 1116 participants) and stool (n=9; 1130 participants). Overall, the use of minimally invasive surgery led to a quicker return of flatus in the order of 1 day (weighted mean difference (WMD): -1.03, 95% CI -1.30 to -0.76) and a quicker return of stool of 0.9 days (WMD -0.93, 95% CI -1.13 to -0.74) compared to patients undergoing open surgery (36).

1.4.2. Chewing gum

Chewing gum is an unintrusive and low-cost intervention which has been explored extensively for its role in preventing ileus after surgery. Several mechanisms have been proposed to explain its potential effect on intestinal motility, including stimulation of a cephalo-vagal reflex and an increase in pro-motility hormones as a result of increased mastication (37). Nevertheless, the findings of numerous RCTs exploring chewing gum as a clinical intervention to reduce ileus have demonstrated mixed results. In a trial by Topcu and colleagues, chewing gum was shown to decrease the time to first flatus (51.07 ± 19.63 vs. 87.83 ± 25.89 hours; $P<0.001$), time to first defaecation (73.33 ± 30.29 vs. 137.20 ± 44.05 hours; $P<0.001$), and time to restart feeding (3.07 ± 1.53 vs. 4.37 ± 1.90 days; $P<0.005$) after major open surgery (38). Similarly, in a trial by van den Heijkant and colleagues, the rate of ileus after open surgery (defined as a lack of flatus/stool and intolerance to oral intake for at least 24 hours) was significantly reduced from 48% in the control group to 27% in the gum group (39). In contrast, a trial by Lim showed no difference in the time to first flatus (42.75 ± 3.92 vs. 50.97 ± 3.79 hours; $P=0.134$) or first defecation (89.64 ± 5.94 vs. 98.61 ± 7.06 hours; $P=0.333$) in a population of 161 patients undergoing open and laparoscopic colorectal procedures (40). A trial by Zaghiyan corroborated these findings by showing no significant difference in the time taken to pass flatus (48.6 ± 33.4 vs. 47.4 ± 29.4 hours; $P=0.83$) or stool (56.9 ± 37.8 vs. 63.2 ± 41.9 hours; $P=0.40$) in a similar population of 114 patients receiving gum and no gum, respectively (41). In keeping with these mixed results, a Cochrane review comprising of 81 studies (1990-2014) was unable to conclude with certainty whether chewing gum provided any clinical benefit due to the limitation of only small and poor-quality studies with a high risk of bias (42). Most recently in 2018, a large, multi-centre trial

of 1000 patients across 12 hospitals in the Netherlands showed that the addition of chewing gum to existing enhanced recovery protocols did not reduce the median length of hospital stay (7 [IQR: 5-10] vs. 7 [IQR: 5-10] days; *P*=0.364) or reduce the median time to pass flatus (23 [IQR: 14-45] vs. 24 [IQR: 13-48] hours; *P*=0.873) or stool (52 [IQR: 29-79] vs. 60 [IQR: 25-88] hours; *P*=0.562) (43). As a result of this, ERAS guidelines for colorectal surgery no longer support the routine use of chewing gum for the purpose of reducing ileus due to a lack of convincing clinical efficacy (4).

1.4.3. Early enteral feeding

Early resumption of oral feeding after surgery is another key principle of enhanced recovery guidelines (4). Previous evidence has shown that early feeding is safe as early as four hours after surgery and may help to reduce the rates of infective complications known to be associated with poor postoperative nutrition (44). A number of RCTs have explored the role of early feeding for reducing ileus after colorectal surgery. In a trial by Zhou and colleagues, early feeding led to a faster return of flatus (3.0 ± 0.9 vs. 3.6 ± 1.2 days; *P*=0.001) and stool (4.1 ± 1.1 vs. 4.8 ± 1.4 days; *P*=0.001) when compared to a traditional protocol of postoperative nutrition, respectively (45). In another trial by Feo and colleagues, early feeding led to a significant reduction in the need for nasogastric decompression (6% vs. 20%; *P*<0.05) (46). In two trials exploring early feeding compared to a traditional feeding protocol, early oral intake was associated with a significantly reduced average length of hospital stay (4.0 ± 3.7 vs. 7.6 ± 8.1 days, *P*<0.001; and 8.4 ± 3.4 vs. 9.6 ± 5.0 days, *P*=0.016, respectively) as well as a faster return of intestinal function across multiple clinical measures (45, 47). In contrast, several other trials reporting on the role of early feeding showed little improvement across multiple measures of intestinal function, including time to first passage of flatus and stool. These studies generally

concluded that early feeding is safe and that there is no clinical benefit to routinely withholding nutrition for prolonged periods of time during recovery (48-51). In light of this, enhanced recovery guidelines now provide a strong recommendation that most patients should be offered food immediately from the day of surgery (4).

1.4.4. Thoracic epidural analgesia

Epidural analgesia is commonly used within programmes of multi-modal and opioid-sparing analgesia. It has also been explored for its potential role to improve postoperative intestinal motility and to reduce ileus. Several mechanisms for this have been cited, including the opioid-sparing effects of local anaesthetic agents, as well as their role in sympathetic blockade, proposed to suppress the systemic immune response and reduce inhibition of intestinal smooth muscle (52). A large number of RCTs have evaluated the role of epidural analgesia for reducing ileus after colorectal surgery. Across three trials comparing a plain local anaesthetic regimen (such as Bupivacaine) to systemic opioids, epidural analgesia was shown to be superior for pain relief but showed no difference across measures of intestinal function (53-55). In a further four trials which compared a mixed local anaesthetic-opioid regimen (such as Bupivacaine and Fentanyl), epidural analgesia was shown to be superior when compared to patients receiving systemic opioids alone. The average time to return of flatus occurred 24-41 hours quicker, whilst the average time to first defaecation occurred 30-36 hours quicker in the epidural groups (56-59). In contrast, only one trial reported a significant improvement in the time taken to fulfil discharge criteria, raising concerns that any potential gains in intestinal motility may be lost due to delays in postoperative mobility and ambulation (26, 60). Of note, whilst enhanced recovery guidelines make strong recommendations for thoracic

epidural analgesia after open colorectal surgery, it is acknowledged that several other choices may be more appropriate for patients undergoing laparoscopy (4).

1.4.5. Systemic lidocaine

Local anaesthetic agents are used most commonly for epidural analgesia but some studies have explored the role of intravenous preparations to reduce ileus. It has been suggested that this may improve intestinal motility by attenuating the systemic inflammatory response after surgery, leading to reduced inhibition of intestinal smooth muscle (26). Across five studies which compared intravenous lidocaine with a saline placebo, the average time to first flatus was 8-19 hours quicker and the average time to first defaecation was 16-28 hours quicker in the lidocaine groups (61-65). In keeping with the proposed mechanism, one study by Herroeder and colleagues demonstrated reduced levels of plasma pro-inflammatory cytokines (interleukin (IL)-6 and IL-8) in patients who received lidocaine as well as a shortened duration of hospital stay of one day (65). A key consideration with intravenous lidocaine is its safety in the perioperative period. Previous studies have evaluated regimens of between 1-3mg/kg per hour with the occurrence of few adverse events (26). However, in 2020 a small handful of serious adverse events (including the death of a patient in the UK) led to a consensus statement on the safe use of intravenous lidocaine by the Association of Anaesthetists. It was agreed that a maximum infusion rate of 1.5mg/kg per hour should be observed along with mandatory cardiovascular monitoring in theatre or a high dependently unit (66). Whilst intravenous lidocaine is typically used for postoperative pain management, the results of a large, definitive multicentre trial for the purpose of reducing ileus is presently awaited (67).

1.4.6. Peripheral μ antagonists

Peripheral μ antagonists block the activation of μ-opioid receptors in the intestinal tract. Since they are selective to these receptors alone, they inhibit the peripheral effects of opioids, helping to reduce opioid-induced ileus without impacting on their central analgesic effects. A common μ antagonist used for this purpose is Alvimopan. This is approved by the US Food and Drug Administration (FDA) for the treatment of ileus but to date is not yet available outside of the US (26). It is administered once before surgery and then twice daily thereafter in the postoperative period. Over the last 20 years, several large RCTs have evaluated the role of Alvimopan for reducing ileus after colorectal surgery. In one trial by Ludwig and colleagues, Alvimopan accelerated the average time to intestinal recovery by 20 hours (Hazard Ratio (HR): 1.5, 95% CI 1.29 to 1.82, *P*=0.001) when measured using a composite endpoint of time to first defaecation and oral tolerance (GI-2) (68). In another trial by Delaney and colleagues using the same endpoint, Alvimopan reduced the average time to intestinal recovery by 15 hours (HR 1.46, 95% CI 1.11 to 1.93; *P*=0.007) (69). In both studies, Alvimopan also reduced the average time to hospital discharge by 14-17 hours. Whilst the efficacy of Alvimopan seems positive, its cost-effectiveness requires further investigation, with previous reports describing a cost of up to $1000 per patient (26).

1.4.7. Prokinetic agents

A wide variety of prokinetic agents have been evaluated to explore their role in reducing ileus. Some have included erythromycin and ghrelin receptor agonists, such as ulimorelin. Despite initial optimism in these drugs, a series of large RCTs showed no improvement across various measures of intestinal recovery (70, 71). Several other serotonin 5-hydroxytryptamine 4 ($5HT_4$) agonists have also been evaluated.

Despite promising early clinical results, the drug cisapride was discontinued from international markets owing to its association with cardiac adverse events such as long QT syndrome and ventricular arrythmias (26). Instead, more recent studies have explored the drug prucalopride, usually licensed for the treatment of chronic constipation. The drug showed excellent promise in pre-clinical studies, where it was shown to significantly reduce ileus in mice via a cholinergic anti-inflammatory pathway leading to reduced intestinal inflammation and preserved motility (72). In contrast, a recent large RCT in humans showed no significant difference in the time taken for intestinal recovery (3.5 [IQR 2-5] vs. 4 (IQR 3-5] days, $P = 0.124$) between patients receiving prucalopride and placebo after surgery (73). The Japanese herbal agent daikenchuto has also been evaluated, however a Cochrane review published in 2018 (later retracted) comprising of seven RCTs (1202 participants) was unable to conclude definitively on its clinical benefit due to the small number of participants available for meta-analysis (74, 75). The seven included studies reported mixed outcomes, with five reporting shorter periods of intestinal recovery (such as shorter time to first defaecation) in the daikenchuto groups (76-82).

1.4.8. Non-steroidal anti-inflammatory drugs

The use of non-steroidal anti-inflammatory drugs (NSAIDs) after colorectal surgery is controversial. Whilst NSAIDs are used commonly as simple analgesic agents for a wide range of indications, concerns exist about their association with higher rates of anastomotic leak reported in previous observational literature (83). Nevertheless, several RCTs have explored the role of NSAIDs to reduce ileus, mainly focussing on the non-selective agent ketorolac. Across 3 trials of intravenous ketorolac, the time to first flatus (0.7-1 days) and time to first defaecation (0.2-0.6 days) were significantly shorter in the NSAID groups. These participants also required significantly less opioid

analgesia, with an overall reduction of 14.8-30mg across their total hospital stay (84-86). In another study evaluating the role of flurbiprofen, the time to first flatus (63 ± 16 vs. 75 ± 11 hours, *P*=0.01) and first defaecation (87 ± 23 vs. 105 ± 19 hours, *P*=0.008) were significantly shorter in the NSAID group, which was also associated with lower plasma concentrations of IL-6 and IL-8 (87). In a trial by Wattchow, a low dose of the cyclooxygenase (COX)-2-specific agent celecoxib, but not diclofenac, was shown to reduce ileus (1% vs. 10% vs. 13%) compared to placebo, respectively (88). Irrespective of these data, a recent large cohort study performed across 332 hospitals showed that only 28% of patients undergoing colorectal surgery actually receive NSAIDs in the postoperative period (1). This is despite enhanced recovery guidelines recommending against their omission from multi-modal analgesia regimens (4).

1.4.9. Coffee

The role of coffee for reducing postoperative ileus has been explored in several fields of surgery, including colorectal, caesarean, and gynae-oncology. The proposed mechanism by which coffee may improve postoperative intestinal dysfunction is still speculative, but hypotheses relating to the effects of caffeine, polyphenols, dietary fibre, and modulation of the gut microbiota have all been put forward (89). In a meta-analysis of 4 RCTs relevant to colorectal surgery (342 participants), coffee consumption was estimated to reduce the time to first defaecation by 14.8 hours (95% CI: -11.9 to -17.7; *P*<0.001) but led to no improvement in the total length of hospital stay (90). Enhanced recovery guidelines do not recommend the use of coffee for this purpose owing to the weak quality of current evidence (4).

1.4.10. Electroacupuncture

Electroacupuncture is a variant of the Traditional Chinese Medicine therapy acupuncture, involving an electrical current applied at prespecified acupoints using acupuncture needles. In recent years, it has gained interest in the West for how it may be used to reduce ileus after abdominal surgery. In a recent systematic review by Ye and colleagues, 18 RCTs involving 1413 participants were meta-analysed. The findings showed that electroacupuncture reduced the time to first flatus (standardised mean difference [SMD]: -1.14, 95% CI -1.54 to -0.73; $P<0.001$), time to first defaecation (SMD: -1.31, 95% CI -1.88 to -0.74; $P<0.001$), and length of hospital stay (mean difference: -1.68 days , 95% CI -2.55 to -0.80, $P<0.001$). Most of this evidence was low to moderate quality, requiring further validation in larger, multi-centre clinical trials (91). In 2022, Wang and colleagues demonstrated similar improvements in the time to first flatus and defaecation across a large population of 249 patients undergoing colorectal resection, suggesting that electroacupuncture could represent an adjunct to enhanced recovery programs after surgery (92).

1.4.11. Vagus nerve stimulation

Stimulation of the vagus nerve has emerged as a new candidate treatment for ileus. Its mechanism involves a vagally-mediated anti-inflammatory pathway, previously shown to reduce the incidence of septic shock in models of endotoxin-induced sepsis (93). In pre-clinical models of ileus, vagus nerve stimulation reduces intestinal inflammation and ameliorates postoperative intestinal dysmotility in mice (94, 95). This typically requires an invasive procedure, however, which is challenging for widespread clinical translation. A small number of clinical studies have explored the role of non-invasive techniques to stimulate the vagus nerve. These involve transcutaneous devices applied to the cymba

conchae of the ear (auricular branch of the vagus nerve) or the neck (cervical vagus nerve) and have been shown to be safe in small populations of patients undergoing major abdominal surgery (96-98). In one proof-of-concept study, Chapman and colleagues demonstrated the feasibility of self-administered stimulation over the cervical surface landmark (97). Owing to the flexibility of administration at home and in hospital, these devices may enable better clinical translation but first require a detailed assessment of feasibility prior to definitive evaluations of clinical benefit.

1.4.12. Other clinical interventions

In the last five years, early evaluations of a number of other candidate interventions to reduce ileus have been reported. Dudi-Venkata and colleagues evaluated the role of stimulant and osmotic laxatives, which led to a significantly reduced time to intestinal recovery (2 [IQR 1.5-4] vs 3 [IQR: 2-5.5] days, *P*=0.029) as well as a smaller incidence of ileus (22% vs. 38%, *P*=0.03) (99). In a small trial by the same group, the acetyl-cholinesterase inhibitor pyridostigmine was shown to be safe after colorectal surgery, justifying the conduct of larger efficacy trials to evaluate its role for reducing ileus (100). Some other studies have explored the role of abdominal massage after surgery and stomal stimulation for patients undergoing closure of temporary ileostomy. Both of these have demonstrated positive results in a small number of studies, but neither has collated sufficient evidence to be adopted widely in practice (101, 102).

1.5. Thesis aims and objectives

1.5.1. Thesis hypothesis

The hypothesis of this thesis is that a definitive, randomised assessment of patient-administered, non-invasive, vagus nerve stimulation to reduce ileus is feasible.

1.5.2. Thesis overall aim

The overall aim of this thesis is to determine the feasibility of a definitive randomised assessment of patient-administered, non-invasive vagus nerve stimulation to reduce ileus and to explore barriers which may preclude its feasibility.

1.5.3. Thesis objectives

The following specific objectives were pre-specified:

a) To explore the vagal mechanisms which modulate intestinal motility after surgery through a systematic scoping review of pre-clinical and clinical evidence
b) To explore and refine key methodological uncertainties relevant to a definitive trial of non-invasive, patient-administered vagus nerve stimulation in a randomised feasibility trial
c) To explore patients' and health professionals' acceptability of non-invasive, patient-administered vagus nerve stimulation and the proposed study methods, as well as any reasons for non-acceptability
d) To seek multi-stakeholder agreement on a set of core study outcomes for postoperative ileus in readiness for a definitive randomised assessment

Chapter 2 – Homeostasis and modulation of the vagus nerve to prevent postoperative ileus: systematic scoping review

Preface

In this chapter, a systematic scoping review of previous evidence relating to the vagus nerve and postoperative ileus is presented. The review first examines pre-clinical evidence describing the mechanistic basis of an innate vagal anti-inflammatory reflex which works to promote homeostasis of intestinal inflammation after surgery. Next, the review summarises all previous pre-clinical studies in which exogenous vagus nerve stimulation is explored to prevent ileus. Finally, the review examines the role of vagus nerve stimulation to reduce ileus in humans undergoing surgery. These insights set the context for work described later in the thesis.

2.1. Introduction

2.1.1. Fundamentals of neuromodulation

Neuromodulation is defined by the International Neuromodulation Society as a field of science, medicine, and bioengineering, encompassing implantable and non-implantable technologies that impact upon neural interfaces (103). The use of electricity to stimulate a peripheral nerve dates back several centuries. In 1860, Gaiffe (French scientist) constructed the first known transcutaneous electrical nerve stimulation device. Around the same time, Althaus (German-English physician) first described the use of direct electrical stimulation of a peripheral nerve in patients with conditions such as ureteric stones and lower limb aneurysms (104). Since then, neuromodulation of peripheral nerves has seen considerable advancements in technology, techniques, nerve targets, and clinical applications.

Neuromodulation extrinsically modulates the activation of peripheral nerves and is based on basic principles of action potential. In brief, action potential describes a rapid sequence of changes in voltage across a cell membrane. It comprises voltage-gated Na^+ channels which facilitate influx of sodium (Na^+) ions through the membrane of nerve cells leading to depolarisation. This is followed by repolarisation, facilitated by voltage-gated potassium (K^+) channels causing a reciprocal efflux of K^+ ions out of the cell. These events propagate along and between nerve cells through the release of neurotransmitters. Methods of electrical neuromodulation artificially modulate the activation of peripheral nerves. The application of electricity using a cathode creates a potential difference across the cell membrane such that the electrical potential outside becomes negative and inside becomes relatively positive. If the membrane potential is

sufficient, voltage-gated Na^+ channels are activated and the cascade of depolarisation and repolarisation is initiated, generating a propagating action potential (105).

The basic unit for electrical stimulation in neuromodulation is the pulse. This comprises the delivery of a specific current amplitude (measured in milliamperes) across a specific pulse width (measured in milliseconds) (106). These parameters are important since the product of amplitude and pulse width (charge per pulse, measured in nanocoulombs) determines whether nerve cells are activated. Typically, narrow pulse widths require higher amplitudes to activate nerve cells, whilst wide pulse widths require lower amplitudes. Frequency is another important parameter and is a measure of the number of pulses per second (measured in Hertz). The frequency of pulses contributes to how often a nerve cell initiates an action potential in response to a stimulus. Different types of nerve cells are capable of entraining (synchronising) to different frequencies, with higher frequencies initiating blocking mechanisms. Charge per pulse and frequency are considered together since they each play a role in whether target nerve cells depolarise to a stimulus (106).

The likelihood of depolarisation depends on several properties of the target nerve cells, including distance from the stimulus, cell myelination, and their size (107). The importance of distance is described by Coulomb's law, which indicates that charge is inversely proportional to the square of the distance from the stimulus. In other words, charge is reduced when the electrode is placed more distantly, leading to a lower likelihood of depolarisation. Myelination refers to the presence of a myelin membrane around nerve cells and is found in A and B type fibres. Myelinated nerves have a high concentration of Na^+ channels at the nodes of Ranvier, creating focal areas of Na^+ influx, as well as charge separation between nodes. These properties increase

the probability of depolarisation compared to unmyelinated C fibres. The size of cells also plays a role, with larger cells capable of depolarising before smaller cells. (107).

2.1.2 Vagus nerve anatomy and physiology

The vagus nerve is one of twelve paired cranial nerves which emerge from the brain and brainstem. Its origin is in the medulla oblongata, where it courses and exits the skull through the jugular foramen. The vagus nerve has an extensive network of branches, supplying organs and supporting functions throughout the body. It first passes through the neck within the carotid sheath, where it supplies muscles responsible for swallowing and vocalisation. These are facilitated by several key branches, including the pharyngeal, superior laryngeal, and recurrent laryngeal branches. In the thorax, the right and left vagus nerves form the posterior and anterior vagal trunk, respectively, innervating the oesophageal smooth muscle. Cardiac branches also emerge, providing the parasympathetic innervation to the heart as well as being responsible for regulating heart rate. The vagal trunks enter the abdomen via the oesophageal hiatus, an opening in the diaphragm through which the oesophagus enters the thoracic cavity. Here the two trunks divide further, providing key parasympathetic innervation to the oesophagus, stomach, small bowel, and colon. The extent of vagal innervation to the colon is speculative, although it is generally considered to terminate at the splenic flexure (108, 109).

The vagus nerve is a major component of the parasympathetic nervous system. Approximately 80% of its fibres are afferent (sensory) and the remaining 20% are efferent (motor). The afferent function of the vagus nerve is important for relaying visceral and somatic information to the central nervous system. Afferent fibres originate from distant organs, such as the gut, where they project to vagal centres in the brainstem such as the nucleus of the solitary tract (NTS). Efferent fibres are responsible

for the control of key functions, such as intestinal motility and secretion, as well as cardiac parasympathetic tone. Preganglionic vagal efferents originate from the dorsal motor nucleus of the vagus (DMV) in the brainstem, where they then project to distant organs to join postganglionic neurons. The relationship of afferent and efferent fibres underpins key vago-vagal reflexes, such as the anti-inflammatory reflex (109).

Vagus nerve fibres are organised into fascicles, with an average of 7 ± 3 fascicles (54 ± 7% myelination) in the cervical vagus nerve and 16 ± 6 fascicles (6 ± 2% myelination) in the abdominal vagus nerve (110). The fascicles comprise a mixture of myelinated A fibres (Aα, Aβ, Aγ, Aδ), myelinated B fibres, and unmyelinated C fibres. The types of fibre vary in diameter and conduction velocity, such that Aα fibres are the largest and fastest (diameter 12-20μm; velocity 80-120 ms^{-1}) and C fibres are the smallest and slowest (diameter 0.2–1.5μm; velocity 0.5–2 ms^{-1}) (111). As described previously, these properties determine the threshold for excitation in response to an electrical charge, with larger and more myelinated fibres (A>B>C) associated with lower thresholds. Typical reported thresholds for nerve excitation are 0.02-0.2mA for A-fibres, 0.04-0.6mA for B-fibres, and ≥2.0mA for C-fibres (112). These values are notable for the design of neuromodulation devices since the human cervical and abdominal vagus nerves are composed of 62.6% and 73.8% small diameter fibres, respectively (110).

2.1.3. The vagus nerve and inflammation

The vagus nerve and its role in modulating the innate immune response has gathered interest across numerous fields of clinical medicine. Tracey and colleagues first demonstrated its role in sepsis, where stimulation of the vagus nerve was shown to prevent the onset of septic shock through reduced expression of pro-inflammatory cytokines (93). Since these studies, numerous potential therapeutic applications of

vagus nerve stimulation have emerged. In psychiatry, vagus nerve stimulation has been used extensively in settings of depression, with some studies showing improvements in standardised outcome instruments (such as the Back Depression Inventory) within 2 weeks of initiating therapy (113). In migraine medicine, stimulation of the vagus nerve for 90 seconds at the point of symptom onset has been shown to reduce both the frequency and intensity of attacks (114). In gastrointestinal medicine, vagus nerve stimulation has been shown to have a possible role in the treatment of acute flares of inflammatory bowel disease, such as ulcerative colitis and Crohn's disease (108). Other candidate clinical applications include the treatment of rheumatoid arthritis, chronic pain conditions such as fibromyalgia, cardiovascular disease such as heart failure and hypertension, ventilator-induced lung injury, cerebrovascular disease, traumatic brain injury, and diabetes. New possible applications continue to emerge, which are mostly underpinned by local or systemic immune-inflammatory disease mechanisms (115).

2.1.4. Stimulation of the vagus nerve

Interest in vagus nerve stimulation and its possible role in medicine has existed since the nineteenth century. During this time, scientists began to make observations about the vagus nerve and its functions, leading to enthusiasm about its therapeutic potential. One such observation was its effect on the intestinal tract. In the 1970s, Abrahamsson and colleagues showed that stimulating the vagus nerve in cats (frequency: 4-20Hz; amplitude 5-8V; pulse width 0.5-2ms) elicited a gastric relaxation effect. This was considered to be via activation of gastric mechanoreceptors and contributed to the regulation of gastric filling (116). They later demonstrated a link between the vagus nerve and paralytic ileus in cats, showing that mechanical manipulation of the jejunum or colon led to gastric relaxation. They concluded that the inhibition of gastric motility was mediated by vagal fibres projecting to the stomach (117). Similarly, In the 1980s

Collman and colleagues showed that stimulating the vagus nerve of ferrets during surgery (frequency: 2-20Hz; amplitude 25V; pulse width 0.5ms) led to a marked increase in colonic motility. This was elicited through a vago-vagal reflex comprising of afferent and efferent limbs, as opposed to a direct pathway to the colon. They concluded that this was a component of the gastro-colic reflex, facilitating a post-prandial increase in colonic motility (118). These early experiments laid the foundation for future animal and human work on the autonomic control of intestinal function and the possible role of vagus nerve stimulation.

One of the most widely reported uses of vagus nerve stimulation in modern medicine is its use in refractory epilepsy. Early work by Zabara and colleagues in the 1980s showed that implantable vagus nerve stimulators in dogs abolished chemically induced seizure activity (119). The first human implantation was reported later in 1990 by Penry and Dean, followed by several RCTs demonstrating significantly reduced seizure activity in patients with epilepsy (120-121). This evidence paved the way for FDA approval of vagus nerve stimulation for epilepsy in 1997. Another use for vagus nerve stimulation is for the treatment of depression. This arose from anecdotal observations in patients with epilepsy, where vagus nerve stimulation was shown to have mood effects, leading to improved quality of life. This was investigated by Rush and colleagues, who reported key evidence supporting the use of long-term vagus nerve stimulation for patients with refractory depression. The FDA approved its use for depression in 2005 (122-123).

Technology for stimulating the vagus nerve usually necessitates the implantation of an invasive device. The device is implanted beneath the pectoral muscles and comprises an electrode placed around the vagus nerve and connected to a pulse generator. Typical stimulation parameters are shown in Table 2.1, which summarises a series of RCTs performed in the contexts of epilepsy and depression (124-131).

Table 2.1 – Previous randomised studies of vagus nerve stimulation for refractory epilepsy and drug resistant depression

Study	Indication	Frequency (Hz)	Current (mA)	Pulse Width (μs)	Adverse events
Holder (1992) (124)	Epilepsy (Adults)	High: 20-50 Low: 1-2	High: ≤3.0 Low: NS	High: 500 Low: 130	Hoarseness (High: 25.8%; Low: 8.7%) Vocal cord paralysis (High 5.0%; Low: 0.0%)
Ben-Menachem (1994) (125, 126)	Epilepsy (Adults)	High: 20-50 Low: 1-2	High: 0.25-3.0 Low: 0.25-3.0	High: 500 Low: 130	Fever (High: 9.7%; Low: 0.0%) Infection (High: 3.2%; Low: 5.6%) Hoarseness (High: 35.5%; Low: 13.9%) Coughing (High: 12.9%; Low: 8.3%) Depression (High: 6.5%%; Low: 5.6%) Headache (High: 3.2%; Low: 0.0%) Insomnia (High: 3.2%; Low: 5.6%) Lethargy (High: 6.5%; Low: 0.0%) Paraesthesia (High: 9.7%; Low: 8.3%) Tremors (High: 3.2%; Low: 0.0%) Abdominal pain (High: 9.7%; Low: 5.6%) Dysphagia (High: 3.2%; Low: 0.0%) Nausea (High: 6.5%; Low: 0.0%) Vomiting (High: 3.2%; Low: 0.0%) Throat pain (High: 12.9%; Low: 13.9%) Chest pain (High: 6.5%; Low: 5.6%) Tinnitus (High: 3.2%; Low: 2.8%) Tooth pain (High: 3.2%; Low: 0.0%) Ear pain (High: 3.2%; Low: 0.0%) Breathlessness (High: 6.5%; Low: 0.0%) Muscle pain (High: 9.7%; Low: 2.8%)
Vagus Nerve Stimulation Study Group (1995) (127)	Epilepsy (Adults)	High: 20-50 Low: 1-2	High: 0.25-3.0 Low: 0.25-2.75	High: 500 Low: 130	Unknown*
Amar (1998) (128)	Epilepsy (Adults)	High: 30 Low: 1	High: ≤3.5 Low: ≤3.5	High: 500 Low: 130	Unknown*
Handforth (1998) (129)	Epilepsy (Adults)	High: 30 Low: 1	High: ≤3.5 Low: NS	High: 500 Low: 130	Unknown*
Klinkenberg (2012) (130)	Epilepsy (Children)	High: 30 Low: 1	High: ≤2.25 Low: ≤2.25	High: 500 Low: 130	Voice alterations (n=8)** Coughing (n=3)**

					Throat pain (n=3)** Tingling sensation in throat (n=2)** Behavioural changes (n=3)** Infection (n=2)** Swelling at stimulator site (n=1)** Pain at stimulator site (n=1)** Itch (n=1)**
Rush (2005) (122)	Depression (Adults)	Active: 20 Sham: N/A	Active: 0.25-3.5 Sham: N/A	Active: 500 Sham: N/A	Voice alteration: (Active 68%; Sham 38%) Cough: (Active 29%; Sham 9%) Dyspnoea: (Active 23%; Sham 14%) Dysphagia: (Active 21%; Sham 11%) Neck pain: (Active 21%; Sham 10%) Paraesthesia: (Active 16%; Sham 10%) Vomiting: (Active 11%; Sham 5%) Laryngismus: (Active 1%; Sham 2%) Dyspepsia: (Active 10%; Sham 5%) Wound infection: (Active 8%; Sham 2%) Palpitations: (Active 5%; Sham 3%)
Aaronson (2013) (131)	Depression (Adults)	High: 20 Medium: 20 Low: 20	High: 1.25-1.5 Medium: 0.5-1.0 Low: 0.25	High: 250 Medium: 250 Low: 130	Voice alteration: (High 76%; Med 77%; Low 64%) Dyspnoea: (High 34%; Med 34%; Low 30%) Paraesthesia: (High 28%; Med 33%; Low 35%) Incision pain: (High 22%; Med 31%; Low 24%) Increased cough: (High 24%; Med 26%; Low 25%) Headache: (High 76%; Med 20%; Low 17%) Depression: (High 23%; Med 13%; Low 19%) Pharyngitis: (High 17%; Med 18%; Low 17%) Hypertonia: (High 20%; Med 16%; Low 15%) Dysphagia: (High 9%; Med 16%; Low 16%) Nasopharyngitis: (High 14%; Med 16%; Low 11%) Insomnia: (High 11%; Med 11%; Low 11%) Nausea: (High 14%; Med 14%; Low 8%) Device site reaction: (High 14%; Med 8%; Low 8%)

** Full text unavailable; **Data on number of adverse events per group not available*
NS: Not specified; High, Medium, and Low relate to different stimulation paradigms, with Low representing lesser or ineffective parameters

As the electrodes are in direct contact with the vagus nerve during invasive stimulation, smaller currents are required to deliver an effective charge compared to non-invasive devices applied at distant locations. Indeed, as charge is inversely proportional to the square of the distance, non-invasive devices require larger currents. This is not only impacted by the site of stimulation (i.e. the neck for cervical stimulation or the ear for auricular stimulation), but also the thickness of soft tissue and the fidelity of placement. The stimulation parameters must also be balanced with the risk of side effects. Whilst few serious adverse events are reported in previous RCTs, such as one episode of vocal cord paralysis (Holder), the most common events include voice changes, coughing, and stimulation site pain and paraesthesia. Only two trials reported on cardiovascular events, including Ben-Menachem (chest pain) and Rush (palpitations), with similar incidences between “High” and “Low” stimulation paradigms. Few adverse gastrointestinal events were reported, mainly comprising nausea and dyspepsia.

2.1.5. Aims and objectives

The aim of this scoping review was to describe the current evidence pertaining to the vagus nerve and its role in the development and/or prevention of postoperative ileus.

Three specific objectives were pre-specified:

1. To explore vagal mechanisms involved in the development and/or prevention of postoperative ileus after abdominal surgery
2. To explore pre-clinical evidence describing the role of vagus nerve stimulation to prevent ileus in experimental models of abdominal or pelvic surgery
3. To explore clinical evidence describing the efficacy of vagus nerve stimulation to prevent ileus in patients undergoing abdominal or pelvic surgery

2.2. Methods

2.2.1. Ethics and governance

A systematic scoping review was performed. Since scoping reviews are not eligible for registration on the PROSPERO database, the study was not prospectively registered prior to the collection of data. The public were not involved in the design or conduct of this review but the results informed wider discussions with patient representatives as part of the broader programme of work. The study described herein is reported with consideration to the PRISMA Extension for Scoping Reviews (132).

2.2.2. Summary of methods

A scoping review is a type of knowledge synthesis which follows a systematic approach to identify concepts, theories, and knowledge gaps on a pre-specified topic (132). As described by Arksey and O'Malley, scoping reviews comprise a five-stage framework (133). In the first two stages, a pre-specified research question is developed followed by a comprehensive search of electronic databases, reference lists, and other relevant sources. In the third stage, a series of eligibility criteria are applied with the possibility that these may change as familiarity with the literature develops. Next, a process of sifting, charting, and sorting of data is undertaken according to key themes that are developed in light of emerging data. The final stage involves a summary of the results to describe the breadth of available literature.

2.2.3. Eligibility criteria

Two groups of eligible articles were pre-specified during this review. The first group was any pre-clinical study describing vagal mechanisms involved in the development of ileus. To be included, experimental models had to be devised specifically to explore

intestinal function after intra-abdominal surgery. The second group was any pre-clinical or clinical study of vagus nerve stimulation to prevent or reduce ileus. To be included, study subjects (animal models or human participants, respectively) had to undergo intra-abdominal surgery alongside a targeted intervention to stimulate the vagus nerve. Some studies were identified in which it was hypothesised but not demonstrated that the intervention stimulated the vagus nerve. In light of this, the eligibility criteria were adapted to exclude studies in which a vagally-mediated mechanism was not confirmed. No exclusions were made based on language. Published conference abstracts were accepted to increase the capture of data from broad formats. Previous reviews and editorials were excluded but reference lists were considered from eligible articles.

2.2.4. Search strategy

A concept table of key terms relevant to the topic area was created and used to develop a search strategy (Table 2.2). The concept table is shown in Appendix A-2.2. Using this strategy, searches of MEDLINE 1947-2022 (via OVID) and EMBASE 1946-2022 (via OVID) were performed for manuscripts published between 1st January 2000 and 1st January 2022 (final search 12th January 2022). These dates were selected to capture contemporaneous data that were most likely to be of scientific and clinical relevance to current practice. During the search, titles, abstracts, and manuscripts were inspected for eligibility by two independent investigators (SC and MK). For eligible conference abstracts, additional searches for publications were performed using key words agreed by both investigators. In instances where full-text publications were identified, these were accepted preferentially. Disagreements between investigators were addressed through discussion until consensus was achieved. Both investigators had a background of formal postgraduate research training. Reference lists of accepted manuscripts

Table 2.2 – Scoping review search strategy (MEDLINE and EMBASE)

ID	Search term	Search results (n=)
1	Ileus	45911
2	Function	6339466
3	Motilit$	312778
4	Dysmotilit$	11686
5	Transit$	1236426
6	Exp Gastrointestinal Motility/	75397
7	Exp Gastrointestinal Transit/	14923
8	Exp Gastric Emptying/	32206
9	Exp Peristalsis/	53894
10	Exp Intestinal Obstruction/	142904
11	Exp Gastrointestinal Diseases/	1117407
12	Exp ileus/	23155
13	Surgery	7017890
14	Procedure	2378912
15	Operation	1036238
16	Postoperative	2048538
17	Perioperative	298674
18	Preoperative	828726
19	Exp General Surgery/	59649
20	Intestin$	1430177
21	Bowel	462885
22	Colon$	1583556
23	Gastrointestinal	1089628
24	Ileum	136094
25	Ileal	77151
26	Jejunum	101223
27	Jejunal	53820
28	Duodenum	198366
29	Duodenal	175854
30	Gastric	725848
31	Stomach	833651
32	Rectum	264147
33	Rectal	295936
34	Exp Colon/	175030
35	Exp Intestines/	994318
36	Exp Ileum/	93486
37	Exp Jejunum/	68483
38	Exp Duodenum/	99793
39	Exp Stomach/	356356
40	Exp Rectum/	93082
41	Exp Gastrointestinal Tract/	750426
42	Exp Lower Gastrointestinal Tract/	201243
43	Exp Upper Gastrointestinal Tract/	212635
44	Vagus	80237
45	Vagal	58456
46	Exp Vagus Nerve/	55752
47	Exp Vagus Nerve Stimulation/	14533
48	1 OR 2-12	8779217
49	13 OR 14-19	9524826
50	20 OR 21-43	4875375
51	44 OR 45-47	109514
52	48 AND 49-51	2491
53	Limit 2000-Current	1653
54	De-duplicate	1339

were reviewed and authors of primary manuscripts were contacted if further clarity was required on any aspect of their methods or findings.

2.2.5. Data charting

A single investigator (SC) charted all data from eligible manuscripts using a semi-structured charting proforma designed and refined for the purpose of this study (Appendix A-2.1). Narrative summaries were produced for each eligible study. These were then reviewed for agreement by an independent investigator (MK). Discrepancies in charting were addressed through further review and discussion between investigators, followed by modification of the summaries as appropriate.

2.2.6. Data items

Across all studies, a standardised series of data points were collected by a single investigator (SC). Where data were not available, efforts to contact the respective study authors were made or otherwise descriptions of the missing data were reported alongside the results. For mechanistic studies, data were collected on the pre-clinical model used for postoperative ileus, including the type of animal species where applicable, as well as details of key experiments and parameters. For pre-clinical studies exploring vagus nerve stimulation, data were collected about the pre-clinical model of ileus as well as details of vagus nerve stimulation, including relevant electrophysiological parameters. Finally, for clinical studies exploring vagus nerve stimulation in humans, data were collected on the study population (including type of surgery and indication), the methodological design, measured outcomes pertaining to intestinal function and postoperative recovery, and details of vagus nerve stimulation along with relevant electrophysiological parameters.

2.2.7. Synthesis of results

Descriptive data were expressed using simple statistics, including proportions, averages, and rates. Cohen's kappa was used to determine agreement between independent investigators prior to discussion and consensus, (values ≤ 0 indicating no agreement; 0.01–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41– 0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement). No quantitative syntheses of outcomes or assessments of study quality were planned or undertaken. A narrative synthesis of data charted from eligible manuscripts is reported.

2.3. Results

2.3.1. Summary of results

Using the pre-defined search strategy, a total of 1339 items were considered for inclusion and 31 were confirmed to be eligible (Figure 2.1). Reasons for exclusion were ineligible article types, studies unrelated to surgery, and studies unrelated to intestinal function. Some 31 articles were excluded since they did not provide justification or evidence to support the role of a vagal mechanism. These commonly comprised interventions related to chewing gum/sham eating or electro-acupuncture. A total of four articles were added from the reference lists of excluded items. Three eligible conference abstracts were identified of which two were subsequently identified as being published.

The search was performed by two independent investigators. Across 1339 items, there were 1306 agreements and 35 disagreements (10 disagreements on included items and 25 disagreements on excluded items; Cohen's k: 0.58 indicating moderate

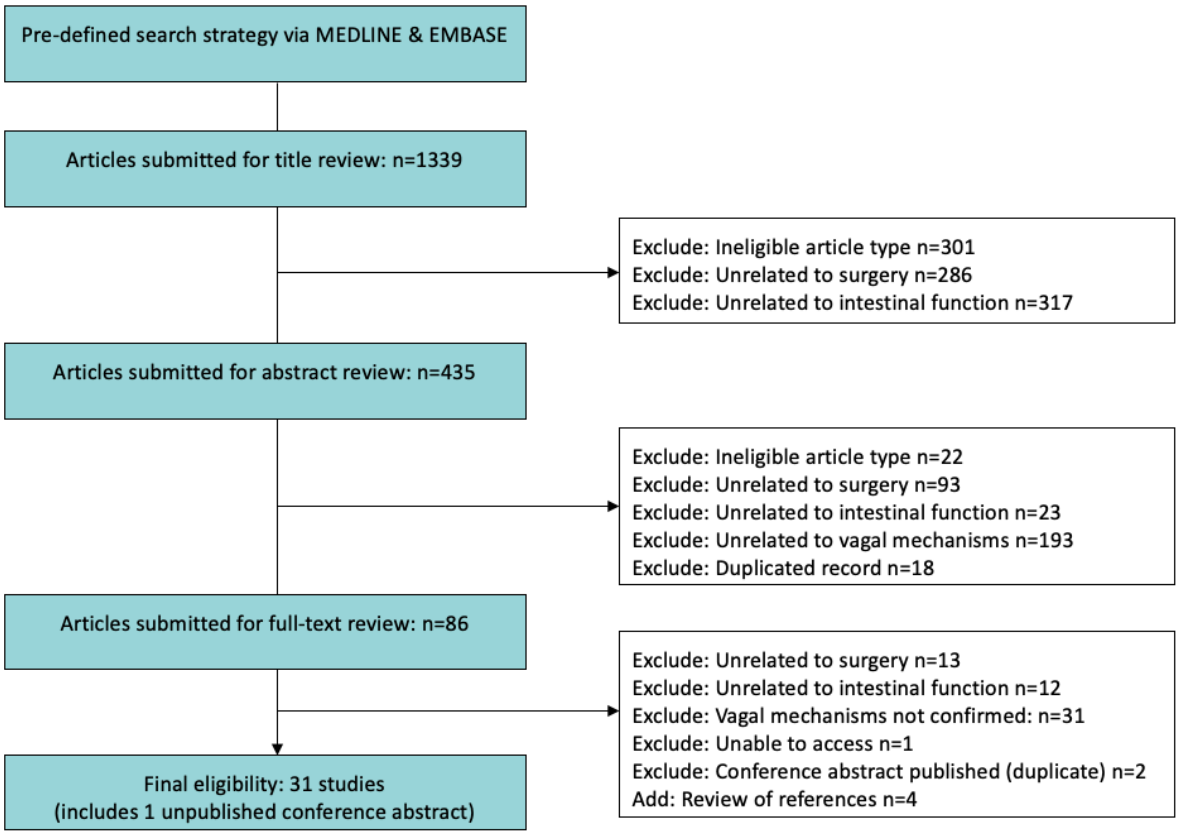
agreement). Following discussion and further appraisal, consensus was achieved between both investigators on the final number of included articles (n=31).

2.3.2. Vagal anatomy and functions in relation to postoperative ileus

2.3.2.1. Summary of studies

A total of 14 studies were identified aiming to describe vagal mechanisms involved in the development of postoperative ileus. Experimental models included mouse (n=9) and rat (n=5) species. The induction of experimental ileus was performed by manually manipulating the small bowel or caecum, usually using two moist cotton applicators. Control procedures usually involved a sham laparotomy procedure performed with no manipulation of bowel (n=10). A full summary of all studies is provided in Table 2.3.

Figure 2.1 – PRISMA flow-chart of inclusion and exclusion of articles



2.3.2.2. Anatomical considerations of the vagus nerve and postoperative ileus

Cytokine production is essential for normal tissue healing but excessive release can lead to uncontrolled inflammation, organ failure, and death (134). In 2002, Tracey and colleagues introduced the concept of an anti-inflammatory vagal reflex capable of attenuating the systemic immune response. In pre-clinical models of sepsis, they showed that stimulating the vagus nerve prevented endotoxin-induced septic shock through reduced expression of pro-inflammatory cytokines from the spleen. This was mediated by nicotinic receptors located on splenic macrophages in response to increased acetylcholine released from vagal efferent nerve endings (93). Whilst this was shown to be true when exogenous vagal stimulation was applied, curiosity developed around a possible endogenous vago-vagal inflammatory reflex. In this concept, it was proposed that the autonomic nervous system detects inflammation and modulates an appropriate immune response aimed at maintaining normal homeostasis (134). This is applicable not only to systemic disease, but also to local immune processes including those characterised by intestinal inflammation such as ileus.

To demonstrate evidence for a vago-vagal inflammatory reflex in the intestinal tract, Cailotto and colleagues set out to further delineate the vagal anatomy (135). First, cholera toxin-b (CTB) was used as a retrograde neuronal tracer to label the innervation of the small intestine and spleen in mice. This was done via injections of tracer into the target organs 15 days before surgery. The labelling identified positive regions in the DMV (origin of vagal efferents in the brainstem), demonstrating the existence of direct vagal efferent connections. Mice then underwent a laparotomy either with or without a standard process of intestinal handling to induce ileus. Handling led to significantly greater activation of the NTS where vagal afferents terminate in the brainstem, as well

as further activating the DMV. It was shown that 42% of activated neurones in the DMV were co-labelled by CTB and that these projected to the inflamed intestinal tissue, supporting the existence of an endogenous vagal anti-inflammatory reflex. Of note, selectively denervating the vagal innervation of the inflamed intestine abolished activation of both the NTS and DMV, confirming the importance of vagal afferent fibres in initiating the vago-vagal response. In summary, it was shown that vagal afferents trigger activation of the NTS in response to inflammation, subsequently activating the DMV, and closing the efferent vagal loop targeting the inflamed tissue (Figure 2.2).

In a later study by the same authors, the interactions between vagal efferents and immune cells such as intestinal macrophages were further interrogated. To do this, Cailotto and colleagues used biotin-/Texas red-dextran amines as anterograde tracers to identify vagal efferent fibres arising from the DMV and to delineate their final course (136). Mice injected with these tracers directly into the DMV showed a distribution of positively labelled pre-ganglionic vagal efferents within the myenteric plexus of the gut. These were located exclusively between circular and longitudinal muscle layers and were completely devoid from the spleen. Further experiments confirmed these to be cholinergic since they were predominantly positive for choline acetyltransferase (ChAT). Immunohistochemistry and immunofluorescence techniques then identified a network of intestinal macrophages in close proximity to the myenteric ganglia, but these were not in direct contact with dextran amine-labelled vagal efferents. It was determined that the vago-vagal reflex is indirect and mediated through interactions between vagal efferent and enteric neurones. Specifically, this involves ChAT positive myenteric neurons, whose nerve endings are in close proximity to intestinal macrophages. Unlike in models of sepsis, there was no modulation by the spleen, indicating that the intestinal vago-vagal inflammatory reflex is mediated primarily by the enteric nervous system.

Table 2.3 – Summary of pre-clinical studies describing vagal mechanisms involved in the development of ileus (n=14)

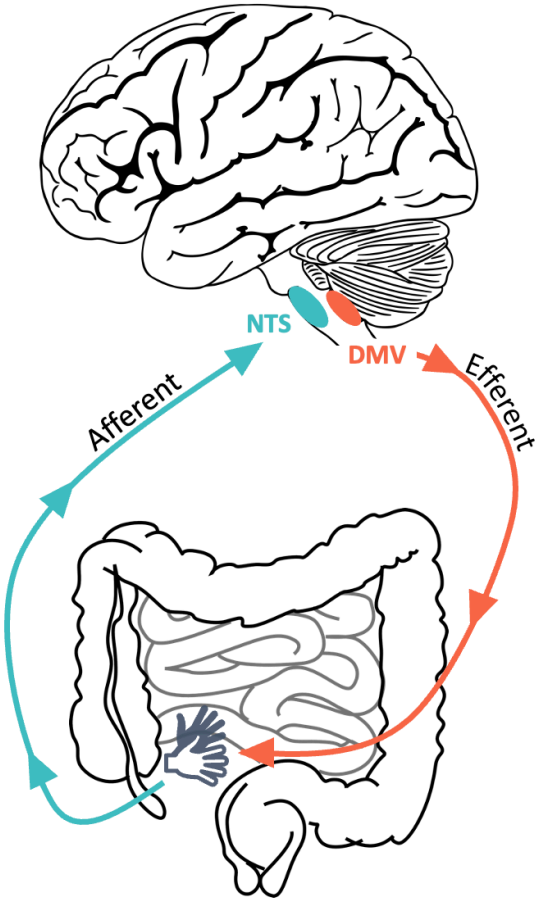
Study	Animal(s)	POI Model	Conditions/Sub-Groups	Key Experiments
Brandlhuber (2022)[145] (Manuscript; English)	C57BL6 mice (male)	Test: Laparotomy with standardised manipulation of small bowel for 15 mins* Control: Sham laparotomy without small bowel manipulation	– Sub-diaphragmatic vagotomy with: surgery or sham surgery – Sham sub-diaphragmatic vagotomy with: surgery or sham surgeryΨ	– Jejunal inflammatory cell infiltration 3h and 9h postop – Brainstem activation (Fos IC) 3h and 9h postop
Costes (2014)[146] (Manuscript; English)	Balb/c mice (female)	Test: Laparotomy with standardised manipulation of small bowel* Control: Sham laparotomy without small bowel manipulation	– Vagal denervation of intestine (celiac branch) with: surgery or sham surgery – Splenic denervation with: surgery or sham surgery – Sham denervation with: surgery or sham surgeryΨ	– Gastrointestinal transit (FD70 tracer) 24h post-op – Ileal inflammatory cell infiltration 24h postop – Ileal and jejunal cytokine expression postop 24h postop
Goetz (2014)[147] (Manuscript; English)	Sprague-Dawley rats (male)	Test: Laparotomy with standardised manipulation of small bowel for 5 mins* Control: Sham laparotomy without small bowel manipulation; and Naïve control with no surgery.	– Surgery with sacrifice at: 12h or 3d post-op. No further sub-groups – Sham surgery with sacrifice at: 12h or 3d post-op. No further sub-groups	– Gastrointestinal transit (semi-solid charcoal solution) 12h and 3d postop – Jejunal inflammatory cell infiltration 12h and 3d postop – Brainstem activation (Fos IC) 12h and 3d postop – Jejunal muscle contractility studies 12h and 3d postop
Cailotto (2014)[136] (Manuscript; English)	Balb/c mice (female)	Not applicable	– Injection of neuronal tracer to DMV (biotin-dextran) – Injection of neuronal tracer to DMV (Texas-red dextran)	– Labelling of vagal pre-ganglionic fibres projecting to small intestine and spleen – Identification of neurochemical phenotype of vagal fibres and enteric neurons (immunofluorescent labelling)
Cailotto (2012)[135] (Manuscript; English)	Balb/c mice (female)	Test: Laparotomy with standardised manipulation of small bowel for 5 mins* Control: Sham laparotomy without small bowel manipulation; and Naïve control with no surgery	– Vagal denervation of intestine (celiac branch) with: surgery or sham surgery – Sham denervation with: surgery or sham surgeryΨ	– Small bowel inflammatory cell infiltration 2h, 6h and 24h postop – Neuronal circuitry of brain stem (Fos IC) 2h, 6h, and 24h postop – Neuronal circuitry of small bowel (Fos IC) 2h, 6h, and 24h postop – Neuronal circuitry of spleen (Fos IC) 24h postop

Mueller (2011)[144] (Manuscript; English)	C57BL6 mice (male)	Test: Laparotomy with standardised manipulation of small bowel for 15 mins* Control: Sham laparotomy without small bowel manipulation	– Sub-diaphragmatic vagotomy with: surgery or sham surgery – Sham sub-diaphragmatic vagotomy with: surgery or sham surgeryΨ	– Jejunal inflammatory cell infiltration at 3h and 9h postop – Intestinal motility (intra-luminal pressure recordings in-vitro) at 3h and 9h postop – Mesenteric afferent nerve recordings (in-vitro) at 3h and 9h postop
Glowka (2011)[148] (Abstract; English)	Murine (no further details)	Test: Surgery with standardised intestinal manipulation (no further details) Control: Sham surgery without intestinal manipulation (no further details)	– Sub-diaphragmatic vagotomy with: surgery or sham surgery – Sham sub-diaphragmatic vagotomy with: surgery or sham surgeryΨ	– Gastrointestinal and colonic transit (no further details) – Intestinal cytokine expression 1h and 3h postop – Intestinal inflammatory cell infiltration 24h postop
Gao (2010)[143] (Manuscript; English)	C57BL6 mice (female)	Test: Laparotomy with standardised manipulation of small bowel for 15 mins* Control: Sham laparotomy without small bowel manipulation	– Sub-diaphragmatic vagotomy with: surgery or sham surgery – Sham sub-diaphragmatic vagotomy with: surgery or sham surgeryΨ	– Intestinal motility (intra-luminal pressure recordings in-vitro) 3h postop – Mesenteric afferent nerve recordings (in-vitro) 3h postop
Mueller (2008)[142] (Manuscript; English)	C57BL6 mice (female)	Test: Laparotomy with standardised manipulation of small bowel for 15 mins* Control: Sham laparotomy without small bowel manipulation	– Surgery with sacrifice at 24h post-op. No further sub-groups – Sham surgery with sacrifice at 24h post-op. No further sub-groups	– Jejunal inflammatory cell infiltration 24h postop – Brain stem activation (Fos IC) 24h postop – Intestinal motility (intra-luminal pressure recordings in-vitro) 24h post-op – Mesenteric afferent nerve recordings (in-vitro) 24h post-op
Mueller (2006)[141] (Manuscript; English)	C57BL6 mice (female)	Test: Laparotomy with standardised manipulation of small bowel for 15 mins* Control: Sham laparotomy without small bowel manipulation	– Injection of capsaicin (1 µm/kg ip) 48h prior to: surgery or sham surgery – No administration of capsaicin prior to: surgery or sham surgery	– Jejunal inflammatory cell infiltration 24h postop – Brain stem activation (Fos IC) 24h postop – Intestinal motility (intra-luminal pressure recordings in-vitro) 24h postop
Boeckxstaens (1999)[138] (Manuscript; English)	Sprague-Dawley rats (male)	Test: Laparotomy with standardised manipulation of small bowel for 5 mins (no further details), followed by excision of caecum without interruption of gut continuity.	– Bilateral cervical vagotomy with surgery – Coeliac/superior mesenteric ganglionectomy with surgery – Infusion of saline to jugular vein with surgery	– Fundic pressure at point of skin incision, laparotomy and manipulation, and resection – Fundic relaxation in response to muscarinic, nicotinic and adrenergic receptor blockage – Fundic relaxation in response to vagotomy, ganglionectomy, or both

Zittell (1998)[110] (Manuscript; English)	Sprague-Dawley rats (male)	Test: Laparotomy with standardised manipulation of small bowel for 5 mins via manual handling	– Local application of capsaicin or vehicle to bilateral cervical vagus nerves	– Colonic transit (carbamine red solution) and stool pellet number/weight
Zittell (1993)[107] (Manuscript; English)	Sprague-Dawley rats (male)	Test: Laparotomy with manipulation of the caecum for 1 min via manual handling Control: Sham laparotomy without manipulation of the caecum; and Naïve control with no surgery	– Surgery with sacrifice after max 8h. No further sub-groups. – Sham surgery with sacrifice after max 8h. No further sub-groups.	– Brain stem activation (Fos IC) 15min, 30min, 1h, 2h, 4h, and 8h postop
Plourde (1993)[109] (Manuscript; English)	Sprague-Dawley rats (male)	Test: Laparotomy with manipulation of the caecum for 1 min via manual handling Control: Anaesthesia only without laparotomy	– Local application of capsaicin or vehicle to bilateral cervical vagus nerves	– Gastric emptying (methylcellulose in distilled water and phenol red solution)

DMV: dorsal motor nucleus of the vagus; FD70: 70 kDa fluorescein isothiocyanate-labelled dextran; Fos: Fos protein; IC: immunochemistry; IP intraperitoneal; Post-op: postoperative
**Manipulation of small bowel performed using two moist cotton applicators; Ψ Sham vagotomy procedure performed with either 1) nerve not dissected or 2) nerve dissected but not cut*

Figure 2.2 – Afferent and efferent components of the vagal 'anti-inflammatory reflex'



DMV: Dorsal motor nucleus of the vagus nerve; NTS: nucleus of the solitary tract

2.3.2.3. Functional considerations of the vagus nerve and postoperative ileus

Whilst anatomical studies confirm the presence of afferent and efferent vagal inputs to the gut, it is important to elucidate their specific role in postoperative ileus. In the 1990s, non-adrenergic noncholinergic (NANC) inhibitory nerves known to provide inhibitory innervation to the gut were considered to be vagally-driven. Zittell and colleagues showed that manipulation of the rat caecum versus laparotomy alone led to significant increases in c-fos gene expression in areas of the brainstem known to receive vagal afferents from the gut, such as the NTS (71 vs. 31 cells per section; $P<0.01$). The

finding of c-fos in these areas, widely used as a marker of brainstem activation by vagal afferents, supported a possible role for a vagal sensory pathway in facilitating the inhibitory effects of surgery (137). This inhibitory role was further supported by Boeckxstaens and colleagues, who provided evidence that gastric relaxation after surgery was mediated by both adrenergic and vagal pathways. They showed that manipulation of the rat caecum activated a vagally-mediated NANC pathway, leading to gastric relaxation which could only be fully abolished when the vagal nerve supply was eliminated via vagotomy. As such, both adrenergic and vagally-driven NANC pathways were considered to be important in the development of gastric ileus after surgery (138). In contrast, Plourde and colleagues explored the effect of selectively ablating afferent neurones in rats to explore whether vagal, spinal, or both types of fibres were involved in the onset of ileus. They did this by pre-treating afferent nerves with capsaicin, a neurotoxin known to functionally ablate unmyelinated (c-fiber) sensory neurons. The results showed that pre-treatment of coeliac/superior mesenteric ganglia significantly diminished the gastric ileus induced by surgery, whereas application to the cervical vagus nerves had no effect (139). These findings were reproduced by Zittell and colleagues, who showed that selective ablation of vagal afferents had no impact on colonic ileus (140). It was later shown by Mueller that vagal afferents do not contribute to the inhibitory effects of surgery after all, but instead may have a protective role by suppressing intestinal inflammation. They showed that surgery led to increased expression of c-fos in the NTS of mice as well as increased myeloperoxidase (MPO) staining of the muscularis (specific for leukocytes). Whilst pre-treatment of vagal afferents with capsaicin led to a decrease in c-fos (8 ± 3 vs. 30 ± 9 at 7.70 mm and 16 ± 8 vs. 107 ± 26 positive neurons at 7.32 mm below bregma; $P<0.05$) it also led to a rapid increase in MPO positive cells (39 ± 9 vs. 72 ± 28 cells/mm^2; $P<0.05$). These findings

supported the revised concept of a vagally-mediated anti-inflammatory pathway, capable of suppressing intestinal inflammation provided that it was intact (141).

Noting that both spinal and vagal afferent fibres seemed to be implicated in some capacity during ileus, further studies set out to explore their differential roles. Using electrophysiology recordings in mice, Mueller and colleagues confirmed that both spinal and vagal pathways are sensitised as a result of the intestinal inflammatory response. Sensitivity to bradykinin, which stimulates only spinal afferents, was augmented compared to control mice (afferent discharge 65 ± 5 vs. 37 ± 6 impulses/sec; $P<0.05$). As well, the expression of c-fos in the NTS increased independently (110 ± 45 vs. 7 ± 4 at 7.32 mm below bregma; $P<0.05$), providing evidence of concurrent sensitisation of vagal afferents (142). Gao and colleagues then explored the temporal relationship between ileus and sensitisation of afferent nerves. At three hours after surgery, the development of ileus and its impact on recordings of intestinal motor events were unchanged following vagotomy, suggesting that vagal innervation is irrelevant at this early time point (143). Instead, it was not until 9 hours that vagotomy led to significant increases in intestinal inflammation, as shown by similar experiments in mice by Mueller and Brandlhuber. In these studies, MPO positive cells in the muscularis increased rapidly in the absence of vagal input (713.2 ± 99.4 vs. 46.9 ± 5.8 cells/mm^2, and 713 ± 99 vs. 47 ± 6; both $P<0.05$) (144, 145). In summary, the data show that afferent vagal activation by intestinal inflammation suppresses the local immune response via an endogenous vago-vagal reflex which is apparent 9 hours after surgery (146-148).

2.3.3. Pre-clinical studies of vagus nerve stimulation to prevent or reduce ileus

2.3.3.1. Summary of studies

A total of 14 pre-clinical studies were identified which explored the effect of vagus nerve stimulation on the prevention of ileus. Experimental models included mouse (n=9) and rat (n=5) species. The induction of experimental ileus was most commonly performed by manipulation of the small bowel using two moist cotton applicators via a laparotomy. Vagus nerve stimulation was performed electrically in 10 studies (of which most were performed using invasive apparatus) and pharmacologically in 4 studies. A full summary of all studies is provided in Table 2.4.

2.3.3.2. Electrical stimulation of the vagus nerve in pre-clinical studies

Drawing on the endogenous actions of the vagus nerve, further studies explored whether exogenous stimulation could be used as a targeted therapeutic for ileus. In 2014, Matteoli and colleagues provided further evidence of a vagal anti-inflammatory pathway mediated by intestinal muscularis macrophages (95). Indeed, stimulating the vagus nerve improved gastrointestinal transit (geometric centre: 8.7 vs. 6; $P<0.01$) and reduced the influx of MPO positive cells (66. vs. 195 cells/0.5mm^2; $P<0.01$) in the muscularis. This process required expression of the nicotinic α7 acetylcholine receptor (α7nAChR) on intestinal macrophages, since stimulation was found to be ineffective in α7nAChR knockout mice. Previous evidence by de Jonge and colleagues corroborated that acetylcholine released by vagal efferents inhibits intestinal macrophages and showed that this is dependent on a Jak2-STAT3 signalling pathway (94). Here, binding of acetylcholine to the α7 subunit recruited Jak2 to the nAChR, initiating the anti-inflammatory STAT3 signalling cascade and supressing the release of pro-inflammatory cytokines. Recent evidence also identified an additional receptor (α4β2nAChR) which is

Table 2.4 – Summary of pre-clinical studies describing vagus nerve stimulation to prevent or reduce ileus (n=14)

Study	Animal(s)	POI Model	Vagus nerve stimulation*
Yang (2021)[155] (Manuscript; English)	C57BL6 mice (sex not disclosed)	Test: Laparotomy with standardised manipulation of small bowel (no further details) once along its entire length Ψ Control: Sham laparotomy without small bowel manipulation	– Electroacupuncture at ST36 acupoint (1mA, 10Hz, 0.4ms. 20 min) – Vagal stimulation confirmed through activation of vagal brainstem centres and JAK2/STAT3 signalling in macrophages
Tian (2020)[151] (Manuscript; English)	Sprague-Dawley rats (male)	Test: Standardised sleeve gastrectomy	– Intra-operative electrical vagus nerve stimulation of the sub-diaphragmatic vagus nerve (2.2 mA, 5Hz, 0.5ms, 30mins)
Stakenborg (2019)[66] (Manuscript; English)	Mice (various) Ω	Test: Laparotomy with standardised manipulation of small bowel using a purpose-designed Plexiglas platform device Control: Sham laparotomy without small bowel manipulation	–Intra-operative electrical vagus nerve stimulation of right cervical vagus nerve (1 mA, 10Hz, 1ms, 5 mins)
Hong (2019)[154] (Manuscript; English)	C57BL6 mice (male)	Test: Laparotomy with standardised manipulation of small bowel performed twice Ψ Control: Sham laparotomy without small bowel manipulation	–Transcutaneous electrical vagus nerve stimulation of the right conchae (1 mA, 10Hz, [wavelength unknown], 10 mins
Murakami (2019)[153] (Manuscript; English)	Sprague-Dawley rats (male)	Test: Laparotomy with standardised manipulation of small bowel for 5 minutes Ψ Control: Sham laparotomy without small bowel manipulation	–Intra-operative electrical vagus nerve stimulation of sub-diaphragmatic vagus nerve (2.2 mA, 5Hz, 0.5ms, 30 mins)
Stakenborg (2017)[152] (Manuscript; English)	C57BL6 mice (sex not disclosed)	Test: Laparotomy with standardised manipulation of small bowel using a purpose-designed Plexiglas platform device Control: Sham laparotomy without small bowel manipulation	–Intra-operative electrical vagus nerve stimulation of right cervical vagus nerve (1mA, 5Hz, 2ms, 20mins) –Intra-operative electrical vagus nerve stimulation of anterior, posterior, and abdominal vagus nerves (1 mA, 10Hz, 1ms, 5mins)
Yuan (2017)[157] (Manuscript; English)	Sprague-Dawley rats (male)	Test: Laparotomy with standardised manipulation of caecum between two fingers for 3 minutes and small bowel for 5 minutes using sterile cotton applicator Control: Anaesthesia only with no surgery	–Central vagus nerve stimulation using thyrotrophin-release hormone agonist RX77368 50ng intracisternal injection

Matteoli (2014)[95] (Manuscript; English)	Mice (various)**	Test: Laparotomy with standardised manipulation of small bowel three times along its entire length for 5-7 minutes Ψ Control: Sham laparotomy without small bowel manipulation	–Intra-operative electrical vagus nerve stimulation of right cervical vagus nerve (1mA, 5Hz, 1ms, 5mins)
Miampamba (2011)[157] (Manuscript; English)	Sprague-Dawley rats (male)	Test: Laparotomy with standardised manipulation of caecum between two fingers for 1 minute Control: Anaesthesia only with no surgery	–Central vagus nerve stimulation using thyrotrophin-release hormone agonist RX77368 50ng intracisternal injection
The (2011)[159] (Manuscript; English)	Balb/C mice (female)	Test: Laparotomy with standardised manipulation of small bowel once for 5 minutes Ψ Control: Sham laparotomy without small bowel manipulation	–Central vagus nerve stimulation using intracerebroventricular semapimod 1μm/kg.
Stengel (2010)[158] (Manuscript; English)	Sprague-Dawley rats (male)	Test: Laparotomy with standardised manipulation of caecum between two fingers for 1 minute Control: Anaesthesia only with no surgery	–Cold-induced vagal activation via exposure to temperatures 4-6°C for 90 minutes after surgery –Central vagus nerve stimulation using thyrotrophin-release hormone agonist RX77368 50ng intracisternal injection
van der Zanden (2010)[149] (Manuscript; English)	C57BL6 mice (sex not disclosed)	Test: Laparotomy with opening of segment of ileum and rinsing with oxygenated Krebs buffer	–Intra-operative electrical vagus nerve stimulation of right cervical vagus nerve (1mA, 5Hz, 2ms, 5mins)
The (2007)[150] (Manuscript; English)	Balb/C mice (female)	Test: Laparotomy with standardised manipulation of small bowel for 5 minutes Ψ Control: Sham laparotomy without small bowel manipulation	–Intra-operative electrical vagus nerve stimulation of left cervical vagus nerve (1mA, 5Hz, 5ms, 20mins)
de Jonge (2005)[94] (Manuscript; English)	Balb/C mice (female)	Test: Laparotomy with standardised manipulation of small bowel performed once Ψ Control: Sham laparotomy without small bowel manipulation	–Intra-operative electrical vagus nerve stimulation of left cervical vagus nerve (1mA, 5Hz, 2ms, 20mins)

** Parameters include pulse current, frequency, wavelength, and duration, where available; Ψ Manipulation of small bowel performed using two moist cotton applicators; Ω Multiple variants, including wild-type C57BL6/JOlaHsd), α7nAChR knockout, CX3CR1GFP/WT and Wnt.1GCaMP3; ** Multiple variants, including wild-type C57BL/6JOlaHsd, B6.129S7-Chrna7tm1Bay, B6.129S7-Rag1tm1Mom/J, B6.SJL-Ptprca Pepcb/BoyJ*

co-activated upon vagal stimulation, causing macrophages to increase their phagocytic actions in response to increased intestinal permeability (149).

Intra-operative vagus stimulation has been explored by several studies, usually involving an invasive surgical procedure on the cervical vagus nerve. In 2007, The and colleagues showed that stimulating the left cervical vagus nerve abrogated the delay in gastric emptying (P<0.05) and reduced the number of inflammatory cells recruited to the muscle layer (P<0.05) following manipulation of the small bowel (150). In another study by Tian and colleagues, vagus nerve stimulation in rats undergoing sleeve gastrectomy was shown to accelerate the time to first drinking (41.2 ± 8.1 vs. 89.1 ± 15.1 hours, P=0.01), first defaecation (38.8 ± 7.1 vs. 124.4 ± 32.1 hours, P=0.02), and gastric emptying at 72 hours (79.4 ± 4.9% vs. 60.8 ± 5.7%, P=0.01), findings that were corroborated by a similar study in mice in 2020 (72, 151). Stakenborg and colleagues later explored the role of abdominal vagus nerve stimulation owing to the clinical challenge of accessing the cervical branches via an invasive procedure. Similarly, this was shown to improve intestinal transit (geometric centre: 7.8 ± 0.6 vs. 5.1 ± 0.2; P<0.01) reduce intestinal inflammation (35 ± 7 vs 80 ± 8 MPO positive cells/field; P<0.05), and decrease serum TNFα (366 ± 33 vs 822 ± 105 pg/mL; P<0.01) (152, 153).

Ambitions to develop less invasive approaches for vagus nerve stimulation shifted attention away from traditional invasive approaches during surgery. In 2019, Hong evaluated a transcutaneous device designed to stimulate the auricular branch of the vagus nerve by attaching it to the cymba conchae of the ear in mice. This activated both the NTS and DMV regions of the brainstem, confirming successful stimulation. It subsequently led to improvements in gastrointestinal transit (geometric centre: 6.8 ± 2.1 vs. 4.2 ± 1.6, P<0.05) and reduced inflammatory cells (414 ± 61 vs. 597 ± 64 cells/mm^2,

P<0.05) to the affected segment of gut (154). Similar findings were observed by Yang, who evaluated the traditional Chinese medicine electroacupuncture. Stimulation at the ST36 acupoint (hindlimb) in mice activated the DMV as well as inhibiting macrophage function by the α7nAChR-mediated JAK2/STAT3 signalling pathway (155).

2.3.3.3. Central stimulation of the vagus nerve in pre-clinical studies

Some authors have explored whether other approaches to stimulate the vagus nerve centrally may offer an alternative intervention. One such approach is pharmacologically through modulation of thyrotropin-releasing hormone (TRH)-receptor-1 signalling, which occurs in neurons of the DMV and plays a major role in vagal regulation of gastric motor and secretory functions in normal health. Experimentally, Yuan and colleagues showed that stimulating this pathway by intracisternal injection of a TRH agonist (RX-77368) inhibited the surgery-induced influx of MPO positive cells by 51% (41.3 ± 2.4 vs. 73.6 ± 4.1 cells/field; *P*<0.001) as well as dampening surgery-induced delayed gastric emptying (46.3 ± 4.9% vs. 20.8 ± 3.2%; *P*<0.01), compared to saline respectively (156). In support of this, Miampamba showed that intracisternal RX-77368 induced a 16- to 17-fold increase in fos protein (a product of the c-fos gene) in the corpus and antrum of the stomach, demonstrating a bidirectional interaction between central vagal activation and myenteric neurones (157). Similar findings were demonstrated through the use of cold ambient temperature as a means to activate TRH signalling (158). Other authors have explored the role of semapimod, a tetravalent guanylhydrazone known to prevent macrophage activation by inhibiting mitogen-activated protein kinase signalling. The and colleagues explored whether this could be used to pharmacologically activate the vagus nerve and inhibit the onset of ileus in mice. Indeed, intra-cerebrovascular injection of semapimod significantly reduced intestinal inflammation (reduction in MPO positive cells

in the muscularis; *P*=0.003) and ameliorated the delay in gastric emptying (reduction in relative gastric contents; *P*=0.02), effects which were abolished by vagotomy (159).

2.3.4. Clinical studies of vagus nerve stimulation to prevent or reduce ileus

2.3.4.1. Summary of studies

Five clinical studies were identified which explored the effect of either invasive (n=2) or non-invasive (n=3) vagus nerve stimulation on the prevention of ileus in humans. All studies were performed with participants undergoing abdominal surgery using a range of stimulator devices. A full summary of all studies is provided in Table 2.5.

2.3.4.2. Invasive vagus nerve stimulation in human studies

Stakenborg and colleagues undertook two early studies of invasive vagus nerve stimulation to reduce ileus in humans. In one of these, 18 patients undergoing elective colorectal surgery were subjected to intra-operative posterior vagus nerve stimulation at either high (20Hz), low (5Hz), or sham frequencies. Importantly, active stimulation did not increase postoperative complications, with similar numbers of minor and major complications observed across all three treatment groups. Using high frequency stimulation, but not low frequency, they showed that stimulation of the vagus nerve significantly reduced the release of pro-inflammatory cytokines (IL-6 and IL-8) on postoperative day 1 (both *P*<0.05) (152). In a later study involving 42 patients undergoing open pancreatic surgery, the effect of abdominal vagus nerve stimulation was explored for its effect on a range of clinical outcomes. In this study population, stimulation did not lead to a reduction in the time to tolerate first solid food, time to first defecation, or the time taken for removal of the nasogastric tube (72).

Table 2.5 – Summary of clinical studies describing vagus nerve stimulation to prevent or reduce ileus (n=5)

Study	Patient population	Study Design	Vagus nerve stimulation
Blank (2021)[160] (Manuscript; English)	Adult patients (n=57) undergoing elective, laparoscopic or open intestinal resection (small bowel or colon)	Randomised controlled trial (multi-centre)	– Non-invasive (percutaneous) auricular vagus nerve stimulation via attachment to the conchae of the right ear using the BRIDGE device manufactured by Innovative Health Solutions (further details not disclosed)*
Chapman (2021)[97] (Manuscript; English)	Adult patients (n=40) undergoing elective, laparoscopic colorectal surgery for bowel cancer	Randomised controlled trial (single-centre)	– Non-invasive (transcutaneous), bilateral, cervical vagus nerve stimulation for five days before and after surgery (peak 60mA, 5kHz sine wave bursts, 1ms, 2mins per administration) using the gammaCore device manufactured by ElectroCore LLCΨ
Stakenborg (2019)[72] (Manuscript; English)	Adult patients (n=42) undergoing open elective laparotomy (Whipple's procedure) for pancreatic neoplasms	Randomised controlled trial (single-centre)	– Invasive, intra-operative anterior and posterior abdominal vagus nerve stimulation performed at beginning and end of surgery (2.5 mA, 20Hz, 1ms, 2 mins per administration) using a device manufactured by Inomed (further details not disclosed)
Hong (2019)[96] (Manuscript; English)	Adult patients (n=14) undergoing open elective laparotomy for any clinical indication	Non-randomised, single arm interventional study (single-centre)	– Non-invasive (transcutaneous), auricular vagus nerve stimulation via attachment to the conchae of the right ear (10 mA, 25Hz, 0.25ms, 10mins per administration) using the Stimulationssonde device manufactured by Inomed
Stakenborg (2017)[152] (Manuscript; English)	Adult patients (n=18) undergoing elective, laparoscopic colorectal surgery for bowel cancer	Randomised controlled trial (single-centre)	– Invasive, intra-operative posterior vagus nerve stimulation performed at beginning and end of surgery (2.5 mA, 5 Hz or 20Hz, 1ms, 2 mins/administration) using a device manufactured by Inomed (further details not disclosed)

** Some participants received sham treatment using an identical but inactive variant of the device; Ψ Some participants received sham treatment using an identical device with parameters: low frequency 0.1 Hz biphasic direct current impulse through 5 kΩ ± 10%*

2.3.4.3. Non-Invasive vagus nerve stimulation in human studies

Recognising the potential clinical advantages of non-invasive vagal stimulation, several authors have explored a range of transcutaneous and percutaneous devices. Hong and colleagues used a transcutaneous device which attached to the cymba conchae of the ear. In a study population undergoing open abdominal surgery, it was shown that non-invasive stimulation decreased the number of muscular action potentials (3.19 ± 1.15 vs. 3.61 ± 1.18 per minute; $P<0.001$) whilst increasing their amplitude (0.25. ± 0.19 vs. 0.19 ± 0.14 mV; $P<0.05$) in the gastric pylorus. Furthermore, the procedure was shown to be safe, with no documented device-related adverse or serious adverse events (96). In a different study by Chapman and colleagues, a self-administered device was used to apply non-invasive vagus nerve stimulation bilaterally before and after surgery. As well as demonstrating a comparable safety profile to sham stimulation, the study suggested that self-administration was feasible, with 4.7 ± 0.9 and 4.4 ± 1.5 out of five stimulations performed by patients before and after surgery, respectively (97). Finally, in a multi-centre study by Blank, percutaneous stimulation of the vagus nerve did not accelerate the return of bowel function but it was shown to reduce opioid consumption in a sub-group of patients over the age of 70 (27.08 ± 19.55 vs 66.80 ± 30.56 oral morphine equivalents; $P=0.01$). There was no difference in their primary outcome of morphine consumption across the entire study population (160).

2.4. Discussion

2.4.1. Summary of results

A large body of previous work has sought to describe the vagal mechanisms involved in the development of ileus, as well as the potential role of vagus nerve stimulation to prevent it. Pre-clinical studies confirm that an endogenous vago-vagal anti-inflammatory

mechanism exists innately, which aims to maintain homeostasis during surgery by reducing manipulation-induced intestinal inflammation. This is facilitated by an inhibitory feedback mechanism which regulates the inflammatory response through activation of nicotinic acetylcholine receptors on intestinal immune cells such as macrophages. Activation of these receptors suppresses the release of pro-inflammatory cytokines and reduces the inflammatory cascade known to inhibit intestinal motility. The same mechanism can be harnessed for therapeutic benefit through the use of exogenous vagus nerve stimulation to reduce ileus. In pre-clinical models, stimulating the vagus nerve increases the release of acetylcholine from vagal efferent fibres, which through modulation of intestinal macrophages via the enteric nervous system, reduces intestinal inflammation. This has been explored using both invasive and non-invasive stimulator devices, all of which have confirmed the safety of vagus nerve stimulation in humans and justified further evaluation.

2.4.2. Context of current practice

A key consideration to emerge from the reported evidence was the vehicle by which vagus nerve stimulation is delivered. In pre-clinical studies, most mechanistic studies were performed using invasive methods of stimulation, most commonly requiring a laparotomy with dedicated dissection of the vagus nerve. In human studies, invasive vagus nerve stimulation was shown to be technically feasible in two studies by Stakenborg and colleagues, but raised several possible challenges (72, 152). Firstly, although no serious adverse events were reported, dissection of the abdominal vagus nerve likely introduces greater operative risk and the need for additional expert skill. Although not reported in these studies, it may also implicate a longer operative time with added complexity in operating room logistics. The generalisability and learning curve of this approach is unclear and may be challenging to scale up in wide-spread clinical

practice. Secondly, invasive stimulation implicates only a limited window of opportunity to stimulate the nerve within the limits of the procedure. This eliminates opportunities for pre-operative stimulation, which some evidence has suggested may offer greater potential for efficacy at the initial point of onset of inflammation (72).

Transcutaneous and percutaneous stimulation offer several advantages, including their relative non-invasiveness and potentially lower surgical risk. Non-invasive methods may be more acceptable to patients as well as offering greater flexibility for administration in the context of a busy and complex healthcare environment. The challenges of non-invasive devices include the logistics of administering the devices in a ward or home environment, where specific training may be required. In settings of self-administration, the factor of user-dependence may introduce a risk of ineffective or inconsistent administration. Early studies, such as the proof-of-concept study by Chapman and colleagues, suggested that self-administration is feasible and practical, although more detailed insights are required prior to wider roll out (97).

2.4.3. Strengths and limitations

The main strength of this review is its design as a scoping review, which permitted a flexible and adaptive approach to describe heterogenous literature. This allowed exploration and reporting of a wide range of considerations and insights relevant to the vagus nerve and its potential role in preventing ileus. In addition, the systematic search was intentionally broad, considering not only just published articles but also conference abstracts. This was important to ensure that the broadest collection of evidence was considered and to reduce bias which may arise from the presentation but non-publication of negative findings. Limitations are also recognised. Firstly, the scope of this review was limited to the original systematic search strategy across defined time limits. On this broad

topic, it is likely that other converging or historic evidence about the vagus nerve and its anti-inflammatory properties exist elsewhere which were not picked up by the eligibility criteria but may have been relevant and useful. This may include mechanistic insights from other disease processes (such as inflammatory bowel disease) or from other intervention settings (such as 5-HT_4 agonists) which share similar therapeutic mechanisms. It may also have included historic evidence from experiments on other mammalian species. Secondly, as a rapidly developing scientific topic, there is a risk that the present review may quickly become outdated as new pre-clinical and clinical studies emerge. It was not possible to comment further on this in the present report since searches for registered (but unpublished) studies on clinical trials databases were not performed. Finally, due to the heterogenous mix of studies expected in this review, assessments of quality and bias were not planned or performed. This is challenging to perform systematically for pre-clinical studies, owing to the diverse nature of experiments and study designs. As such, this must be taken into consideration when interpreting and drawing conclusions from the data and inferences presented.

Chapter 3

Non-invasive, self-administered vagus nerve stimulation to reduce ileus: randomised feasibility trial

Preface

In this chapter, a feasibility randomised controlled trial is presented. This explores the feasibility of undertaking a definitive trial of self-administered vagus nerve stimulation using the gammaCore device to reduce ileus after colorectal surgery. Key uncertainties to be addressed include whether it is possible to recruit patients to a future study, whether participants will comply with the planned treatment schedule, and whether it is possible to blind participants using a sham intervention, amongst others. Using pre-defined progression criteria, the study will provide an answer as to whether such a trial can be delivered as planned, with modification, or not at all.

3.1. Introduction

3.1.1 Vagus nerve stimulation in clinical medicine

Vagus nerve stimulation is most commonly known for its role in treatment-refractory epilepsy. This requires implantation of a stimulator device which transmits electrical stimuli to the cervical vagus nerve. It is approved by the FDA and is offered to patients in who conservative epilepsy treatments have failed (161). In recent years, interest in the potential role of vagus nerve stimulation in broad clinical settings has grown rapidly. Pre-clinical studies have shown that stimulating the vagus nerve has systemic and local anti-inflammatory properties which may be exploited for the treatment of a wide range of inflammatory conditions. These aspirations have been enabled by advances in technology, including the development of non-invasive devices capable of stimulating the vagus nerve transcutaneously (115).

The therapeutic role of vagus nerve stimulation has been demonstrated for several conditions, including for the management of sepsis. It was previously shown that vagal denervation increased mortality in pre-clinical models of sepsis as a result of sympathetic-parasympathetic disequilibrium, leading to an uncontrolled immune response (162, 163). Stimulation of the vagus nerve attenuated this response via a cholinergic anti-inflammatory pathway which was mediated by nicotinic acetylcholine receptors located on the surface of splenic macrophages. This reduced the expression of pro-inflammatory cytokines, including TNFα, interleukin IL1-beta, and IL-6, ultimately preventing the development of septic shock (164). Vagus nerve stimulation has also attracted attention for the management of several cardiovascular conditions, such as coronary artery disease and cerebrovascular disease. Both share common aetiological mechanisms, involving the formation of atherosclerotic plaque, lipid accumulation, cell

death, and fibrosis, which are driven by low-grade vascular inflammation. It has been proposed that vagus nerve stimulation reduces inflammation and inhibits plaque progression through the same cholinergic anti-inflammatory pathway observed in models of sepsis (165). Another proposed role for vagus nerve stimulation is for the management of rheumatoid arthritis. Evidence suggests that autonomic dysfunction is closely associated with the development of rheumatoid arthritis and that vagal tone may predict the response to treatment (166). It was previously shown that stimulation of the vagus nerve down-regulates the expression of pro-inflammatory mediators in synovial fluid, attenuating the local inflammatory response and improving standard measures of clinical symptoms (167). Other potential indications include traumatic brain injury, asthma, chronic pain, and acute pancreatitis (115).

In keeping with these conditions, vagus nerve stimulation has been shown to improve gut function in pre-clinical models of ileus via the same cholinergic anti-inflammatory pathway. Previous evidence has shown that stimulation of the vagus nerve reduces the expression of intestinal TNFα, IL-1 beta, and IL-6 occurring as a result of intestinal handing during surgery and is mediated by nicotinic acetylcholine receptors found on intestinal macrophages (94, 95). Inhibition of these mediators suppresses the pathognomonic increase in intestinal permeability to luminal bacteria, impaired muscular contractility, and activation of inhibitory neural pathways which are all seen during the development of ileus (9). Pre-clinical studies have shown that vagus nerve stimulation prevents neuromuscular dysfunction and facilitates a quicker return to normal intestinal function in pre-clinical models (95,152,153). Early clinical studies have translated these findings to humans, with vagus nerve stimulation shown to reduce systemic markers of inflammation, including pro-inflammatory cytokines, after abdominal surgery (152).

3.1.2. Non-invasive approaches to vagus nerve stimulation

Vagus nerve stimulation conventionally requires an indwelling electrical device which is implanted during a single invasive procedure. Whilst this may be acceptable in chronic conditions with a long-term therapeutic scope, it is challenging to justify in acute settings due to the balance of short-term risks and healthcare costs. Non-invasive vagus nerve stimulation offers a solution to broaden the range of possible clinical indications. It is typically performed using a transcutaneous approach over known surface landmarks of the vagus nerve and its branches. These include the cymba concha (auricular branch of the vagus nerve) and the carotid pulse (cervical vagus nerve).

Several commercial devices are available for the purpose of non-invasive vagus nerve stimulation. One such device is gammaCore (electroCore, New Jersey, US). This is a handheld device commercialised for the treatment of migraine and cluster headache (168). It is self-administered by patients by placing the device and a small volume of conducting gel over the surface landmark of the cervical vagus nerve. Each stimulation cycle lasts for 2 minutes and can be repeated on both sides of the neck. Typical stimulation parameters comprise a 5-kHz sine wave burst lasting for 1 millisecond (ms) with each burst repeated every 40 ms (25Hz). The stimulation amplitude is adjusted by the user, with a maximum voltage of +24V and a maximum output current of 60-mA.

Another device is the NEMOS system (Cerbomed, Erlangen, Germany). This attaches to the cymba concha of the ear and delivers a transcutaneous stimulus to the auricular branch of the vagus nerve. The ear electrode is connected to a battery unit via an electrical wire and is administered without any action from the patient. Each stimulation lasts for one hour and can be used in up to four sessions per day. Typical parameters

comprise a 0.25ms monophasic square pulse repeated every 40ms (25Hz). The amplitude is adjusted by the user with a maximum voltage of +25V (114).

The P-Stim device (Biegler GmbH, Mauerbach, Austria) offers a percutaneous approach to stimulate the auricular branch of the vagus nerve. Unlike other devices, this comprises 2-3 miniature needle electrodes which penetrate the skin in the region of the auricular nerve. The device produces a monophasic rectangular pulse (1Hz) with a maximum amplitude of +4V and is recommended for regular intermittent treatment, such as two days of stimulation followed by several days of pause (114).

3.1.3. GammaCore device

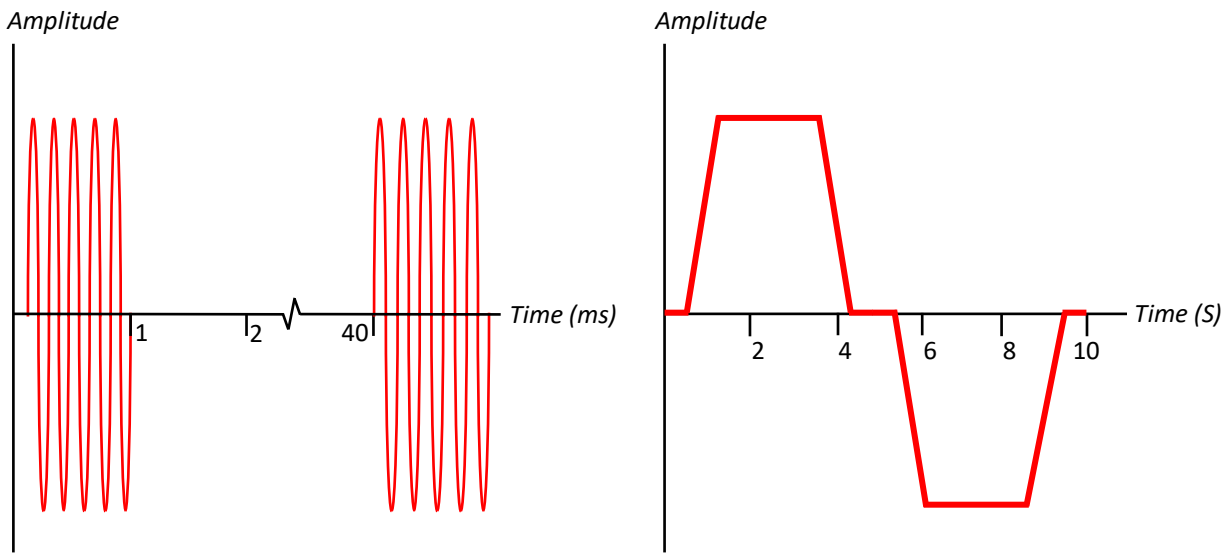
3.1.3.1. Summary of GammaCore Device

GammaCore is one of the most widely used devices for non-invasive stimulation. Studies in healthy volunteers have shown that it successfully stimulates the vagus nerve when administered over the cervical surface landmark (169, 170). The device received FDA approval in the US for the treatment of cluster headache in 2017 and for acute migraine in 2018. In the United Kingdom (UK), guidance from the National Institute for Health and Care Excellence (NICE) supports the use of gammaCore for the treatment of cluster headache in the National Health System (NHS) (168, 171). During the coronavirus disease 2019 (COVID-19) pandemic, the device received emergency FDA approval for its use in patients with respiratory compromise and COVID-19 infection.

The gammaCore device is an FDA Class II, non-invasive electrical stimulator powered by an integrated lithium battery. Active and Sham variants of the device exist for the purpose of research and development. The Active variant produces a 5000Hz (+/-100Hz) sine wave burst for 1ms (five sine waves of duration 200 microseconds), which

is repeated every 40ms (25Hz +/- 10%). Users are able to adjust the amplitude of the stimulus, with a voltage range of 48V (+/- 10%) peak-to-peak (+24V to -24V) and a maximum current of 60mA. The Sham variant produces a direct current (DC) stepped square-wave pulse which is repeated every 10 seconds (0.1Hz +/- 10%). Users are able to adjust the amplitude of the stimulus, with a voltage range of of 12V (+/- 10%) peak-to-peak (+6V to -6V) and a maximum current of 2.7mA. A detailed illustration of both waveforms is provided in Figure 3.1.

Figure 3.1 – Active and sham stimulation waveforms



Left waveform depicts the Active variant. This is a sine-wave pulse (maximum amplitude +24V +/- 10%) occurring in bursts of five waves across 1ms and repeated every 40ms (25Hz +/-10%). Right waveform depicts the Sham variant. This is a stepped square-wave pulse (maximum amplitude +6V +/- 10%) with a frequency of 0.1Hz (+/- 10%). The waveform comprises 0.65 seconds at 0V; 0.7 seconds from 0 to +6V (max); 2.3 seconds at +6V (max); 0.7 seconds from +6 (max) to 0V; 1.3 seconds at 0V; 0.7 seconds from 0 to -6V (max); 2.3 seconds at -6V (max); 0.7 seconds from -6V (max) to 0V; 0.65 seconds at 0V.

3.1.3.2. Previous evidence for gammaCore device

Key evidence to support the use of gammaCore for the treatment of cluster headache has been reported in three RCTs, namely ACT1, ACT2, and PREVA (172-174). ACT1 and ACT2 trials evaluated mixed populations of patients with episodic and chronic

cluster headache, comparing active treatment with sham. Neither study reported a superior benefit with active treatment for their primary endpoint (incidence of pain-free status within 15 minutes of treatment) but sub-group analyses revealed a beneficial effect in participants with episodic attacks (ACT1: 34.2% vs. 10.6%; *P*=0.008; and ACT2: 48.0% vs. 6.0%; *P*<0.01). The PREVA trial later demonstrated a significant benefit of active compared to sham treatment in participants with chronic cluster headache. According to its primary endpoint, active stimulation led to significantly fewer headache attacks compared to baseline per week (-5.9; SE: 1.2 vs. -2.1; SE: 1.2 episodes; *P*=0.02). Across all three studies, active treatment was well tolerated by participants and the safety profiles of active and sham treatments were comparable.

In the setting of migraine, key evidence to support the use of gammaCore has been reported in two RCTs, namely the PRESTO and PREMIUM studies (175, 176). In the PRESTO study, patients with episodic migraines were randomised to active and sham treatment, with the former showing a statistically significant improvement in pain-free status 60 minutes after stimulation (21.0% vs. 10.0%; *P*=0.023). The PREMIUM study recruited a similar population but showed no difference in the reduction of migraine days per month (2.26 vs. 1.80; *P*=0.15). Across both studies, adverse events were mostly mild and similar between groups, with application site pain (3.0% vs. 5.8%), erythema (1.8% vs. 4.7%), rash (0.6% vs. 7.0%) and dizziness (3.0% vs. 1.7%) occurring infrequently in active and sham groups, respectively.

A summary of device and study characteristics (including blinding and sham procedures) as well as device related adverse events reported across five pivotal cluster headache and migraine trials are shown in Table 3.1.

Table 3.1 – Device and study characteristics from previous pivotal RCTs in cluster headache and migraine groups

Study	Study Design	Devices	Device-related adverse events
ACT1[172] (Cluster headache) (2016)	Randomised, superiority, parallel group (1:1), double blinded	Active: 5kHz sine wave burst (1ms) repeated at 25Hz (+24V peak voltage; 60mA peak current). Control: Sham device; 0.1Hz direct current square pulse with maximum amplitude 0-28V peak to peak	• Application site discomfort: Active 2/73 (2.7%); Sham 7/77 (9.1%) • Application site redness: Active 0/73 (0.0%); Sham 9/77 (11.7%) • Facial/lip twitch: Active 8/73 (11.0%); Sham 0/77 (0.0%) • Dysgeusia/metallic taste: Active 0/73 (0.0%); Sham 7/77 (9.1%)
ACT2[173] (Cluster headache) (2018)	Randomised, superiority, parallel group (1:1), double blinded	Active: 5kHz sine wave burst (1ms) repeated at 25Hz (+24V peak voltage; 60mA peak current). Control: Sham device; 0.1Hz direct current square pulse with maximum amplitude 0-28V peak to peak	• Application site irritation: Active 2/50 (4.0%); Sham 0/52 (0.0%) • Application site paraesthesia: Active 2/50 (4.0%); Sham 1/52 (1.9%) • Skin rash: Active 1/50 (2.0%); Sham 2/52 (3.8%) • Skin irritation: Active 2/50 (4.0%); Sham 0/52 (0.0%) • Myalgia: Active 0/50 (0.0%); Sham 1/52 (1.9%) • Myokymia: 0/50 (0.0%); Sham 0/52 (0.0%)
PREVA[174] (Cluster headache) (2016)	Randomised, superiority, parallel group (1:1), open-label	Active: 5kHz sine wave burst (1ms) repeated at 25Hz (+24V peak voltage; 60mA peak current). Control: Standard of care (no sham device)	• Overall participants with at least one device related adverse event: Active 13/48 (27.0%) (Includes depressed mood, malaise, oropharyngeal pain, cluster headache, paraesthesia, muscle twitching, muscle spasms, hot flush, acne, pain, throat tightness, dizziness, hyperhidrosis, toothache, decreased appetite and skin irritation.
PRESTO[175] (Migraine) (2018)	Randomised, superiority, parallel group (1:1), double blinded	Active: 5kHz sine wave burst (1ms) repeated at 25Hz (+24V peak voltage; 60mA peak current). Control: Sham device; 0.1Hz direct current square pulse with maximum amplitude 0-28V peak to peak	• Overall participants with at least one device related adverse event: Active 7/122 (5.7%); Sham 10/126 (7.9%) • Application site discomfort: Active 3/122 (2.5%); Sham 1/126 (0.8%) • Application site redness: Active 0/122 (0.0%); Sham 3/126 (2.4%) • Application site pain: Active 0/122 (0.0%); Sham 3/126 (2.4%) • Dizziness: Active 0/122 (0.0%); Sham 3/126 (2.4%)
PREMIUM[176] (Migraine)	Randomised, superiority, parallel group (1:1), double blinded	Active: 5kHz sine wave burst (1ms) repeated at 25Hz (+24V peak voltage; 60mA peak current). Control: Sham device; 0.1Hz direct current square pulse with maximum amplitude 0-28V peak to peak	• Application site rash: Active 1/169 (0.6%); Sham 12/172 (7.0%) • Application site pain: Active 5/169 (3.0%); Sham 10/172 (5.8%) • Application site redness: Active 3/169 (1.8%); Sham 8/172 (4.7%) • Application site discomfort: Active 7/169 (4.1%); Sham 5/172 (2.9%) • Dizziness: Active 5/169 (3.0%); Sham 3/172 (1.7%)

3.1.3.3. Justification for selection of gammaCore device

The gammaCore device was selected for assessment in the present setting for several reasons. Firstly, the device holds a Conformité Européene (CE) mark for disorders of gastrointestinal motility, having been previously explored for its role in treating chronic gastroparesis, amongst other clinical indications (177). Secondly, several clinical trials have demonstrated an acceptable safety profile for the gammaCore device in broad populations of patients. Whilst its safety is still to be determined in the present population undergoing major surgery, no concerns about device related adverse events have been reported elsewhere. Thirdly, a number of clinical trials have successfully completed recruitment using the gammaCore without any clear barriers to feasibility (172-176). Whilst most of these have been in non-hospitalised patients, no generalisable challenges have been reported. This provides a signal of confidence that the device may be feasible in future healthcare practice. Finally, the gammaCore device is approved by the US FDA and recommended by NICE in the UK for the treatment of cluster headaches (171). Although potential challenges to uptake must be explored in the present surgical population, its existing uptake in the NHS is a strength and demonstrates in principle that the device can be introduced successfully in the NHS.

3.1.4 Aims and objectives

This study aimed to determine the feasibility of a multicentre, phase-III, RCT of non-invasive, self-administered vagus nerve stimulation to reduce ileus after colorectal surgery. As a feasibility study, no clinical hypothesis testing was pre-planned.

The following objectives were pre-defined to explore whether it was feasible to progress to a definitive RCT:

- To estimate the proportion of screened patients who were eligible for approach
- To estimate the number of patients approached who agreed to be randomised
- To assess the performance of participant blinding to the allocated treatment
- To assess participant compliance to the allocated treatment
- To explore safety of the study treatment
- To estimate rates of missing clinical outcome data
- To estimate the rate of participant loss-to-follow up

Variation in outcome data for a series of candidate primary endpoints was assessed to inform sample size considerations. These objectives included:

- To estimate time (days) to first passage of flatus
- To estimate time (days) to first passage of stool
- To estimate time (days) to tolerate oral intake
- To estimate time (days) to GI-2 (composite of oral intake and stool) (178)
- To estimate the rate of insertion of nasogastric tube
- To estimate the total length of inpatient hospital stay (days)

3.2. Methods

3.2.1. Ethics and governance

The trial was undertaken according to the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. Approval by the NHS Health Research Authority (HRA) and the Tyne & Wear South Research Ethics Committee (REC) was confirmed on 2nd July 2019 (19/NE/0217). The study was registered on the ISRCTN registry on 11th October 2019 prior to the start of enrolment (ISRCTN62033341) and the protocol was published prospectively following external

peer review (179). The study was funded by the National Institute of Health and Care Research (NIHR), with devices provided through the manufacturer's Investigator Initiated Trial Programme. Neither had a role in the study design, data analysis, or interpretation of results. The report described herein is reported according to the CONSORT 2010 Extension for Randomised Pilot and Feasibility Trials as well as the Template for Intervention Description and Replication (TIDieR) Checklists (180, 181).

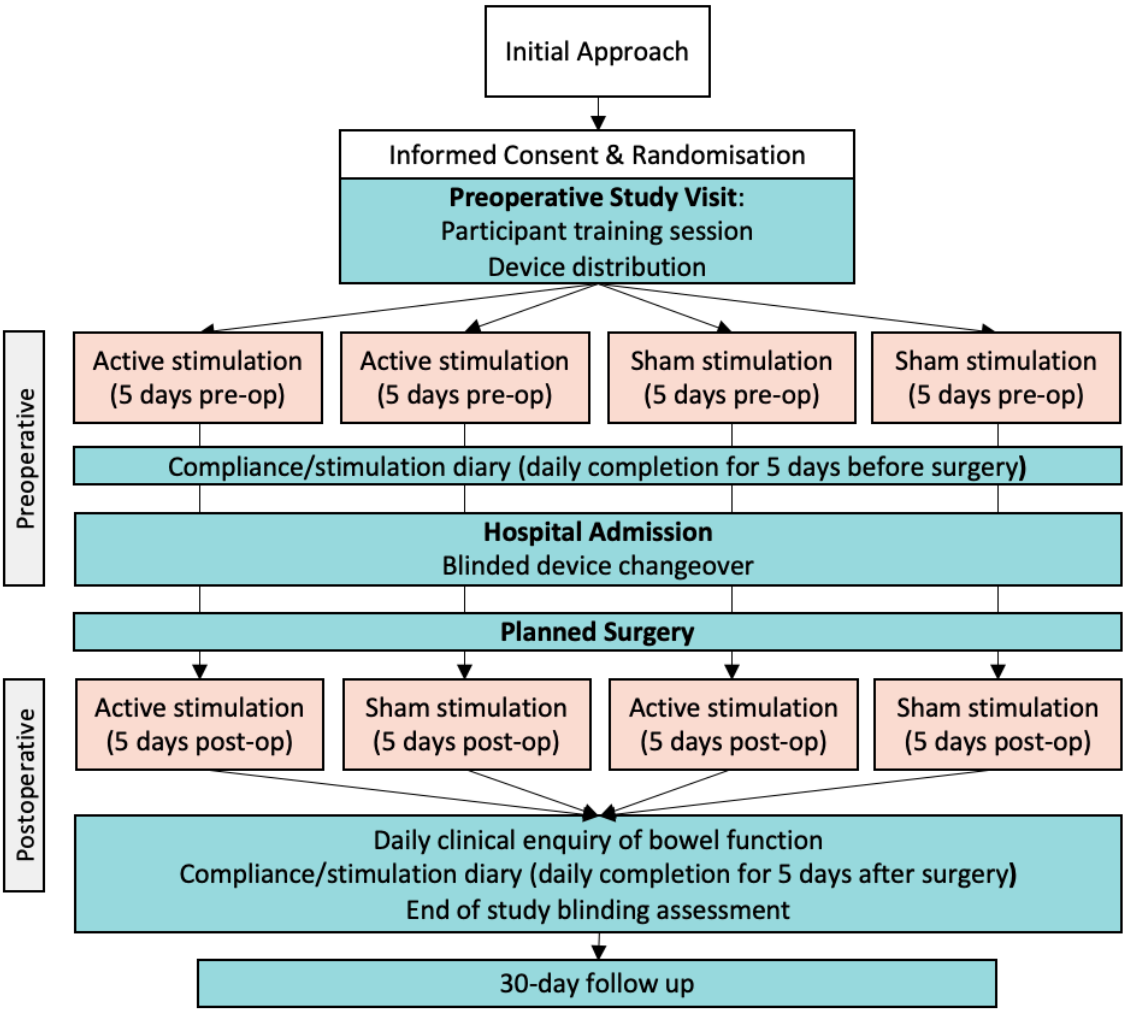
3.2.2. Summary of trial design

A parallel-group, participant-blinded, sham-controlled, multi-site, randomised, feasibility trial was undertaken with participants randomised equally across four treatment groups (1:1:1:1) (Figure 3.2). This was a Stage 2b ("Exploration") study according to the IDEAL Framework for surgical innovation (182). There were no substantial changes to the trial design after the commencement of recruitment on 1st January 2020. The trial was temporarily suspended between 18th March 2020 and 1st July 2020, in line with national guidance on the prioritisation of COVID-19 research, after which all sites were invited to re-open recruitment in line with local operating procedures. Details of all amendments occurring during the course of the study are described in Appendix A-3.1.

3.2.3. Setting and participants

The trial was undertaken across two NHS hospital sites in England: St. James's University Hospital (SJUH) in Leeds; and Bradford Royal Infirmary (BRI) in Bradford. SJUH is a tertiary-care centre serving a local population of 812,000 (16% Aged 65 and over; 18.9% Black and Minority Ethnic groups) as well as a wider population of approximately 5 million across the West Yorkshire region (183). BRI is a secondary-

Figure 3.2 – Feasibility trial schema



care centre serving a local population of 546,000 (15.2% Aged 65 and over; 36.1% Black and Minority Ethnic groups) (184). Both provide acute and planned surgical services, including laparoscopic colorectal surgery within programmes of enhanced recovery. A series of hospital-level characteristics is provided in Table 3.2.

Table 3.2 – Feasibility trial recruitment settings

Recruitment Site	Type of NHS organisation	University affiliation	Inpatient bedspace	Annual bowel cancer resections*
St. James's University Hospital, Leeds, UK	NHS Trust	University of Leeds	2000 Ψ	268
Bradford Royal Infirmary, Bradford, UK	NHS Foundation Trust	University of Bradford	780 Ω	107

** Taken from the National Bowel Cancer Audit 2021 (185); Ψ Estimated beds across Leeds Teaching Hospitals NHS Trust, taken from latest CQC report (186); Ω Estimated beds across Bradford Teaching Hospitals NHS Foundation Trust taken from latest CQC report (187)*

Patients were eligible to take part if they were aged 18 or over, able to provide written informed consent, and were planned to undergo elective minimally invasive (laparoscopic or robotic) colorectal resection with an anastomosis and no routine plans for a diverting stoma. Intraoperative decisions to convert to open surgery or to form an unplanned stoma did not lead to exclusion, provided that these decisions were made after randomisation. All procedures listed in Table 3.3 were eligible for inclusion.

Table 3.3 – Included procedures

Right-sided resection	Left-sided resection
Ileo-colic/caecal resection Right hemicolectomy Extended right-hemicolectomy Transverse colectomy	Extended left hemicolectomy Left hemicolectomy Sigmoid colectomy Rectosigmoid colectomy Anterior resection

Miscellaneous segmental resections were defined according to the respective right or left side of resection

Patients were excluded if they satisfied any of the following criteria: 1) severe cardiac disease (myocardial infarction within 12 months; congestive heart failure with New York Heart Association Scale > 2, second- or third-degree atrioventricular block, previous atrial fibrillation/flutter or ventricular tachycardia/fibrillation); 2) seizures or recurrent syncope in the last 5 years; 3) previous transient ischaemic attack or cerebrovascular accident; 4) previous vagotomy; 5) inflammatory bowel disease, 6)

neuroendocrine tumour, 7) existing intestinal stoma, 8) implanted electrical device; 9) structural abnormality of the neck anatomy precluding administration of the device; 10) belonging to a vulnerable group 11) patients who were pregnant or breast feeding during the course of the study. These criteria reflected known contraindications to non-invasive vagus nerve stimulation, factors which may impact on its mechanism (such as previous vagotomy), and factors which may significantly impede on its use (such as structural abnormality of the neck anatomy). Co-enrolment to observational studies was permitted without restriction. Co-enrolment to other interventional studies was also permitted unless the intervention aimed to change the trajectory of surgical recovery or if its mechanism of action was considered to impact on postoperative bowel motility.

3.2.4. Recruitment

Potential participants were identified from multi-disciplinary team meetings and screened for eligibility according to the pre-defined eligibility criteria by an approved member of the direct care team. They were then approached in a face-to-face clinic with written information and a copy of the study consent form (Appendix A-3.2). A verbal explanation of the study was provided, including its rationale, purpose, design, and all expectations of study participants. It was acceptable for potential participants to provide consent at the point of approach or alternatively they were invited to take the written information away for further consideration followed by a telephone call to confirm their decision. Written informed consent was confirmed following a final assessment of eligibility by a member of the study team.

In light of social distancing guidelines during the COVID-19 pandemic, a substantial amendment to the protocol was approved on 23rd June 2020 to enable recruitment

activities to be facilitated via telephone or post if required (Appendix A-3.1). This was necessary to ensure that the feasibility assessment could continue without an indefinite and exceptional disruption to recruitment and was designed and agreed in close collaboration with patient representatives. The amended two-step consent process comprised an initial process of audio-recorded consent via telephone using the existing consent form as a verbatim script. This was followed by written confirmation of consent upon admission to hospital. The timeline for recruitment suspensions and amendments to the recruitment protocol are shown in Figure 3.3.

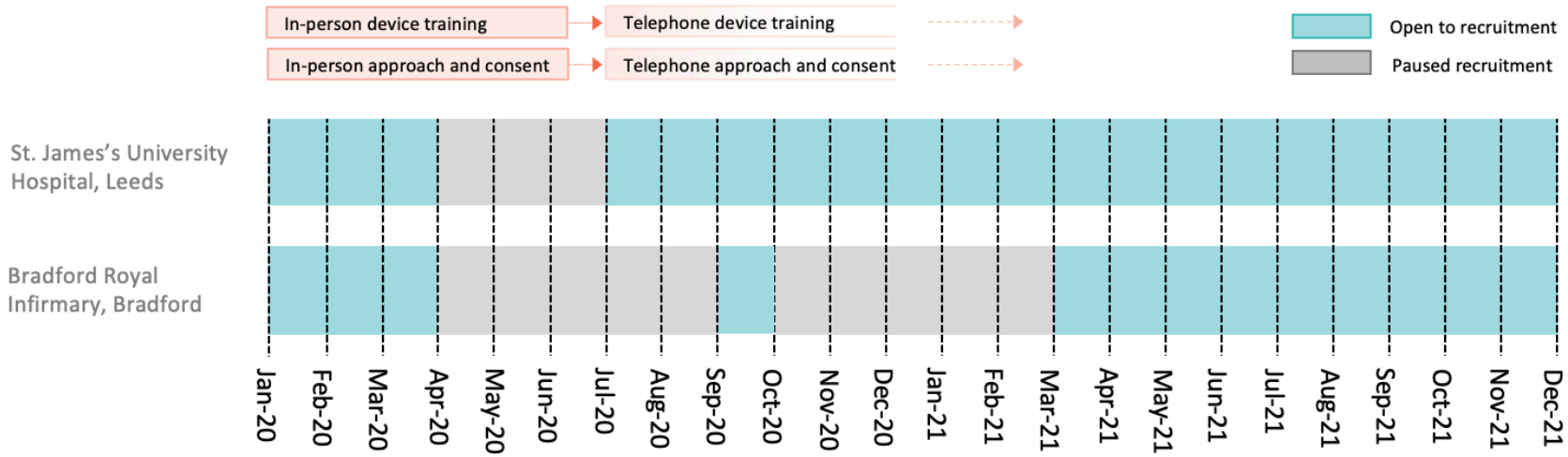
Withdrawal from the trial was permitted at any point if requested by participants. As a feasibility trial exploring treatment compliance, unplanned cessation of the study treatment did not lead to withdrawal unless participants withdrew consent for other trial activities such as the collection of personal data. Loss of capacity following consent led to withdrawal from subsequent trial-related activities, with all data collected up to that point retained unless otherwise requested by the participant's legal delegate.

3.2.5. Interventions

3.2.5.1. Study devices

The gammaCore device (electroCore, New Jersey, US) is a non-invasive, hand-held, electrical stimulator used for cervical vagus nerve stimulation. The device produces a low-voltage stimulus comprising a 5-kHz sine wave burst lasting for 1 ms (five waves of 200 microseconds), with each burst repeated every 40 ms (25Hz). This generates a +24V maximum voltage and 60mA maximum current which users can manually adjust. A sham device produces a low frequency (0.1Hz) biphasic stimulus that does not stimulate the vagus nerve (169). It is identical in appearance, weight, audible feedback, user-interface, and packaging. All devices are supplied with conductive gel.

Figure 3.3 – Timeline of recruitment suspensions and protocol amendments



3.2.5.2. Study site processes

The devices were introduced to study sites according to local operating and approval processes. Local investigators (Principal Investigator and Research Delivery Team) attended a study initiation visit facilitated by the study team which took place at local sites. This involved a summary presentation of the study protocol, a demonstration of the device, an introduction to the standard operating procedure for participant training (Appendix A-3.3), and an open question and answer session. Devices were stored securely at local sites according to the manufacturer's standard instructions.

3.2.5.3. Participant training

After enrolment in the trial, participants attended a face-to-face training session delivered by a local investigator. The session included a practical demonstration on how to locate the surface landmark of the cervical vagus nerve using the carotid pulse and how to activate and adjust the stimulation amplitude. Participants were invited to self-administer the device under supervision using a demonstration (inactive) device until they felt confident. A "Quick Guide" resource comprising of step-by-step written and graphical instructions was provided to take home (Appendix A-3.4). In July-21, face-to-face training was converted to a telephone format in light of COVID-19 social distancing restrictions. Devices were securely couriered to participants in advance of the training session, which was facilitated via telephone using the Quick Guide as a visual cue.

3.2.5.4. Device administration

Participants self-administered the device twice-daily for five consecutive days before and five days after surgery. The precise timing of administration was not pre-specified but participants were instructed to perform one administration in the morning and another 12 hours later. Each administration comprised a 2-minute cycle of continuous

stimulation performed sequentially on each side of the neck. The device shut down automatically after two minutes. Participants were instructed to apply conductive gel to the stimulation surfaces and to adjust the amplitude to the highest tolerated level.

3.2.5.5. Standard care

No additional changes to routine standard care were made during the study. At both study sites, participants were treated within programmes of enhanced recovery, comprising key principles of the ERAS Society guidelines, including (4):

- Pre-admission: Patient education, preoperative optimisation, and routine screening of anaemia with correction as appropriate
- Preoperative: Pharmacological prevention of nausea and vomiting, prophylactic antibiotics prior to skin incision, avoidance of mechanical bowel preparation in colonic surgery, and fasting from 6 hours before surgery
- Intraoperative: Maintenance of normovolaemia and normothermia throughout, as well as the avoidance of routine abdominal drainage
- Postoperative: Avoidance of routine gastric drainage, opioid-sparing analgesia, mechanical and chemical thromboprophylaxis, maintenance of normovolaemia, early resumption of oral feeding, and early mobilisation

As a feasibility study, surgical technique and anaesthetic protocols were not standardised or prescribed during the course of the study, and neither was the routine management of postoperative ileus if and when it occurred.

3.2.6. Outcomes

The following outcomes were assessed to explore the feasibility of a phase-III RCT:

- Proportion of eligible patients identified from screening logs per month

- Number of eligible patients recruited per month and reasons for approach failure
- Adequacy of participant blinding according to a modified Bang Index (188)
- Average compliance to the study treatment according to participant-reported diaries (expressed as a proportion of 20 stimulation cycles across 10 days)
- Rate of missing clinical endpoint data
- Rate of participant loss-to-follow up after enrolment in the study
- Incidence of postoperative complications occurring within 30 days of surgery (Definitions for complications provided in Appendix A-3.5) (189-192)

Feasibility outcomes were assessed using a series of progression criteria ("Stop": not feasible; "Modify": likely feasible with change; and "Progress": feasible without change) (Table 3.4). These were pre-defined to reflect realistic targets to inform a potential

Table 3.4 – Feasibility progression criteria

Criteria	Stop	Modify	Progress
Proportion of eligible patients identified from screening logs	<10%	10-20%	>20%
Number of eligible patients randomised over 24 months (site: SJUH)	≤2 per month	3-4 per month	≥5 per month
Number of eligible patients randomised over 24 months (site: BRI)	<1 per month	1-2 per month	≥3 per month
Adequacy of participant blinding (according to the Bang Blinding Index)	Index < -0.5 Or Index > 0.5	Index -0.2 to -0.5 Or Index 0.2 to 0.5	Index 0 to -0.19 Or Index 0 to 0.19
Average participant-reported compliance to the study treatment schedule	<10/20 stimulations across 10 days	10-15/20 stimulations across 10 days	≥16/20 stimulations across 10 days
Rate of randomised patients lost to follow up	≥40%	15-39%	<15%
Rate of missing clinical endpoint data	≥40%	15-39%	<15%
Incidence of complications or serious complications	>20% increase in complications	5-20% increase in complications	<5% increase in complications

SJUH: St. James's University Hospital, Leeds; BRI: Bradford Royal Infirmary, Bradford

future RCT. Modify outcomes were considered using the ADepT framework, a systematic approach to decision-making in feasibility studies involving the identification, appraisal, and agreement of changes to the study design (193). No changes to the progression criteria were made during the course of the study.

The following candidate primary endpoints were assessed to explore clinical variability and to inform future sample size calculations:

- Time (days) to first passage of flatus
- Time (days) to first passage of stool
- Time (days) to tolerate oral intake
- Time (days) to GI-2 (composite of oral intake and passage of stool) (178)
- Need for insertion of a nasogastric tube
- Total length of inpatient hospital stay (days)

3.2.7. Sample size

As a feasibility study, a sample size calculation based on a defined clinical hypothesis was not undertaken. A maximum sample size of 35 participants per study arm (total sample: 140) was considered appropriate to explore the pre-defined feasibility outcomes and to assess variation in the candidate primary endpoints. This was guided by Teare and colleagues, who proposed that an external pilot study should include at least 35 participants in each arm and at least 70 in the study overall to estimate the SD of a continuous outcome (194). Whilst this study explored factors beyond this, a sample of 35 participants in each group was considered to be proportionate. There were no plans to stop the trial early and the end of the trial was considered to be when the planned sample was achieved or when 24 months of recruitment had elapsed. Feasibility assessments of

missing outcome data and loss-to-follow-up were planned at 6-monthly intervals to enable re-assessment and optimisation of the method if necessary. All other feasibility assessments were undertaken at the end of the trial.

3.2.8. Randomisation and blinding

Participants were randomised equally (1:1:1:1) to one of four treatment groups:

- Group 1: Preoperative stimulation and postoperative stimulation
- Group 2: Preoperative stimulation and postoperative sham
- Group 3: Preoperative sham and postoperative stimulation
- Group 4: Preoperative sham and postoperative sham

A computer-generated random allocation sequence was developed by a statistician at the Leeds Clinical Trials Unit who was independent to the trial. Randomisation was performed by minimisation with two stratification variables including the type of surgery (right-sided or left-sided colorectal resection) and study site (SJUH or BRI). Local investigators randomised participants using an automated 24-hour online service, who were also responsible for assigning patients to the randomised group. Participants were blinded to the allocation through the use of a sham device which was identical in appearance, weight, audio feedback, and packaging. Participant training activities and written material were the same across all treatment groups. The preoperative assigned device was replaced with a new postoperative device immediately after surgery. This took place routinely, irrespective of whether the same type of device was assigned before and after surgery to ensure standardisation of the study processes. Study site clinicians and outcome assessors were not blinded to the allocation.

3.2.9. Data collection

For all participants, data were collected on baseline, disease, operative, bowel function, and clinical outcome variables. Treatment compliance and stimulation data were collected using participant diaries which were self-recorded at the time of each self-administration. The performance of blinding was assessed following the last stimulation cycle. All participants were followed up 30 days after surgery by telephone to determine if any postoperative complications had occurred after discharge (Table 3.5).

3.2.10. Statistical methods

All feasibility and clinical outcomes were presented descriptively as rates (categorical) or means (continuous) with standard deviation. No statistical comparisons across study arms were planned or undertaken.

Blinding was assessed using a modified Bang Blinding Index. The original index (BI) described by Bang provides an assessment of blinding for a two-arm RCT comprising of a Treatment and Control arm (188). It is expressed as a value between -1 and 1 with 0 representing random guessing and is calculated according to the following:

$$BI = \frac{n_c - n_i}{n_{ci}} \qquad \text{(E.2.1)}$$

where n_c represents correct guesses, n_i represents incorrect guesses, and n_{ci} represents the total number of responses received.

Since multiple arms existed in this study and it was possible for ‘incorrect’ guesses to be spread across any number of arms, the index was modified (BI_m) as follows:

$$BI_m = \frac{n_c - \overline{n_x}}{(n_c + \overline{n_x})} \quad \text{(E.2.2)}$$

where n_c represents correct guesses, $\overline{n_x}$ represents the average of incorrect guesses across all other arms, and $n_c + \overline{n_x}$ was the respective modified total, thus normalising the equation to produce a comparable output to the original index.

Analyses of feasibility outcomes were performed on the intention-to-treat population, which included all participants as originally randomised. Analyses to explore variation in clinical endpoint data were performed on both intention-to-treat and per-protocol populations. Reasons for exclusion from the per-protocol population included: non-compliance to the study treatment (defined as fewer than 16 out of 20 administered stimulations, in keeping with the study progression criteria), conversion to open surgery, formation of an unplanned stoma, return to theatre prior to the return of bowel function, study or treatment withdrawal for any reason, and randomisation errors.

3.2.11. Patient and public involvement

A patient advisory group consisting of 6 individuals (female n=3; male n=3) was convened during the initial design of the trial. All members of the group had previously undergone abdominal surgery and two had existing experience of using the gammaCore device during an earlier development study (IDEAL 2a). The members represented a range of different levels of experience in public involvement activities. The group met either in person or remotely at regular 3-month intervals to review progress, challenges, and emerging data. The sessions were co-chaired by the lead investigator and an experienced public representative, who was also responsible for providing peer support and signposting members towards sources of support and training. The advisory group contributed to the development of patient-facing materials (such as recruitment and training materials), the design of key study activities (such as

Table 3.5 – Schedule of study activities

	Events	Baseline	Preop visit/call	5 days pre-admission	Day of surgery	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6-10	30-day phone F/U
Study Procedures	Approach and consent	✓										
	Device training		✓									
	Device distribution		✓		✓							
	Device daily self-administration			✓		✓	✓	✓	✓	✓		
	Self-reported compliance diary			✓		✓	✓	✓	✓	✓		
	Blinding assessment										✓	
Data collection	Eligibility CRF	✓										
	Baseline CRF	✓										
	Operative CRF				✓							
	Bowel function CRF (POD 1-10)					✓	✓	✓	✓	✓	✓	
	Clinical Outcome/Follow-up CRF											✓

CRF: Case Report Form; F/U: follow up; POD: postoperative day

blinding procedures and the approach used to measure self-reported compliance with the device), as well as troubleshooting unexpected challenges throughout the trial and interpreting the final data. The group had a prominent role in adapting the recruitment protocol to ensure compatibility with social distancing restrictions due to the COVID-19 pandemic. A detailed approach to telephone consent, participant training, and remote support was co-designed and approved by the group prior to being submitted for consideration by the REC. They also contributed to the final discussions around feasibility and progression by providing personal insights to support discussions about possible changes and adaptations to the study protocol.

3.3. Results

3.3.1. Summary of recruitment

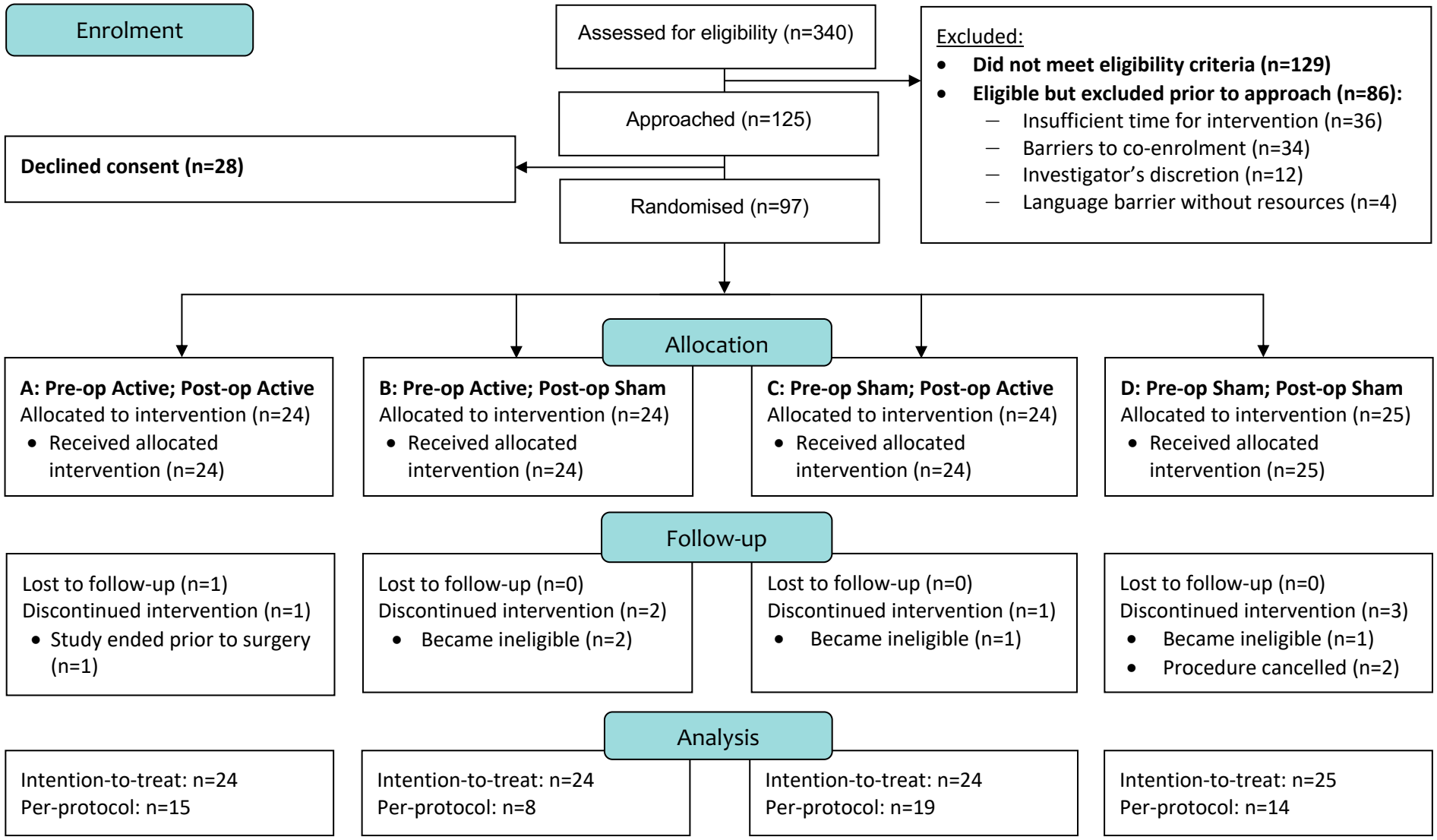
A total of 340 patients were considered for participation. Of these, 211 were confirmed to be eligible, 125 were approached, and 97 provided consent and were randomised. Common reasons for being eligible but not approached were insufficient time to start treatment before surgery (n=36) and barriers to co-enrolment (n=34). Of 97 participants, all were considered in the intention-to-treat population and 56 were considered in the per-protocol population. Reasons for exclusion from the per-protocol population included: a change from minimally invasive to open surgery after randomisation (n=13), formation of an unplanned stoma (n=8), withdrawal of the study treatment (n=7), and non-compliance to the treatment (n=19). Six participants were excluded due to multiple reasons. Basic demographics for all patients considered for participation are shown in Table 3.6. A summary of recruitment is shown in Figure 3.4.

Table 3.6 – Summary of demographics for all patients considered for participation

	Screened	Eligible	Approached	Declined	Enrolled (ITT)	Enrolled (PP)
All Sites	(n=340)	(n=211)	(n=125)	(n=28)	(n=97)	(n=56)
Sex						
Female	150 (44.1%)	103 (48.8%)	62 (49.6%)	16 (57.1%)	46 (47.4%)	21 (37.5%)
Male	190 (55.9%)	108 (51.2%)	63 (50.4%)	12 (42.9%)	51 (52.6%)	35 (62.5%)
Age	68.5 ± 10.3	66.6 ± 10.1	66.4 ± 9.4	66.7 ± 11.4	65.7 ± 9.2	65.0 ± 8.7
SJUH	(n=276)	(n=176)	(n=104)	(n=19)	(n=85)	(n=49)
Sex						
Female	118 (42.8%)	84 (47.7%)	52 (50.0%)	12 (63.2%)	40 (47.1%)	18 (36.7%)
Male	158 (57.2%)	92 (52.3%)	52 (50.0%)	7 (36.8%)	45 (52.9%)	31 (63.3%)
Age	68.0 ± 10.2	66.3 ± 10.2	65.7 ± 9.2	65.0 ± 9.9	65.9 ± 9.1	65.0 ± 9.0
BRI	(n=64)	(n=35)	(n=21)	(n=9)	(n=12)	(n=7)
Sex						
Female	32 (50.0%)	19 (54.3%)	10 (47.6%)	4 (44.4%)	6 (50.0%)	3 (42.9%)
Male	32 (50.0%)	16 (45.7%)	11 (52.4%)	5 (55.6%)	6 (50.0%)	4 (57.1%)
Age	70.5 ± 10.7	67.9 ± 9.8	69.8 ± 9.6	75.8 ± 7.0	66.1 ± 9.3	65.0 ± 7.3

BRI: Bradford Royal Infirmary; ITT: Intention-to-treat population; PP: Per-protocol population; SJUH: St. James's University Hospital

Figure 3.4 – CONSORT flow-chart of recruitment, allocation, and analysis



3.3.2. Characteristics of participants

Of 97 participants recruited to the trial, a small majority were male (n=51/97; 52.6%) and the average age was 65.7 (SD: 9.2) years. Over one-third of participants described having a previous history of abdominal surgery (n=37/97; 38.1%). The most common baseline co-morbidities were diabetes mellitus (n=8/97; 8.2%) and COPD (n=7/97; 7.2%) and the average body mass index was 28.9 (SD: 6.3). On average, baseline haemoglobin (136.3; SD: 17.0 g/L), albumin (38.6; SD: 5.0 g/L), and estimated glomerular filtration rate (eGFR) (80.8; SD: 12.2 g/L) were within clinically normal limits. A full description of participant characteristics is provided in Table 3.7. A breakdown of characteristics for randomised strata are provided in Appendices A-3.6 and A-3.7.

Table 3.7 – Summary of clinical characteristics for enrolled participants

	Group 1: Stim/Stim n=24	Group 2: Stim/Sham n=24	Group 3: Sham/Stim n=24	Group 4: Sham/Sham n=25	Total n=97
Sex					
Male	16 (66.7%)	5 (20.8%)	18 (75.0%)	12 (48.0%)	51 (52.6%)
Female	8 (33.3%)	19 (79.2%)	6 (25.0%)	13 (52.0%)	46 (47.4%)
Age (years)	65.5 (7.1)	64.3 (12.1)	67.3 (7.2)	65.6 (9.7)	65.7 (9.2)
BMI (kg/m^2)	30.0 (7.7)	27.9 (5.2)	28.9 (5.1)	28.6 (7.2)	28.9 (6.3)
Current smoker	2 (8.3%)	2 (8.3%)	2 (8.3%)	1 (4.0%)	7 (7.2%)
Prior abdominal surgery	6 (25.0%)	9 (37.5%)	11 (45.8%)	11 (44.0%)	37 (38.1%)
Ischaemic heart disease	1 (4.2%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
Diabetes mellitus	3 (12.5%)	1 (4.2%)	3 (12.5%)	1 (4.0%)	8 (8.2%)
Chronic kidney disease	1 (4.2%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	2 (2.1%)
COPD	1 (4.2%)	1 (4.2%)	4 (16.7%)	1 (4.0%)	7 (7.2%)
PVD	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (4.0%)	2 (2.1%)
Regular opioid use	0 (0.0%)	1 (4.2%)	2 (8.3%)	0 (0.0%)	3 (3.1%)
Baseline Hb (g/L)	142.6 (17.2)	133.4 (18.7)	137.5 (14.9)	131.9 (16.0)	136.3 (17.0)
Baseline albumin (g/L)	40.2 (8.6)	38.4 (2.8)	37.6 (3.5)	38.5 (3.3)	38.6 (5.0)
Baseline eGFR*	77.5 (13.6)	80.7 (11.0)	83.3 (11.5)	81.4 (12.4)	80.8 (12.2)

** Units are ml/min/1.73 m^2; Categorical variables expressed as rates (%); continuous variables expressed as mean (standard deviation); BMI: Body Mass Index; eGFR: estimated glomerular filtration rate; COPD: chronic obstructive pulmonary disease; Hb: haemoglobin; PVD: peripheral vascular disease*

The average operating time (initial skin incision to final skin closure) was 190 (SD: 62) minutes. Most procedures started laparoscopic (n=86/97; 88.7%) or robotic (8/97; 8.2%), with a small number (n=2/97; 2.1%) starting open following a change to the initial planned surgery after randomisation. A further 11 (n=11/97; 11.6%) were converted to open

during the procedure. The most common procedures were anterior resection (n=32/97; 33.0%) and right hemicolectomy (n=31/97; 32.0%). Ninety-four participants underwent an anastomosis (n=93/97; 95.9%) of which most were performed using a stapled technique. (n=90/93; 96.8%). Eight patients (n=8/97; 8.2%) received an unplanned stoma. A full outline of surgical characteristics is shown in Table 3.8.

Table 3.8 – Summary of surgical characteristics for enrolled participants

	Group 1: Stim/Stim n=24	Group 2: Stim/Sham n=24	Group 3: Sham/Stim n=24	Group 4: Sham/Sham n=25	Total n=97
ASA					
1	4 (16.7%)	4 (16.7%)	4 (16.7%)	5 (20.0%)	17 (17.5%)
2	10 (41.7%)	16 (66.7%)	13 (54.2%)	17 (68.0%)	56 (57.7%)
3	8 (33.3%)	4 (16.7%)	6 (25.0%)	3 (12.0%)	21 (21.6%)
4	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Unavailable	1 (4.2%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	2 (2.1%)
Operative Approach					
Laparoscopic	20 (83.3%)	20 (83.3%)	23 (95.8%)	23 (92.0%)	86 (88.7%)
Robotic	2 (8.3%)	3 (12.5%)	1 (4.2%)	2 (8.0%)	8 (8.2%)
Open	1 (4.2%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
Unknown	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Conversion to open*					
Yes	3 (13.0%)	3 (13.0%)	0 (0.0%)	5 (20.0%)	11 (11.6%)
No	19 (82.6%)	20 (87.0%)	24 (100.0%)	20 (80.0%)	83 (87.4%)
Unavailable	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Procedure					
Ileo-caecal resection	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (4.0%)	2 (2.1%)
Right hemicolectomy	6 (25.0%)	8 (33.3%)	9 (37.5%)	8 (32.0%)	31 (32.0%)
Ext right hemicolectomy	4 (16.7%)	1 (4.2%)	3 (12.5%)	3 (12.0%)	11 (11.3%)
Transverse colectomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Left hemicolectomy	4 (16.7%)	3 (12.5%)	1 (4.2%)	2 (8.0%)	10 (10.3%)
Sigmoid colectomy	3 (12.5%)	1 (4.2%)	0 (0.0%)	5 (20.0%)	9 (9.3%)
Anterior resection	6 (25.0%)	10 (41.7%)	10 (41.7%)	6 (24.0%)	32 (33.0%)
Other	0 (0.0%)	0 (0.0%)	1 (4.2%) Ψ	0 (0.0%)	1 (1.0%)
Unavailable	1 (4.2%) Ω	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Anastomosis					
Handsewn	2 (8.3%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	3 (3.1%)
Stapled	21 (87.5%)	24 (100.0%)	22 (91.7%)	23 (92.0%)	90 (92.8%)
No anastomosis	0 (0.0%)	0 (0.0%)	1 (4.2%)	2 (8.0%)	3 (3.1%)
Unavailable	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Unplanned stoma	0 (0.0%)	2 (8.3%)	3 (12.5%)	3 (12.0%)	8 (8.2%)
Duration of surgery (mins)	203 (64)	166 (55)	195 (51)	191 (73)	190 (62)
Spinal analgesia					
Yes – with opioid	16 (66.7%)	17 (70.8%)	19 (79.2%)	22 (88.0%)	74 (76.3%)
Yes – no opioid	1 (4.2%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	2 (2.1%)
No	6 (25.0%)	7 (29.2%)	4 (16.7%)	3 (12.0%)	20 (20.6%)
Unknown	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Intra-operative NGT	0 (0.0%)	1 (4.2%)	1 (4.2%)	0 (0.0%	2 (2.1%)

*Categorical variables expressed as rates (%); continuous variables expressed as mean (SD); *Values exclude n=2 participants (Group 1: n=1; Group 2: n=1) whose surgery started open; Ψ Abandoned procedure without resection; Ω Surgery postponed beyond closure date of study; ASA: American Society of Anesthesiologists; NGT: Nasogastric tube*

3.3.3. Screening and eligibility assessment

Of 340 patients screened,129 (37.9%) did not meet the eligibility criteria and were excluded. Common reasons included a history of cardiac dysrhythmia (n=53/129; 41.1%), cerebrovascular disease (n=31/129; 24.0%), and seizures or recurrent episodes of syncope (n=9/129; 7.0%). Of the remaining 211 eligible patients, a further 86 (86/211; 40.8%) were excluded. The most common reasons were insufficient time to initiate the treatment prior to surgery (n=36/86; 41.9%), barriers to co-enrolment (n=34/86; 39.5%), and discretionary exclusions relating to patients' capacity to consent (n=12; 14.0%). The majority of co-enrolment barriers were due to exclusions set by other studies (n=25/36; 69.4%). A full outline of screening is provided in Table 3.9.

Table 3.9 – Summary of participant screening

Reason for exclusion		N (%)
Excluded at Screening (n=129)	Cardiac dysrhythmia (2° or 3° AV block, AF, VF, VT)	53 (41.1%)
	Cerebrovascular accident or transient ischaemic attach	31 (24.0%)
	Seizures or recurrent syncope in the last 5 years	9 (7.0%)
	Belonging to a vulnerable group	9 (7.0%)
	Existing intestinal stoma	7 (5.4%)
	Implanted electrical device	5 (3.9%)
	Myocardial infarction (NSTEMI/STEMI in the last 12 months)	4 (3.1%)
	Neuroendocrine tumour	3 (2.3%)
	Neck anatomy that distorts self-administration	3 (2.3%)
	Previous vagotomy	2 (1.6%)
	Inflammatory bowel disease	2 (1.6%)
	Heart failure with NYHA grade greater than II	1 (0.8%)
	Pregnant or nursing during the course of the study	0 (0.0%)
Excluded pre-Approach (n=86)	Insufficient time to start intervention schedule prior to surgery	36 (41.9%)
	Patient recruited to another study where co-enrolment was precluded	34 (39.5%)
	Clinician/research team discretion not to approach	12 (14.0%)
	Language barrier without resources precluded approach and consent	4 (4.7%)

AF: Atrial fibrillation/flutter; AV: Atrio-ventricular; NSTEMI: Non-ST-elevated myocardial infarction; STEMI: ST-elevated myocardial infarction; NYHA: New York Heart Association; VF: Ventricular fibrillation; VT: Ventricular tachycardia

At SJUH, recruitment was open for 21 out of 24 months and temporarily suspended for the remaining 3 months due to disruptions caused by the COVID-19 pandemic. The proportion of patients who were considered to be eligible each month ranged from 33.3%

to 80.0%. Since this surpassed the feasibility threshold of 20%, it represented a "Progress" outcome for each of the 21 months of recruitment according to the prospective progression criteria. At BRI, recruitment was open for 14 months and temporarily suspended for 10 months due to the COVID-19 pandemic. The proportion of patients who were confirmed to be eligible each month ranged from 0.0% to 100%. For 13 out of 14 months, the proportion of eligible patients surpassed 20%, representing a "Progress" outcome according to the prospective progression criteria (Table 3.10).

Table 3.10 – Summary of participant eligibility assessment

		St. James's University Hospital (SJUH)			Bradford Royal Infirmary (BRI)		
Month		Screened (n=276)	Eligible (n=176)		Screened (n=64)	Eligible (n=35)	
1	Jan-20	25	13 (52.0%)	(P)	7	3 (42.9%)	(P)
2	Feb-20	22	12 (54.5%)	(P)	1	1 (100.0%)	(P)
3	Mar-20	9	5 (55.6%)	(P)	1	1 (100.0%)	(P)
4	Apr-20	Suspended	N/A	-	Suspended	N/A	-
5	May-20	Suspended	N/A	-	Suspended	N/A	-
6	Jun-20	Suspended	N/A	-	Suspended	N/A	-
7	Jul-20	14	7 (50.0%)	(P)	Suspended	N/A	-
8	Aug-20	9	3 (33.3%)	(P)	Suspended	N/A	-
9	Sep-20	9	6 (66.7%)	(P)	4	2 (50.0%)	(P)
10	Oct-20	11	8 (72.7%)	(P)	Suspended	N/A	-
11	Nov-20	16	9 (56.3%)	(P)	Suspended	N/A	-
12	Dec-20	14	10 (71.4%)	(P)	Suspended	N/A	-
13	Jan-21	11	7 (63.6%)	(P)	Suspended	N/A	-
14	Feb-21	8	5 (62.5%)	(P)	Suspended	N/A	-
15	Mar-21	13	10 (76.9%)	(P)	3	1 (33.3%)	(P)
16	Apr-21	15	12 (80.0%)	(P)	2	0 (0.0%)	(S)
17	May-21	11	7 (63.6%)	(P)	4	3 (75.0%)	(P)
18	Jun-21	14	7 (50.0%)	(P)	6	4 (66.7%)	(P)
19	Jul-21	12	9 (75.0%)	(P)	7	5 (71.4%)	(P)
20	Aug-21	10	8 (80.0%)	(P)	6	3 (50.0%)	(P)
21	Sep-21	16	11 (68.8%)	(P)	7	4 (57.1%)	(P)
22	Oct-21	11	7 (63.6%)	(P)	6	3 (50.0%)	(P)
23	Nov-21	13	10 (76.9%)	(P)	8	4 (50.0%)	(P)
24	Dec-21	13	10 (76.9%)	(P)	2	1 (50.0%)	(P)

BRI: Bradford Royal Infirmary; N/A: Not applicable; SJUH: St. James's University Hospital; (P) indicates a "Progress" feasibility outcome (i.e. >20% of screened patients eligible) and (S) indicates a "Stop" feasibility outcome (i.e. <10% of screened patients eligible), as per the prospective progression criteria. "Suspended" indicates months during which recruitment was suspended due to the COVID-19 pandemic.

3.3.4. Approach and consent

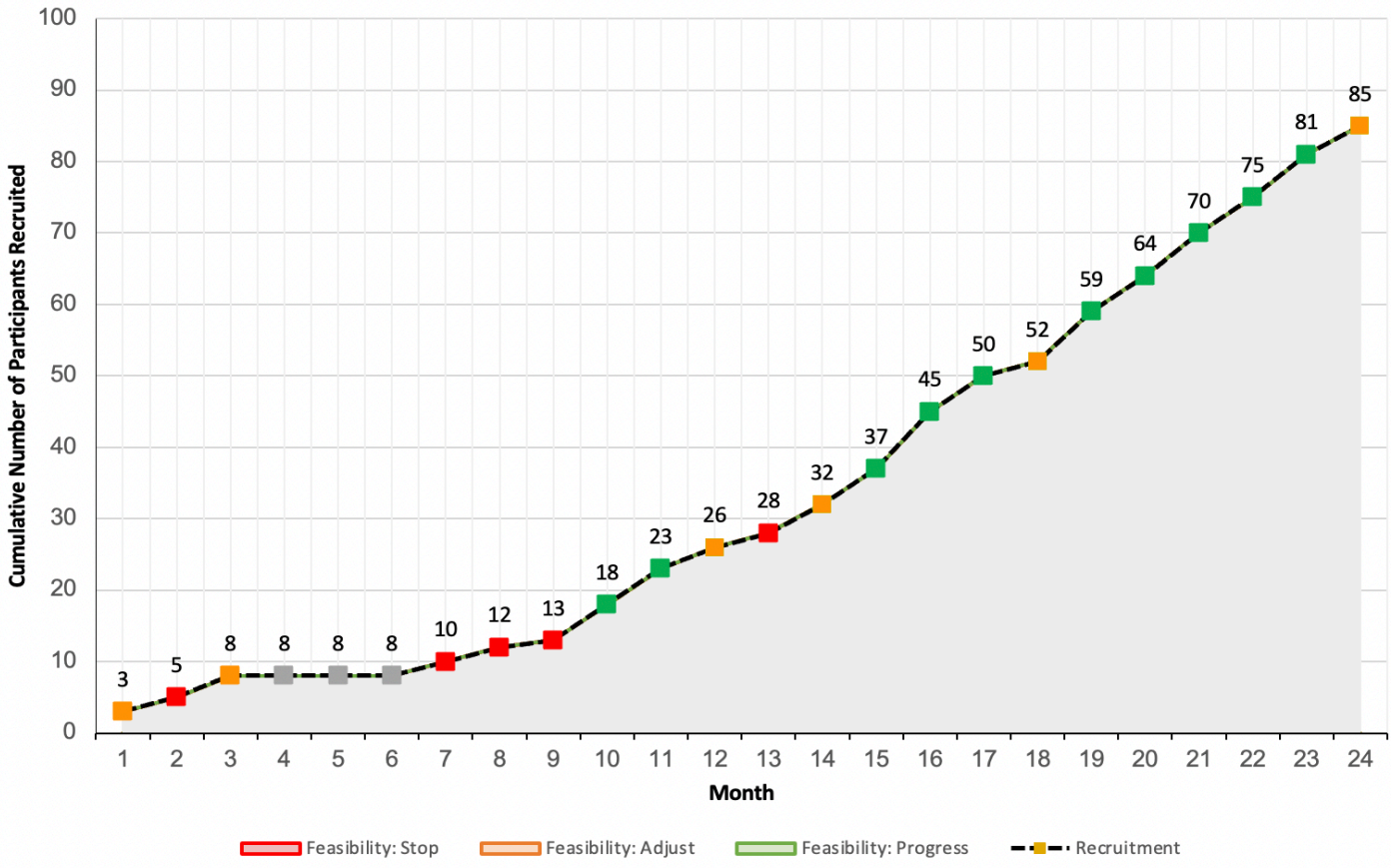
Of 125 patients approached to take part, 97 (n=97/125; 77.6%) provided consent, including 85 from SJUH and 12 from BRI. The remaining 28 declined, most commonly due to concerns about treatment burden (n=14/28; 50.0%) and the feeling of being too unwell to take part (n=3/28; 10.7%) (Table 3.11). At SJUH, the median number of participants randomised per month was 4 (IQR: 2-5; range 1-8). Across 21 months of recruitment, five triggered a “Stop” feasibility outcome (≤2 randomisations per month), six triggered a “Modify” outcome (3-4 randomisations per month), and ten triggered a “Progress” outcome (≥5 randomisations per month). The majority of “Stop” outcomes were observed during the early months of recruitment and immediately following the temporary suspension. The number of randomisations increased during the latter months, with eight of the final ten months triggering a “Progress” outcome (Figure 3.5).

Table 3.11 – Summary of reasons for participant declining consent

Reason for declined consent	Total (n=28)
Patient felt too overburdened with clinical treatment	14 (50.0%)
Patient was not contactable after approach to confirm participation	3 (10.7%)
Patient considered him/herself too ill to take part	3 (10.7%)
Patient was concerned about possible side-effect of the intervention	2 (7.1%)
Patient was not interested in taking part in research	1 (3.6%)
Participant did not feel confident with self-administering the device	1 (3.6%)
Travel burden/time precluded enrolment	1 (3.6%)
No reason given	3 (10.7%)

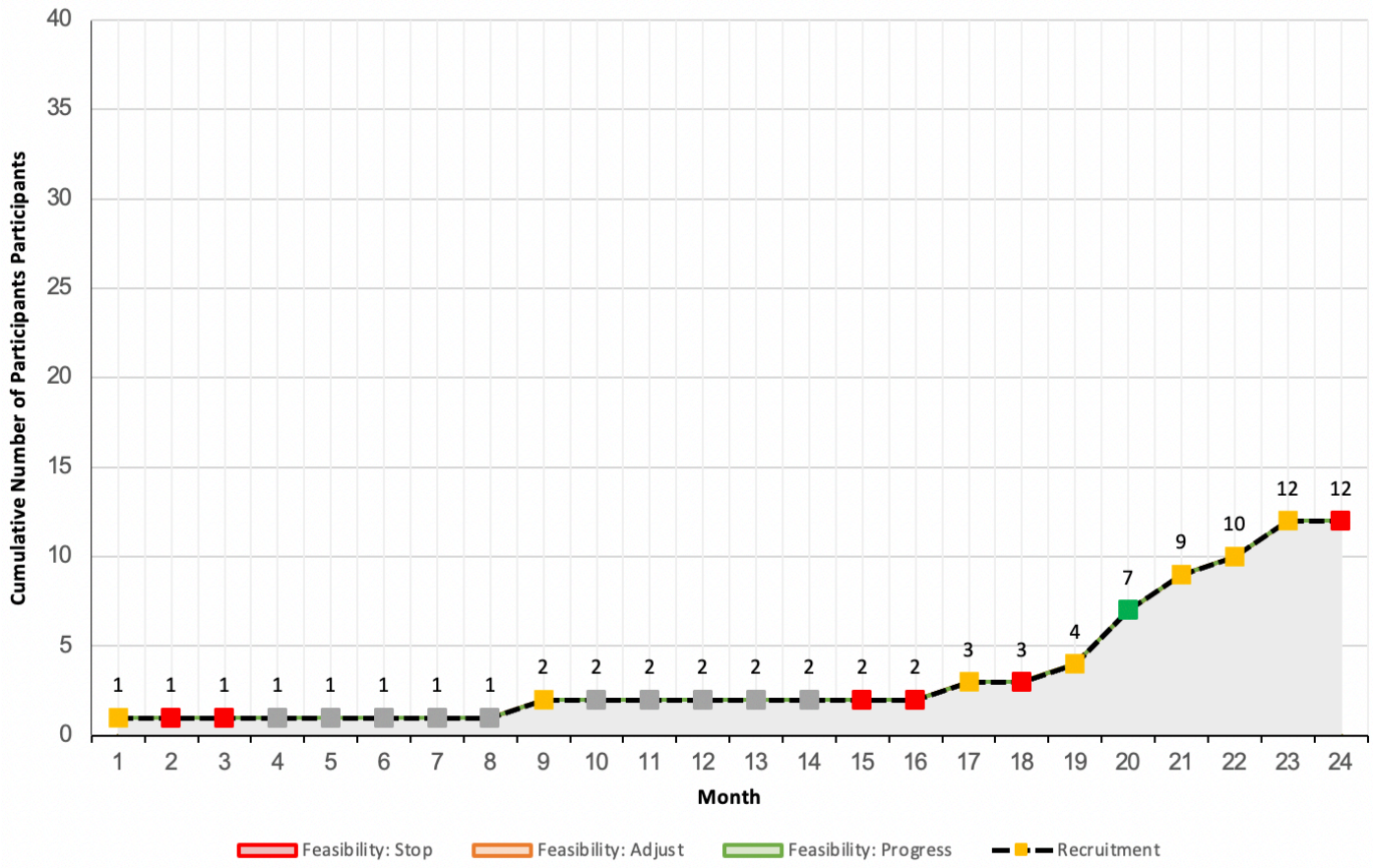
At BRI, the median number of participants recruited per month was 1 (IQR: 0-1; range 0-3). Across 14 months of recruitment, five triggered a “Stop” outcome (<1 randomisation per month), six triggered a “Modify” outcome (1-2 randomisations per month), and one triggered a “Progress” outcome (>3 randomisations per month). Similar to SJUH, the rate of randomisation was slower during the early months of recruitment. This increased during the latter months, with the majority of “Modify” and “Progress” outcomes occurring during the final ten months of uninterrupted recruitment (Figure 3.6).

Figure 3.5 – Cumulative participant recruitment chart for St. James's University Hospital, Leeds, UK



Red, amber, and green squares indicate monthly recruitment outcomes according to the prospective progression criteria (Progress, Modify, and Stop, respectively) for St. James's University Hospital. Grey squares indicate months during which recruitment was temporarily suspended due to the COVID-19 pandemic

Figure 3.6 – Cumulative participant recruitment chart for Bradford Royal Infirmary, Bradford, UK



Red, amber, and green squares indicate monthly recruitment outcomes according to the prospective progression criteria (Progress, Modify, and Stop, respectively) for Bradford Royal Infirmary. Grey squares indicate months during which recruitment was temporarily suspended due to the COVID-19 pandemic

3.3.5. Adequacy of participant blinding

A total of 96 out of 97 (99.0%) participants completed the blinding assessment. Participant blinding in Group 1 (preoperative stimulation; postoperative stimulation) and Group 4 (preoperative sham; postoperative sham) triggered "Modify" outcomes with a BI_m of 0.40 and -0.27, respectively. This contrasted with Group 2 (preoperative stimulation; postoperative sham) and Group 3 (preoperative sham; postoperative stimulation), which both triggered "Stop" outcomes, with a BI_m of 0.67 and 0.84, suggesting a high level of unblinding across both of these groups (Table 3.12).

Table 3.12 – Assessment of blinding

	Guess Group1	Guess Group2	Guess Group3	Guess Group4	Average of incorrect guesses ($\overline{n_a}$)	Total responses	BI_m
$Assigned_{Group1}$	**10**	7	3	3	4.33 (Groups: 2,3,4)	23*	0.40
$Assigned_{Group2}$	1	**15**	5	3	3.00 (Groups: 1,3,4)	24	0.67
$Assigned_{Group3}$	3	2	**19**	0	1.67 (Groups: 1,2,4)	24	0.84
$Assigned_{Group4}$	7	8	6	**4**	7.00 (Groups: 1,2,3)	25	-0.27

Group1: Preoperative Stimulation/Postoperative Stimulation; Group2: Preoperative Stimulation/Postoperative Sham; Group3: Preoperative Sham/Postoperative Stimulation; Group 4: Preoperative Sham/Postoperative Sham; BI_m: modified blinding index; and $\overline{n_a}$: average incorrect guesses across all other groups, as per the Method (3.2.10)
** A total of 23 out of 24 participants entered the analysis, with one participant lost to follow up*

3.3.6. Compliance to study treatment

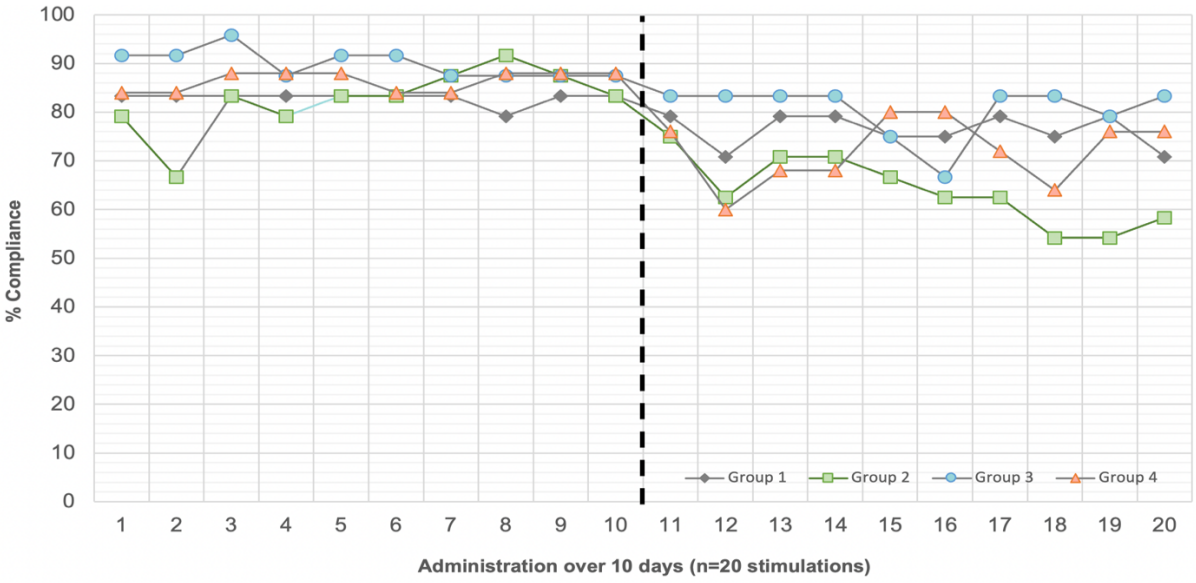
Across all groups, the median self-reported compliance to the study treatment was 19 out of 20 stimulations (IQR: 17-20), with a median preoperative compliance of 10 out of 10 (IQR; 10-10) and a median postoperative compliance of 10 out of 10 (IQR 8-10). Since this surpassed the feasibility threshold of 16 out of 20 stimulations over 10 days, it represented a "Progress" outcome according to the prospective progression criteria.

Compliance within each of the intervention groups was broadly similar, with median compliances of 20 (IQR 17-20), 17 (13-20), 19 (18-20), and 20 (19-20) for Groups 1-4 respectively. Across all groups, compliance was marginally higher during the

preoperative period (median 10; IQR 10-10) compared to the postoperative period (median 10; IQR 8-10). The largest decline in compliance was observed in Group 4 (preoperative sham; postoperative sham), which occurred early during the postoperative period and then recovered. A similar decrease was observed in Group 2 (preoperative stimulation; postoperative sham) but this was sustained throughout the postoperative period and did not recover to its preoperative baseline (Figure 3.7).

When considered across all groups, the median amplitude setting for active and sham devices was 27 (IQR: 20-33) and 30 (IQR: 25-40), respectively.

Figure 3.7 – Device compliance over time across intervention groups



Dashed line represents time of surgery and thus divides pre- and postoperative administration periods

3.3.7 Loss to follow up

Overall, one participant (n=1/97; 1.0%) was lost to follow-up. This occurred in Group 1 (preoperative stimulation; postoperative stimulation) and was due to cancellation of the participant's surgery which surpassed the pre-planned closure date of the trial.

The rate of loss-to-follow up was lower than the feasibility rate of 15% and so this represented a “Progress” outcome according to the prospective progression criteria.

3.3.8. Missing data

Across all predefined clinical outcomes, the rate of missing data measured at 6 monthly intervals and at the end of the trial was 0% (Table 3.13). This was lower than the feasibility rate of 15% and so represented a “Progress” outcome according to the prospective progression criteria. The final rate of missing data across most other individual data variables was also 0% (Appendix A-3.8). The highest rates were observed for the variables: baseline serum albumin (22.7%) and eGFR (11.3%). These were missing either because the samples were not collected as part of routine practice or because samples were collected outside of the predefined reference timeframe of 30 days prior to surgery. No changes were made to the approach used to collect data in light of the interim 6 monthly assessments.

Table 3.13 – Summary of missing data for predefined clinical outcomes

Data Variable		Expected data availability*	Actual data availability	Missing data
Predefined clinical outcome data				
	Time to first passage of flatus	n=96/97 (99.0%)	n=96/96 (100.0%)	0 (0.0%)
	Time to first passage of stool	n=96/97 (99.0%)	n=96/96 (100.0%)	0 (0.0%)
	Time to tolerate oral intake	n=96/97 (99.0%)	n=96/96 (100.0%)	0 (0.0%)
	Time to GI-2 outcome Ψ	n=96/97 (99.0%)	n=96/96 (100.0%)	0 (0.0%)
	Need for insertion of nasogastric tube	n=96/97 (99.0%)	n=96/96 (100.0%)	0 (0.0%)
	Total length of inpatient hospital stay	n=96/97 (99.0%)	n=96/96 (100.0%)	0 (0.0%)

**Data for one participant not expected due to loss to follow up as a result of surgery being cancelled; Ψ GI-2: A composite outcome comprising time to first tolerance of oral intake and passage of first stool*

3.3.9. Safety and adverse events

Overall, postoperative complications were observed in 46 of 97 (47.4%) participants. This included 10 in Group 1 (n=10/24; 41.7%), 12 in Group 2 (n=12/24; 50.0%), 12 in

Table 3.14 – Summary of device-related adverse events and postoperative complications

	Group 1: Stim/Stim (n=24)	Group 2: Stim/Sham (n=24)	Group 3: Sham/Stim (n=24)	Group 4: Sham/Sham (n=25)	Total (n=97)
Device-related adverse events					
Headache	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (4.0%)	2 (2.1%)
Stimulation site pain	0 (0.0%)	1 (4.2%)	2 (8.3%)	0 (0.0%)	3 (3.1%)
Tooth pain	0 (0.0%	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (1.0%)
Neck strain	0 (0.0%)	1 (4.2%)	1 (4.2%)	1 (4.0%)	3 (3.1%)
Hoarseness/change in voice	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dry mouth/change in taste	0 (0.0%)	1 (4.2%)	1 (4.2%)	0 (0.0%)	2 (2.1%)
Skin irritation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (1.0%)
Postoperative complications					
Acute coronary syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acute kidney injury	2 (8.3%)	1 (4.2%)	1 (4.2%)	0 (0.0%)	4 (4.1%)
Anastomotic leak	1 (4.2%)	1 (4.2%)	1 (4.2%)	1 (4.0%)	4 (4.1%)
Cardiac arrythmia	1 (4.2%)	3 (12.5)	1 (4.2%)	0 (0.0%)	5 (5.2%)
Cerebrovascular accident	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Postoperative collection	2 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
Pneumonia	5 (20.8%)	1 (4.2%)	1 (4.2%)	0 (0.0%)	7 (7.2%)
Surgical site infection	3 (12.5%)	5 (20.8%)	7 (29.2%)	3 (12.0%)	18 (18.6%)
Urinary tract infection	0 (0.0%)	1 (4.2%)	2 (8.3%)	1 (4.0%)	4 (4.1%)
Venous access infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Venous thrombo-embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (1.0%)
Other					
Electrolyte disturbance*	1 (4.2%)	0 (0.0%)	1 (4.2%)	1 (4.0%)	3 (3.1%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (1.0%)
Loose stools	0 (0.0%)	1 (4.2%)	1 (4.2%)	4 (16.0%)	6 (6.2%)
Omental infarct	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Pleural effusion	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Rectal bleeding	2 (8.3%)	2 (8.3%)	0 (0.0%)	1 (4.0%)	5 (5.2%)
Splenic infarct	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Vaso-vagal syncope	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (1.0%)
Surgical site bleeding Ψ	0 (0.0%)	2 (8.3%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
Wound dehiscence	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (4.0%)	2 (2.1%)
Unplanned critical care	2 (8.3%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	3 (3.1%)
Unplanned readmission	0 (0.0%)	3 (12.5%)	2 (8.3%)	0 (0.0%)	5 (5.2%)
Clavien-Dindo Classification					
Grade 1-2	9 (37.5%)	12 (50.0%)	12 (50.0%)	11 (44.0%)	44 (45.4%)
Grade 3-4	3 (12.5%)	0 (0.0%)	1 (4.2%)	2 (8.0%)	6 (6.2%)
Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

**Includes hypokalaemia (n=2) and hypophosphataemia (n=1); Ψ Includes wound site (n=1) and peristomal bleeding (n=1)*

Group 3 (n=12/24; 50.0%), and 12 in Group 4 (n=12/25; 48.0%). The largest absolute per cent difference between Group 4 (control) and any other treatment group was 2%, representing a “Progress” feasibility outcome according to the progression criteria. The most common types of complication were surgical site infection (n=18/97; 18.6%),

postoperative pneumonia (n=7/97; 7.2%), and loose stools after surgery (n=6/97; 6.2%). No deaths occurred within 30 days of surgery. A total of three participants had unplanned admissions to critical care (Group 1: n=2; Group 4: n=1) and five were readmitted to hospital after discharge (Group 2: n=3; Group 3: n=2) (Table 3.14).

Device-related adverse events were infrequent, with neck strain (n=3/97; 3.1%) and stimulation site pain (n=3/97; 3.1%) occurring most commonly. Others included headache (n=2/97; 2.1%), tooth pain (n=1/97; 1.0%), dry mouth or change in taste (n=2/97; 2.1%), and skin irritation over the stimulation site (n=1/97; 1.0%). The incidences of these events were well balanced across groups.

3.3.10. Variability in clinical outcome measures

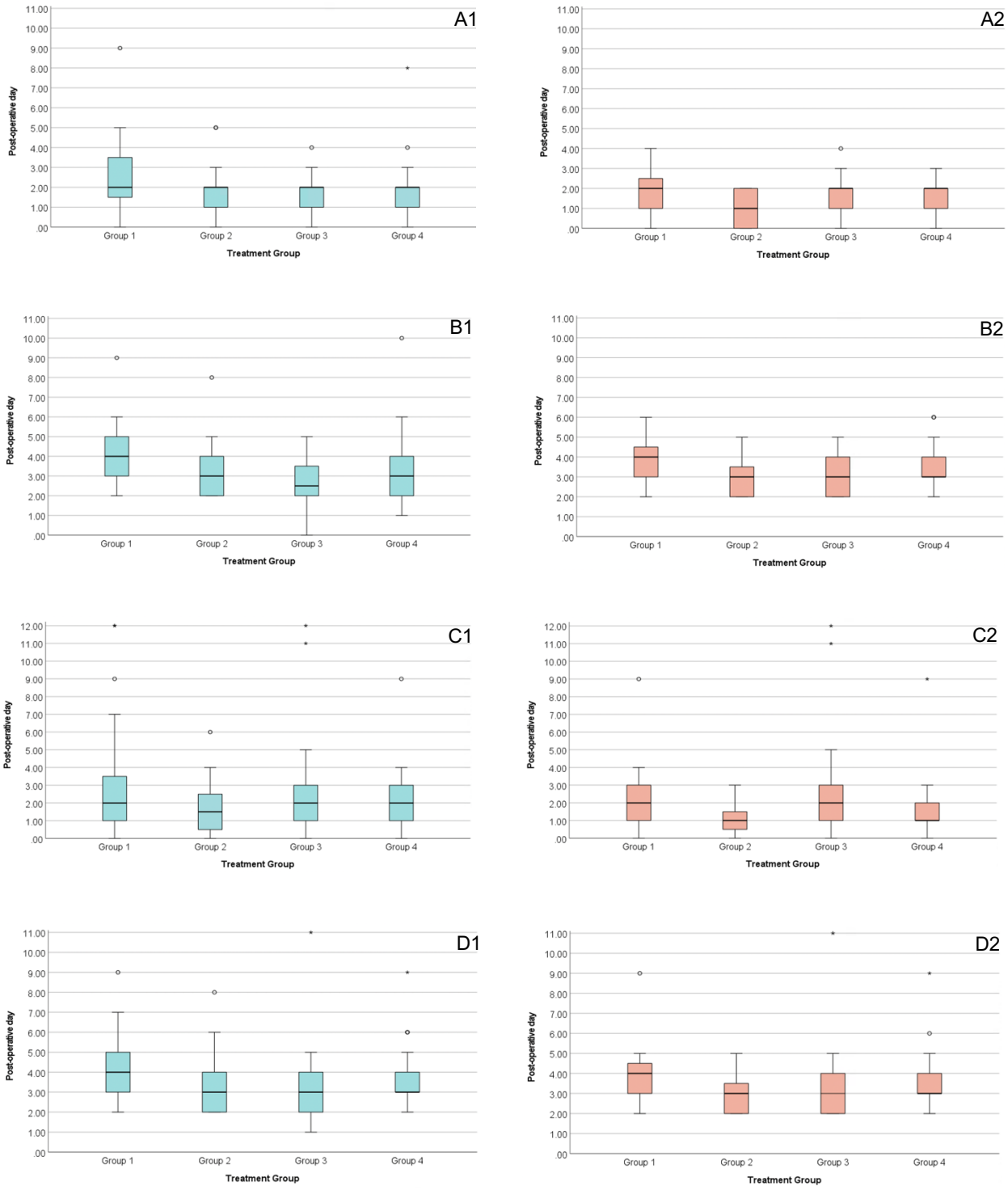
In the intention-to-treat population (n=97), the median time (days) to the first passage of flatus was 2 (IQR: 1.5-3.5), 2 (IQR: 1-2), 2 (IQR: 1-2), and 2 (IQR: 1-2) and the median time (days) to first passage of stool was 4 (IQR: 3-5), 3 (IQR: 2-4), 2.5 (IQR: 2-3.5), and 3 (2-4), for Groups 1 to 4, respectively. The median time (days) to tolerate oral diet was 2 (IQR: 1-3.5), 1.5 (IQR: 0.5-2.5), 2 (IQR: 1-3), and 2 (1-3) and the time (days) taken to achieve gastrointestinal recovery (GI-2) was 4 (IQR: 3-5), 3 (IQR: 2-4), 3 (IQR: 2-4), and 3 (3-4), for Groups 1 to 4 respectively. A total of 18 (n=18/97; 18.6%) participants required insertion of a nasogastric tube after surgery, including eight (n=8/24; 33.3%) in Group 1, four (n=4/24; 16.7%) in Group 2; four (n=4/24; 16.7%) in Group 3, and two (n=2/25; 8.0%) in Group 4. The median length of postoperative hospital stay was 6 (IQR: 4.5-10), 5 (IQR: 3.75-8), 6 (IQR: 3.75-8), and 4 (IQR: 3-6) days for participants in Groups 1-4 respectively. Similar variation in clinical outcomes was observed in the per-protocol population (n=56) and is shown in Figure 3.8. A full description of raw clinical outcome data is provided in Table 3.15.

Table 3.15 – Description of clinical outcome data

	Group 1: Stim/Stim (n=24)	Group 2: Stim/Sham (n=24)	Group 3: Sham/Stim (n=24)	Group 4: Sham/Sham (n=25)	Total (n=97)
Time to first flatus (days)					
Mean	2.61	1.79	1.58	1.83	2.01
Median	2	2	2	2	2
Mode	2	2	2	2	2
Interquartile range	1.5-3.5	1-2	1-2	1-2	1-2
Range	0-9	0-5	0-4	0-4	0-9
Time to first passage of stool (days)					
Mean	4.52	3.13	2.67	3.29	3.46
Median	4	3	2.5	3	3
Mode	4	2	2	3	2
Interquartile range	3-5	2-4	2-3.5	2-4	2-4
Range	2-13	2-8	0-5	1-6	0-13
Time to tolerate oral intake (days)					
Mean	3.35	1.67	2.71	2.04	2.56
Median	2	1.5	2	2	2
Mode	1	2	1	1	1
Interquartile range	1-3.5	0.5-2.5	1-3	1-3	1-3
Range	0-12	0-6	0-12	0-9	0-15
Time to GI2 outcome (days)					
Mean	4.87	3.38	3.54	3.63	3.96
Median	4	3	3	3	3
Mode	4	2	3	3	3
Interquartile range	3-5	2-4	2-4	3-4	2-4
Range	2-13	2-8	1-12	2-9	1-15
Total length of inpatient hospital stay (days)					
Mean	4.75	6.54	5.58	9.35	6.81
Median	4	6	5	6	5
Mode	4	3	4	5	3
Interquartile range	3-5.25	3.75-8	3.75-8	4.5-10	4-8
Range	2-12	1-15	0-12	3-30	0-30

Data are summarised from the Intention-to-treat population (n=97)

Figure 3.8 – Clinical outcomes across treatment groups



A1-2: Time to first flatus (days); B1-2: Time to first stool (days); C1-2: Time to tolerate oral diet (days); D1-2: Time to gastrointestinal recovery (GI-2) (days). Analyses were performed on intention-to-treat (green) and per-protocol (orange) populations, respectively. Group 1: Preoperative stimulation, postoperative stimulation; Group 2: Preoperative stimulation, postoperative sham; Group 3: Preoperative sham, postoperative stimulation; Group 4: Preoperative sham, postoperative sham.

3.4. Discussion

3.4.1. Summary of findings

This study explored the feasibility of a definitive RCT of self-administered vagus nerve stimulation to reduce ileus after colorectal surgery. The feasibility of recruitment was clearly demonstrated, with a large pool of patients considered to be eligible and a satisfactory number agreeing to be randomised. Some disruption to recruitment occurred due to the COVID-19 pandemic, affecting the rates of approach and consent at both study sites. This was addressed successfully by introducing a revised approach to remote consent. Patients reported high compliance to the study treatment according to self-reported diaries, suggesting that self-administration was possible before surgery (at home) and after surgery (in hospital). Throughout the study, only one patient was lost to follow up and there were no missing clinical outcome data, indicating that data collection was feasible alongside clinical care. In contrast, blinding of participants to the study treatment was challenging and the results showed clear evidence of unblinding. In some treatment groups (Groups 2 and 3), the degree of unblinding triggered a “Stop” outcome, indicating that blinding within the present design was not feasible. Possible solutions were appraised and it was considered that alternative approaches to blinding would be required along with a re-assessment of feasibility if these groups were to remain in the final study design. In the other treatment groups (Groups 1 and 4), where the same types of devices were used before and after surgery, the rate of unblinding was less and was considered to be potentially feasible. Finally, the rates of postoperative complications between groups were similar, representing a “Progress” feasibility outcome. These added to previous evidence describing an acceptable safety profile across broad clinical settings (99, 195). A summary of feasibility findings is shown in Table 3.16.

Table 3.16 – Summary of feasibility findings

Criteria	Outcome
Proportion of eligible patients identified from screening logs	Progress
Number of eligible patients randomised over 24 months (site: SJUH)	Progress
Number of eligible patients randomised over 24 months (site: BRI)	Modify
Adequacy of participant blinding (Bang Blinding Index)	Stop
Average compliance to the study treatment schedule	Progress
Proportion of randomised patients lost to follow up	Progress
Proportion of missing clinical outcome data	Progress
Incidence of complications or serious complications	Progress

3.4.2. Interpretation

This assessment of feasibility was necessary to define and address possible challenges for the successful completion of a definitive RCT. Firstly, the study aimed to recruit a complex population of patients undergoing major surgery for bowel cancer and other intestinal diseases. It was important to consider barriers to recruitment, such as the impact of physical and emotional burden, which have challenged the success of recruitment in previous trials with similar patient populations (196). Secondly, as a self-administered treatment it was important to explore whether participants would comply to the treatment schedule as planned. Previous research has shown that patients seek autonomy and empowerment in their hospital care but this may be challenging to achieve in acute settings such as major surgery (197). Finally, it was important to consider the role of blinding and whether this could be feasibly operationalised. Previous research has advocated strongly for the use of sham-controlled interventions in neuromodulation studies, but concerns have been expressed about the feasibility of delivering these with sufficiently robust blinding procedures (198).

Whilst recruitment to the study was shown to be feasible, it was necessary to adapt the pre-planned recruitment strategy in response to the COVID-19 pandemic. This was achieved by working closely with public representatives to develop a two-step process

for telephone consent rather than obligating a face-to-face consultation. The new process enabled recruitment to continue successfully despite logistical barriers brought about by social distancing rules. Conversely, it meant that the feasibility of the pre-planned face-to-face strategy could not be evaluated as intended. Previous evidence has shown that remote and telephone consent improves participant recruitment due to reduced travel, time, and cost barriers (199). As such, it would be important for a future RCT to offer both approaches for consent to ensure that the present findings remain transferable. This would strengthen a future study by offering potential participants a choice according to what aligns with their personal circumstances. Whilst telephone consent is not used widely in interventional research, previous work has set out a clear role for its use in trials that are low risk. Key benefits include greater efficiency for investigators and improved convenience for participants, whilst challenges include barriers to communication and a risk of appealing to a selected population (200).

Compliance to the study treatment was shown to be readily feasible in this study but tended to decline during the early postoperative period. The reason for this cannot be drawn from the feasibility data alone, however, it might be speculated that this related to challenges of self-administration whilst participants were burdened by pain, nausea, and drowsiness. These data provide useful insights about periods of time during which participants may benefit from additional support to administer the device. Possible solutions include prompt cards, verbal or visual cues, positive reinforcement from the investigators, or direct assistance from the clinical team (201). This must be balanced carefully, however, to ensure that participants retain autonomy to self-administer the device themselves. Previous research has demonstrated an important role for empowering patients to take an active role in their recovery, which may lead to broader gains in confidence, motivation, and other aspects of recovery (197).

There was clear evidence of unblinding during the study, which was most prominent in the treatment groups which exposed participants to both active and sham devices (i.e., Group B: preoperative active, postoperative sham; and Group C: preoperative sham, postoperative active). In contrast, the treatment groups comprising the same study treatment throughout (i.e., Group A: preoperative active; postoperative active; and Group D: preoperative sham; postoperative sham) performed better albeit still demonstrating some evidence of unblinding. Whilst the cause of unblinding cannot be confirmed from these data alone, it may be speculated that participants were unblinded due to unanticipated differences between devices. Both devices had the same visual appearance and feedback but it is possible that the user experience was unique and this may have been apparent to some users during their participation. These findings show that a blinded study comprising of Groups B and C would not be feasible but one comprising of Groups A and D may be feasible with an optimised approach to blinding. Previous research involving neuromodulation interventions have explored various types of sham intervention, such as inactive devices, planned misplacement, or adjustments to stimulation parameters (such as frequency and amplitude) to produce an ineffective stimulus (198). These may offer a solution to improve blinding but would need to be further assessed for feasibility prior to being operationalised in a future definitive RCT.

Finally, the collection of clinical data was shown to be readily feasible in this study with no missing data recorded for any of the measured clinical outcomes. Whilst this represented a “Progress” feasibility outcome, it may have been facilitated in part by simple logistics associated with a small study. In a definitive trial recruiting across a much larger number of clinical sites, it would be important to plan for some proportion of missing primary outcome data and participant attrition. This would inform adjustments to the final sample size and would mitigate against unexpected underpowering.

3.4.3. Justification for study design

As a feasibility study, a number of methodological design features were explored to enable a constructive assessment. Firstly, the study used an external pilot design to explore whether key components of a definitive trial were possible in the future. This differs from an internal pilot design, which usually represents the first part of a definitive trial and provides little scope for changes once the study begins (202). The choice of an external pilot in this setting was appropriate as there was a notable level of uncertainty around randomisation, device compliance, and data completeness. It was important to retain sufficient flexibility to learn from these feasibility findings and to adapt aspects of the method in light of unknown challenges. Secondly, the study comprised four randomised arms with permutations of active and sham stimulation. This enabled an assessment of blinding applicable to several possible designs of RCT, including parallel and factorial designs. Parallel trials are designed to answer a single question whilst factorial trials explore two or more questions by examining combinations of interventions or doses (203). This approach was considered appropriate as some earlier evidence supports the role of pre- and post-operative vagus nerve stimulation as a way to reduce ileus. A factorial design would enable this efficiently within the scope of a single trial. The findings, however, showed that blinding participants to a combination of devices was not feasible due to tactile differences between both types of devices. This provides evidence against a factorial design but still supports a possible parallel design in which devices are not used in combination.

3.4.4. Limitations

Several limitations of this study are recognised and should be considered when interpreting the findings. Firstly, recruitment to the study was limited to two NHS

hospitals in the North of England. These were selected to introduce wider variation and to broaden the generalisability of the feasibility findings. It is unlikely, however, that the findings are generalisable to all NHS hospitals and unknown residual barriers to feasibility may still persist in a future definitive RCT. These can be explored further in an internal pilot phase to confirm whether study processes that are known to be feasible in principle can be delivered at scale. Whilst major changes to the protocol would not be possible during or after an internal pilot, it would provide an opportunity for learning and minor adjustments prior to rolling out recruitment more widely. Secondly, the findings of this study showed that the procedures used to blind participants to the intervention were not feasible with the present study design. In other settings, the importance of blinding in neuromodulation studies has been well documented owing to statistically significant improvements in clinical outcomes seen with sham interventions (198). It was not possible to adapt the blinding procedures and re-assess their feasibility within the scope of the present study. This would have provided an opportunity to interrogate deficiencies in the blinding procedure and to explore whether different stimulation parameters (such as peak voltage and current) would offer a viable solution for improved blinding. Other approaches may have included placement of the device over the sternocleidomastoid muscle as a way to reduce or prevent stimulation of the vagus nerve whilst still leading participants to believe that they were administering the treatment appropriately. These considerations remain important prior to a definitive RCT in the future. Finally, although participants reported high compliance with the device, the findings did not necessarily confirm that they were competent at administering it effectively. This assumption was drawn from previous research confirming that administration of the gammaCore device successfully stimulates the vagus nerve and that patients are able to administer it competently with a comparable schedule of training (169,170,204). The study treatment

has been used in several clinical settings in the past, including patients treated for migraine, cluster headache, gastroparesis, and chronic pain (114). No concerns have been expressed about patients' ability to self-administer the treatment but this remains a possibility in a new and challenging clinical setting.

3.4.5. Further considerations

This study focussed on the feasibility of key aspects of trial delivery, including recruitment, blinding, treatment compliance, and data completeness, amongst others. It was not able to provide explanations for all of the observations seen and neither was it able to propose alternative solutions. Further considerations in the next chapter include an examination of the barriers and facilitators of recruitment, possible mechanisms leading to unblinding, insights into participants' experiences and confidence in self-administering the device, and clinicians' perspectives on possible implementation of the device in everyday NHS practice.

Chapter 4

Acceptability and feasibility of non-invasive vagus nerve stimulation to reduce ileus: interviews with patients and health professionals.

Preface

In this chapter, perspectives from semi-structured interviews with trial participants and healthcare professionals are presented. These explore the acceptability of non-invasive vagus nerve stimulation as a self-administered treatment to reduce ileus after surgery. They also explore the feasibility of a definitive trial by adding important insights to the findings of the earlier randomised feasibility trial. The results and lessons drawn from these data are essential for building a justified argument for or against a future definitive trial as well as guiding necessary adaptations to the method, if necessary.

4.1. Introduction

4.1.1 Patient-administered health interventions

Patient-administered health interventions are components of care that can be delivered independently by patients. These can take place in hospital or at home at a time of their choosing and typically do not involve direct supervision by medical professionals. Common examples include diabetes care, wound management, and urethral self-catheterisation, which are self-managed by patients after a period of dedicated training (205-207). Proposed benefits of patient-administered interventions include better patient experience through self-empowerment and reduced healthcare costs owing to less burden on healthcare staff and resources. In recent times, there has been growing interest in whether other medical procedures that are usually administered by trained medical professionals can be performed safely by patients. Examples of this include home-based haemodialysis and administration of intravenous antibiotics (208).

In 2017, the Institute for Healthcare Improvement (IHI) published its report on patient-administered self-care, describing four components for a successful self-care intervention (208). Firstly, it described that patients must be sufficiently capable and motivated to be involved in their care. This involves health professionals applying appropriate eligibility criteria and ensuring that patients are clinically well enough to engage. Secondly, procedures must be protocolised in such a way that they can be delivered by patients in a consistent manner. Self-administered procedures are typically repetitive, with little or no variation in approach. Thirdly, the surrounding healthcare system should support patients and minimise unnecessary disruptions to their self-care. This may include systems to facilitate rapid access to expert advice and reliable supply chains to ensure availability of equipment. Finally, health professionals must be trained

to empower patients in their self-care and to instil confidence. This requires excellent communication between patients and health professionals as a pre-requisite.

Many initiatives which seek to enable or promote self-care are relevant to patients with long-term and chronic conditions. To date, studies undertaken in these contexts have shown only modest gains in patient benefit. A possible explanation is that many self-care interventions focus solely on the patient, whilst overlooking important considerations that are relevant to health professionals and health systems (209). Examples of these considerations include the necessity of support skills amongst healthcare professionals and funding within systems. It is important that all of these are taken into account in a “whole systems” approach to ensure that self-care interventions are implemented seamlessly into practice and within patients’ everyday lives.

4.1.2 Patient-administered health interventions during recovery after surgery

Enhanced recovery after surgery programmes are collections of evidence-based guidelines which aim to optimise recovery and facilitate early discharge from hospital (4). Whilst the majority of recommendations are focussed on clinician-led interventions, interest is growing in how patients can contribute to their care and take more control of their recovery. Previous evidence has demonstrated that patients undergoing intestinal surgery want to be pro-actively involved in managing their care in order to re-engage quickly and successfully with their everyday lives. A study by Poland and colleagues showed that this can be achieved through providing good patient education, leading to a more situated understanding of their surroundings in hospital (197). Similarly, in a study by Gillis, the importance of patients becoming knowledgeable partners and working alongside health professionals was identified as a key target for improving patients’ experience during their recovery (210).

Previous evidence has identified a small number of opportunities that exist for patients to engage in their care around the time of surgery. In a qualitative study by Short and colleagues, patients undergoing major intestinal surgery took responsibility for guiding and re-introducing nutrition into their diet. Nausea was a problem and patients sought better information on how to manage this to feel more in control (211). In another qualitative study by Taylor, patients explored ways in which they could take control of their recovery at home following early discharge from hospital (212). The role of non-invasive vagus nerve stimulation after intestinal surgery has been explored by previous studies but none of these have involved a self-administered device. This is a novel intervention that requires a detailed examination of barriers and facilitators for successful self-administration in order to consider its implementation in practice.

4.1.3 Aims and objectives

This study explored insights from patients and health professionals to inform the development of a possible definitive trial of non-invasive vagus nerve stimulation.

For participants who were approached to take part in the feasibility trial and provided consent, the following objectives were pre-defined:

- To explore participants' acceptability of the gammaCore® device
- To explore participants' acceptability of the stimulation schedule after training
- To explore participants' acceptability of a blinded RCT and reasons for unblinding

For participants who were approached to take part but declined to provide consent, the following objectives were pre-defined:

- To explore reasons for non-recruitment to the study
- To explore factors which may improve the rate of recruitment in the future

Across a range of healthcare professionals who were involved in the feasibility study and others who were not involved, the following objectives were pre-defined:

- To explore healthcare professionals' views of the device as a candidate intervention to reduce ileus after surgery
- To explore healthcare professionals' perceived barriers to implementation of the device into everyday clinical practice

4.2. Methods

4.2.1. Ethics and governance

This study was undertaken in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. Research ethics approval was confirmed by the NHS HRA and the Tyne & Wear South REC on 2nd July 2019 (19/NE/0217). The study described herein is reported in line with the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist (213).

4.2.2. Summary of study design

A qualitative study comprising of semi-structured interviews was undertaken alongside a sham-controlled, participant-blinded, randomised feasibility trial. This explored the feasibility of a definitive RCT of non-invasive vagus nerve stimulation to reduce ileus after colorectal surgery. It was undertaken at two hospitals in England (St. James's University Hospital, Leeds; and Bradford Royal Infirmary, Bradford). Patients who were approached for participation in the feasibility trial and healthcare professionals involved in the care of patients undergoing surgery in the NHS were invited to take

part. The qualitative findings from interviews were considered alongside quantitative findings from the trial and contributed to the final assessment of feasibility.

4.2.3. Research team and reflexivity

All interviews were performed by a male investigator (SC). This investigator was a medical doctor with a background of surgical training. He held a basic postgraduate research training qualification and had early experience of facilitating focus groups and interviews with health service users and providers. At the time of the study, he worked as a non-practising clinical researcher at St. James's University Hospital. He introduced himself to all participants as an academic researcher but gave no further detail about his medical background or reasons for doing the study unless specifically asked. At the time of the interview, a non-clinical relationship existed between the investigator and patient-participants owing to their role in the preceding feasibility trial. No day-to-day relationships existed between the investigator and healthcare professional-participants although some professional familiarity was possible.

4.2.4. Theoretical framework

The Theoretical Framework of Acceptability (TFA) was considered when undertaking this study. This describes a series of constructs that capture key dimensions of acceptability when developing, evaluating, and implementing healthcare interventions in practice. The constructs include: affective attitude, burden, ethicality, perceived effectiveness, intervention coherence, opportunity costs, and self-efficacy. According to the TFA, acceptability is the extent to which those delivering or receiving a healthcare intervention consider it to be appropriate based on cognitive and emotional responses (214). The framework was used to develop semi-structured topic guides (Appendix A-4.1), supplemented with considerations to explore barriers and enablers of study feasibility.

4.2.5. Study setting

The study coincided with the COVID-19 pandemic, during which national social distancing restrictions were in place. Patient-participants were recruited from St. James's University Hospital (Leeds, UK), a tertiary-care hospital and one of the study sites involved in recruiting participants to the feasibility trial. Healthcare professional-participants were recruited from the two study sites as well as from professional networks of colorectal surgeons and specialist nurses elsewhere in the NHS.

4.2.6. Participants and recruitment

All patients approached for participation in the feasibility trial were eligible to take part in the qualitative study. They were sampled purposively using a maximum variation approach, accounting for age, sex, type of surgery (right- versus left-sided) and reason for surgery (benign versus malignancy). Patients who declined enrolment to the trial were also invited to take part. Potential participants were approached in person (on the ward) or by telephone (at home) no more than 30 days after surgery with the recruitment materials (Appendix A-4.2). Sampling ceased at the point of data saturation, defined as the point at which no new themes were developed and existing themes had been comprehensively explored (215). Irrespective of data saturation, a maximum of 20 patient-participants was pre-planned.

For healthcare professionals, two cohorts of participants were predefined. The first included colorectal surgeons, specialist nurses, and research delivery teams (research nurses) working at study sites who were familiar with the study intervention and/or had been involved in recruitment to the trial. The second included colorectal surgeons and specialist nurses from any other NHS hospital which had not been involved in the trial. Expressions of interest were invited using a snowball technique at study sites and via

professional interest groups acting as gatekeepers. Participants were sampled purposively using a maximum variation approach, accounting for sex, profession, time since primary qualification, and work setting (district general or academic hospital). They were then approached for consent using the recruitment materials (Appendix 4.2). Sampling ceased at the point of data saturation or when a maximum of 20 participants had been recruited to the study (215).

4.2.7. Data collection

All participants took part in a single, semi-structured interview facilitated by a single investigator (SC). For patient-participants, interviews took place after hospital discharge and for healthcare professional-participants they took place during the course of recruitment to the feasibility trial. There were no additional observers during the interviews although patient-participants were welcome to invite a non-participant family member for support. A combination of telephone and face-to-face interviews were initially planned but these were converted to telephone and video-conference (Microsoft Teams) in light of social distancing restrictions. Interviews lasted between 17:03 and 53:28 minutes and were digitally recorded, pseudo-anonymised, and transcribed verbatim by an approved individual in preparation for analysis. Field notes were recorded by the investigator after each interview to add context to the data and to facilitate reflexive thinking. Transcripts were not routinely sent to participants for review due to the risk of excessive burden but were available on demand. Participants were free to withdraw up to 7 days after taking part.

Patient- and healthcare professional-specific topic guides were used to explore key issues but remained flexible and responsive to new ideas (216). The guides were initially designed with consideration to the TFA and iteratively refined in light of

emerging data, reflexive notes, and consultation with public representatives. Interviews with patients and healthcare professionals at study sites drew on their experiences of the trial and study intervention. Interviews with healthcare professionals from non-study sites drew on their perspectives of recovery after surgery and a short explanatory video of the study intervention shown during the interview (Appendix A-4.3). This provided a factual summary of the intervention, including its purpose and a demonstration.

4.2.8. Qualitative analysis

A thematic framework analysis of transcripts was undertaken according to previous descriptions by Braun and Clarke (217). Transcripts from patient- and health-professional-participants were analysed separately owing to unique perspectives expected from each group which were deserving of tailored analysis. For each analysis, the transcripts were reviewed by a single investigator to build close familiarity with the data. The initial coding frameworks were generated from early transcripts and iteratively adapted as new data emerged (Appendices A-4.4 and A-4.5) (218). An experienced, qualitative researcher independently coded two transcripts followed by a discussion of interpretative findings and resolution of discrepancies as a means of validation. The final coded extracts were used to construct draft themes through a process of graphical mapping and cross-comparison. These were then iteratively adapted and finalised with consideration to between-theme relationships. Quotations expressed with pseudonyms and simple demographic data were reported. No dedicated analysis software was used during the analysis process.

4.2.9. Patient and public involvement

A patient advisory group consisting of six individuals was convened remotely at regular 3-month intervals to advise on all aspects of the feasibility work. Specifically

relating to the qualitative study, the panel provided guidance on patient-facing materials, review of emerging data to refine the topic guides for subsequent interviews, and insights into the findings to inform the final feasibility assessment. The panel was instrumental in guiding the revised approach to interviews during social distancing restrictions, which took place remotely via phone or teleconference.

4.3. Results

4.3.1. Summary of patient recruitment

Across 24 months of recruitment to the feasibility trial, 125 patients were approached and 97 provided consent to be randomised. Of 97 participants who took part, 18 were approached for the interview study and 16 agreed. Of the remaining 28 who declined, 3 were approached to take part in an interview and all agreed. Recruitment was stopped after 19 interviews as the data were considered to be saturated.

All participants were sampled purposively to maximise the capture of diverse perspectives. Ten out of nineteen (52.6%) were female and the median age was 66 (IQR: 61.5-75). The sampling approach ensured that a range of participants exposed to different intervention groups, types of surgery, and deviations from the prospective protocol were represented. A total of five participants deviated from the protocol, including two whose surgery was converted from laparoscopy to open, two whose compliance to the intervention was below a predefined threshold (self-administration of <16 out of 20 stimulations over ten days), and one who underwent an unplanned formation of stoma. Unexpectedly, all participants underwent surgery for malignancy despite the indication for surgery being a factor for purposive sampling. This was due to the prioritisation of patients with cancer during the COVID-19 pandemic, which meant

that surgical procedures for other benign diseases were postponed. A full series of demographic and characteristic data are provided in Table 4.1.

4.3.2. Summary and description of patient themes

Overall, it was found that patients' motivations to engage in the study were driven by broader goals of recovery which sometimes went beyond the device and its proposed

Table 4.1 – Demographics of patient-participants taking part in an interview

Pseudonym	Intervention Group	Sex	Age	Type of Surgery	Indication for surgery	Exclusion from PP population*
Leslie	A (Stim/Stim)	Male	66	Right	Malignancy	No
Nina	D (Sham/Sham)	Female	64	Right	Malignancy	No
Greg	D (Sham/Sham)	Male	78	Right	Malignancy	Yes - conversion
Angela	B (Stim/Sham)	Female	61	Left	Malignancy	No
Kevin	C (Sham/Stim)	Male	76	Right	Malignancy	No
Cynthia	B (Stim/Sham)	Female	81	Right	Malignancy	No
Mary	B (Stim/Sham)	Female	65	Right	Malignancy	Yes – compliance
Susan	A (Stim/Stim)	Female	74	Right	Malignancy	Yes – conversion
Jim	C (Sham/Stim)	Male	60	Left	Malignancy	No
Paul	A (Stim/Stim)	Male	55	Left	Malignancy	No
Donald	C (Sham/Stim)	Male	77	Left	Malignancy	No
Geoffrey	D (Sham/Sham)	Male	50	Right	Malignancy	No
Barbara	C (Sham/Stim)	Female	69	Right	Malignancy	No
Theresa	D (Sham/Sham)	Female	83	Left	Malignancy	Yes – stoma
Peter	B (Stim/Sham)	Male	62	Left	Malignancy	No
Rhonda	B (Stim/Sham)	Female	61	Right	Malignancy	Yes – compliance
Janice	Non-participantΩ	Female	64	Left	Malignancy	N/A
Christine	Non-participantΩ	Female	67	Left	Malignancy	N/A
Wanda	Non-participantΩ	Male	70	Left	Malignancy	N/A

** Indicates reasons why participants were excluded from the per-protocol (PP) study population; Ω Indicates interview participants who declined to take part in the feasibility trial (non-participant interviews); "conversion" indicates unplanned conversion from laparoscopic to open surgery; "compliance" indicates reduced compliance to the study intervention (defined as <16/20 administered stimulations across 10 days); "stoma" indicates unplanned formation stoma; N/A: Not applicable; Group A: preoperative stimulation; postoperative stimulation: Group B: preoperative stimulation; postoperative sham; Group C: preoperative sham; postoperative stimulation; Group D: preoperative sham; postoperative sham.*

purpose to reduce ileus. From these observations, unique insights into the acceptability of the study and the study intervention were drawn. These were depicted graphically to facilitate discussions about their relationships and how they mapped to the study feasibility objectives (Figure 4.1). Four discrete themes were developed: 1) Drivers and barriers to self-participation in recovery; 2) Navigating the learning curve and mitigative strategies; 3) Developing confidence through familiarity and knowledge; 4) Investment and commitment to medical research.

4.3.2.1. Theme 1 – Drivers and barriers to self-participation in recovery

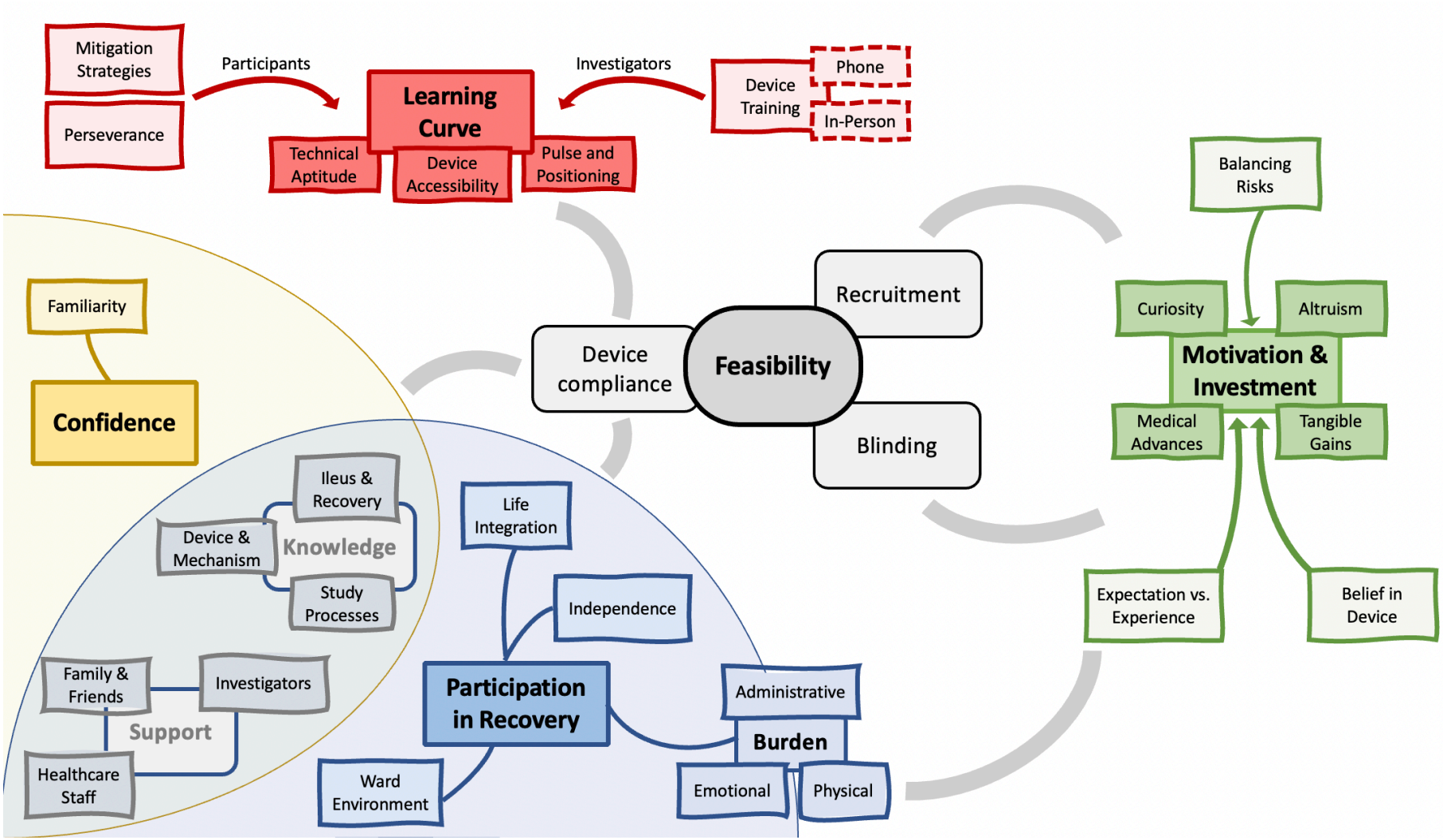
Commonly, patients were highly motivated to take an active role in their care. They sought opportunities to enable a quick and uneventful recovery and the device offered an opportunity for them to explore this. When considering its possible benefits, some participants focussed on those relating to improved bowel function, such as reduced nausea, less pain, and quicker discharge from hospital. Others saw the device as an opportunity to get back to 'normal' quicker, possibly reflecting the broader and interwoven nature of recovery.

> *"…I'd visions of my bowel not getting back going, you know I'd sort of panic… so, I was keen on anything that I could do to help it get back going again". (Rhonda, 61F, Group B).*

> *"I think my motivation was specifically to get myself back to normal as quickly as possible… So, I would do anything to help that and the [device] was part of that process. (Peter, 62M, Group B)*

In contrast, some participants viewed the device as a distraction from the emotional burden of treatment. As an activity which occupied frequent periods of their time

Figure 4.1 – Final graphical map used to develop themes for patient-participants



throughout each day at home and in hospital, the device seemed to offer respite from the apprehensions of undergoing major surgery. This was particularly true for participants who lived alone or had limited family and support networks.

> *"…when I found out what I had um, I took it pretty bad and all my nerves started up. But after that I just blocked it all out…Cause otherwise if I hadn't I might have been really, made myself really poorly, you know thinking about it. So, I thought the machine might help". (Barbara, 69F, Group C).*

> *"I thought, well, I am going to be occupied in doing that twice a day. So, I probably think well that's a good thing um, rather than just sitting about and waiting for unknown things to happen. (Theresa, 83F, Group D).*

Participants described several barriers to using the device. Some reported how their motivation to use it waned during times of feeling unwell or drowsy after surgery. In these circumstances, the device became an inconvenient burden rather than being seen as a vehicle to improve recovery. This was most apparent during the early postoperative period where adherence initially declined and then improved as participants begun to feel better. The impact of this on actual adherence varied between participants and depended on their self-motivation. For some (Mary, 65F; and Rhonda, 61F), their adherence declined substantially, whereas other participants (Jim 60M; and Susan 74F) persevered and maintained a high level of adherence despite the challenges.

> *"I was just feeling too poorly after the surgery really to be bothered with it… it was really not being bothered to do anything at that point" (Mary, 65F, Group B).*

> *"For the first couple of days erm, I couldn't use it; I was a bit out of it with the operation. Erm, I did use it, I think, on the third day…". (Rhonda, 61F, Group B).*

"After the operation you're feeling a bit rough, a bit delicate, and can't be too bothered to move… I think people, if they're feeling groggy as I did, two days when I felt rubbish, I just couldn't be bothered doing it…" (Jim, 60M, Group C).

"I um, did struggle with the five days after my op because I had er, pain from the operation…So, I did find it hard for those five days afterwards to, you know, complete what I had to do, but I think I did it". (Susan, 74F, Group A).

The experience of major surgery left some participants lacking self-esteem and this impacted on their drive to engage in recovery and to self-administer the device. In some cases, this precluded participants from taking part in the study at all owing to being overwhelmed by their existing cancer treatment (Non-participants: Janice 64F and Christine 67F). In these circumstances, participants suggested that the device would be more acceptable if it was administered by healthcare professionals rather than by themselves.

"…people are generally umm, down…they've had a six-hour operation and they're feeling pretty low, low self-esteem with themselves" (Paul, 55M, Group A).

"It were too much with what I was going through" (Janice, 64F, non-participant).

"I was focused on having the operation, which took all my energy to do it" (Christine, 67F, non-participant).

"I mean, if somebody had come round, I guess, like taking the pulse er… then that would've probably been all right. Er, the motivation wasn't there to do it myself (Mary, 65F, Group B).

4.3.2.2. Theme 2 – Navigating the learning curve and mitigative strategies

Participants reflected on their initial experiences of the device and the time taken to become skilful at self-administering it. Whilst some developed this skill quickly, others found it challenging. Common reasons for this were uncertainty about positioning the device on the neck and the ergonomics of holding it in the correct position. These factors contributed to a variable learning curve across different participants, which seemed to play a key role in defining their acceptance of the device.

> *"It was straightforward. It wasn't an onerous task…" (Angela, 61F, Group B).*
>
> *"I think once you've done it once or twice, it just sort of came naturally" (Geoffrey, 50M, Group D).*
>
> *"It was difficult to do… if you imagine, you find it with one hand and then trying to put the device on. It was a bit cumbersome really". (Peter, 62M, Group B).*

A prominent challenge for participants whilst positioning the device was identifying the carotid pulse and using it as a landmark for the vagus nerve. This was an unfamiliar activity and several participants considered it to need dedicated "medical" expertise. This did not deter participants from using the device since adherence to the planned stimulation schedule remained high. On the other hand, some participants revealed that they had resorted to just guessing the position of the carotid pulse, likely increasing the risk of inaccurate or ineffective stimulation.

> *"Biggest problem was finding my pulse and getting it in the right place". (Susan, 74F, Group A).*

“Not being a medical person, you don’t always know where, you know where to find [the pulse]”. (Nina, 64F, Group D).

“I couldn’t find the pulse on my neck, so I more or less. . . just guessed where it should be” (Jim, 60M, Group C).

These problems were compounded after surgery as a result of practical challenges in the ward environment. Several participants described difficulties in manoeuvring the device around their oxygen tubes, surgical drains, and other equipment which tended to impede their efforts to self-administer it. Another participant (Theresa, 83F) found it challenging to find time for the device owing to a large burden of treatment-related disruptions from clinical teams throughout the day.

“It’s not so easy to find [the pulse] at times. And there were times when I had an oxygen thing round me as well, which was getting in the way of the vein which I had to take out of the way (Greg, 78M, Group D).

“At home…I knew there was nobody going to interrupt what I was doing. In the hospital you never know who might be coming to er, take your blood pressure or you know what was a good time” (Theresa, 83F, Group D).

Participants explored solutions and mitigative strategies to address these challenges. Several participants described using a bathroom or handheld mirror to position the device visually, which tended to replace the pulse as a positioning aid. At home, using a mirror gave participants a greater sense of assurance but this generated an unexpected challenge in hospital when mirrors were no longer readily accessible. Commonly, this was due to poor mobility in the early postoperative period which precluded many from walking to the bathroom. Participants had to change their

approach and re-adapt to using the device in hospital, likely introducing a new or extended learning curve.

> *"…a few times I had to go in the bathroom and look in the mirror to make sure I had [the device] in the correct position" (Leslie, 66M, Group A).*

> *"And that's really what I went on was the mirror…But that was when I was at home. Um, in the hospital it was a bit more difficult because I didn't have a mirror" (Theresa, 83F, Group D).*

> *"The only thing about in hospital um… I was laid down, which did make it slightly more awkward because I couldn't get up and go look in a mirror" (Paul, 55M, Group A).*

The format and content of the training programme emerged as a modifiable factor to shorten the learning curve. A number of participants emphasised the importance of face-to-face training as opposed to training done remotely. One reason for this was the perceived value of in-person explanations, which were felt to provide greater clarity on complex topics such as device positioning. Another reason was the potential to use visual models to demonstrate the carotid pulse. In contrast, other participants felt that training delivered remotely or in written format was readily acceptable. There was a general acceptance that approaches to learning are variable between different people and a broad availability of formats may offer the best approach in a definitive trial.

> *"I think the face-to-face bit certainly was a big help because I knew what [the device] was, where it was going, rather than just listening to somebody trying to explain how to do it… [over a] telephone call". (Peter, 62M, Group B).*

“I [favour] face-to-face probably in a perfect world. It-it, it's there in a practical basis of exactly what a pulse is and where to find a vein”. (Greg, 78M, Group D).

“Er, and the paperwork explains it very clearly. So, I think, you know it would work either way (Angela, 61F, Group B).

“I suppose different people have different learning styles and different ways…for me personally the demonstration was the best part, you know, most useful part”. (Peter, 62M, Group B).

4.3.2.3. Theme 3 – Developing confidence through familiarity and knowledge

Taking control of some aspect of care was a new responsibility for most participants. Many tackled this by integrating the device into a familiar routine, usually involving their home environment and aligning it with everyday activities, such as mealtimes. This seemed to introduce a sense of regularity, helping participants to build confidence and adhere to the administration schedule. On the other hand, participants identified several disruptors to this confidence. A common example was when participants were required to self-administer the device in hospital, an environment that was distinctly unfamiliar from their usual home routine. Another was the work environment, which emerged as a source of anxiety and apprehension when considering how to manage the device in different environments.

“I literally just got into a routine so, you know I didn’t even think about it. Same time in the morning. Same time in the evening”. (Peter, 62M, Group B).

“…It was just like taking a tablet or um, you know remembering to do something on a daily routine”. (Kevin, 76M, Group C).

"The first five days when I were at home, literally I got up, made me pot of tea, sat down, and used it then. In the hospital, the first couple of days I had to remind myself to do it, you know". (Jim, 60M, Group C).

"Er, I were at home doing it, fair enough, but I wouldn't like to think I've got to take it to work and do because the job what I'm in…". (Jim, 60M, Group C).

The role of trusted individuals, such as family and friends, emerged as a key contributor to developing confidence. Family members were not routinely involved in study activities, such as recruitment and training, but some participants gained great confidence from their support. This was most evident whilst learning how to use the device and during the first instances of self-administration. One participant (Peter, 62M) and his wife approached the study together as a partnership, demonstrating a potential important role for family members during recruitment to a future definitive study.

"At first I wanted my husband there just in case I did it wrong" (Barbara, 69F, Group C).

"And there was no such hesitation about taking part…you know, [my wife and I] were both in the same mind" (Peter, 62M, Group B).

Another key factor in building confidence was the role of good information. Participants developed confidence through a well-informed understanding of the device. They sought to understand fully why the bowel became dysfunctional and through what mechanism the device may help. This was initially unclear to some participants, who found the prospect of stimulating a nerve in the neck to be a perplexing idea. This highlighted the importance of informed knowledge at the point of recruitment. In some instances, the provision of information from trusted healthcare professionals was poor

and this was a challenge for maintaining confidence. In particular, explanations about ileus and its impact on recovery were inconsistent across different members of staff. One participant (Leslie, 66M) described these as “stories”, suggesting that they lacked assurance and clarity.

> *“Any gadget I get, I have to always read the instruction book”. (Leslie, 66M, Group A).*

> *“I mean I did it for the full five days ‘cause I thought this is what they want, but there must be a reason for this five days…” (Greg, 78M, Group D).*

> *“I just wondered how the, this research came about, you know, what makes you think that the, in the first instance, that the stimulation would be helpful to bowel surgery”. (Susan, 74F, Group A).*

> *“I heard stories about your bowel stopping working after a few days. But, I were getting a different story from everybody I asked about, about the subject” (Leslie, 66M, Group A).*

Similar to the training activities, the approach to information-giving during the study (including at the point of recruitment) changed to a telephone format as a result of COVID-19 social distancing restrictions. This was well received by many participants, since it brought benefits of reduced time and travel burden. One participant (Donald, 77M) felt that face-to-face contact in the first instance was important to build rapport and familiarity during future telephone communication. These experiences highlighted the important role of a flexible approach to recruitment and information-giving during a future definitive trial.

“I was pleased with [the telephone contact] actually because I didn’t want to come into [city] into the hospital. I can’t drive there myself”. (Cynthia, 81F, Group B).

“I think it’s best face to face in particular for a first meeting. Er, you can feel a bit more comfortable and maybe you don’t know them all that well…” (Donald, 77M, Group C).

4.3.2.4. Theme 4 – Investment and commitment to medical research.

Important insights emerged about participants’ reasons for taking part in the study and how these impacted on key feasibility outcomes, such as blinding. Reasons to take part were commonly motivated by altruistic views of research and the desire to give back to the health system. Participants commonly expressed wishes to help future patients in similar situations as themselves and this was enabled by knowing that the device was non-invasive.

“…if it can help anybody so be it. As I say, five minutes of my time, you know your research is there for a reason, isn’t it”. (Nina, 64F, Group D).

“I mean it’s something I've never heard or seen before, I thought well, if it’s, if it’s not painful to do or difficult to do um, why shouldn’t I help”. (Greg, 78M, Group D).

These views were held so profoundly that clear instances of unblinding did not deter participants from engaging with the device. Instead, participants were invested in the scientific process and this led to a high level of adherence across randomised groups despite becoming unblinded to the group allocation.

“It’s in the interest of science, somebody’s got to do these, these placebo things haven’t they…”. (Greg, 78M, Group D).

“[The allocation] didn’t bother me really. As I say, to me if I'm helping ya, whether it’s a live device or not. It's all part of your, your research”. (Nina, 64F, Group D).

“…but even though I didn’t have the same effects er, it didn’t affect my decision to continue”. (Angela, 61F, Group B).

Common reasons for unblinding were echoed by multiple participants. Some reported that there was little or no sensation associated with their device and this led to suspicions that it was a sham. For one participant (Rhonda, 61F), the lack of sensation was so surprising that she thought the device must be faulty. Other participants (such as Peter, 62M) became unblinded by differences in sensation between pre- and post-operative devices. They considered a stronger sensation to be associated with an active device and correctly identified their group by comparing differences in the stimulation character and amplitude. In keeping, some participants using the same type of device (such as Leslie, 66M) avoided this challenge and remained appropriately blinded throughout. It suggested that the problem of unblinding was not universal across all groups and that blinding procedures may still be feasible in a study design where devices are not switched.

“I wasn’t getting any great impact um, from it whichever level I put it on”. (Greg, 78M, Group D).

"…the first day I used it [after surgery], it didn't feel like there was anything there. Erm, that was the only concern I had with it that it basically it was a dud". (Rhonda, 61F, Group B).

"The first device that I had before the [operation] um, seemed to be a lot more power than the second one". (Peter, 62M, Group B)

"I could not tell the difference between the two devices. It might have been the same device for all I knew". (Leslie, 66M, Group A).

4.3.3. Summary of healthcare professional recruitment

Healthcare professionals were approached and recruited via multiple routes. Three were recruited from feasibility sites using a snowball approach, including two research nurses and one specialist nurse who were familiar with the study device. Expressions of interest were also invited from healthcare professionals from non-study sites, all of who were unfamiliar with the device. Fifteen expressed an interest and seven were purposively sampled, including five surgeons and two specialist nurses. Overall, 10 healthcare professionals were recruited and subsequently interviewed, following which the data were considered to be saturated. The sampling approach ensured that a range of perspectives were captured from participants working in different hospital settings and with a range of professional experiences. A full outline of demographics is shown in Table 4.2.

4.3.4. Summary and description of healthcare professional themes

Healthcare professionals' perspectives of the device tended to be drawn more widely from their experiences of ileus and treatments. Key considerations were mapped graphically to facilitate discussion around the study objectives (Figure 4.2). Four themes

Table 4.2 – Demographics of healthcare professional-participants taking part in an interview

Pseudonym	Sex	Professional role	Years since qualification	Type of Hospital	Feasibility study site
William	Male	Research Nurse	>20	University-affiliated	Yes
Jen	Female	Research Nurse	>20	District general	Yes
Louise	Female	Specialist Nurse	1-9	University-affiliated	Yes
Scott	Male	Surgeon	10-19	District general	No
Matthew	Male	Surgeon	10-19	University-affiliated	No
Liz	Female	Surgeon	>20	University-affiliated	No
Maria	Female	Specialist Nurse	>20	University-affiliated	No
Dawn	Female	Specialist Nurse	>20	University-affiliated	No
Jonathan	Male	Surgeon	>20	University-affiliated	No
Craig	Male	Surgeon	>20	District general	No

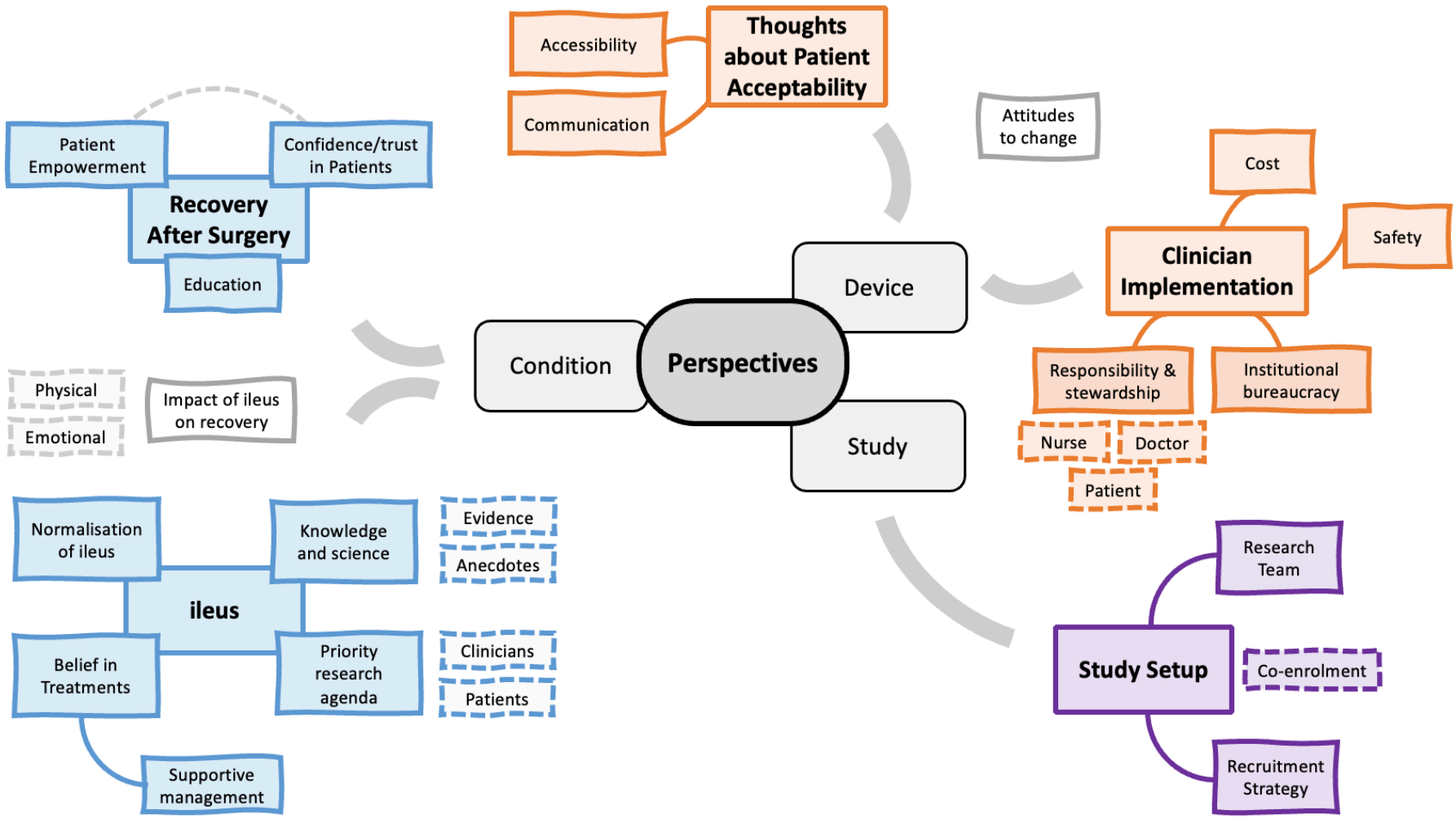
were developed, including: 1) Perspectives, knowledge, and experiences of ileus; 2) The challenge of implementing vagus nerve stimulation; 3) Putting patient empowerment into practice during recovery; and 4) Overcoming barriers to recruitment.

4.3.4.1. Theme 1 – Perspectives, knowledge, and experiences of ileus

Amongst health professionals, there was widespread uncertainty surrounding the topic of ileus. In particular, there was a lack of confidence when describing its underlying physiology and this propagated through discussions about new treatments and their potential for patient benefit. Participants tended to have insight about their lack of knowledge, but there were few expressions about how this could be improved. It was common for participants to propose hypotheses for why they think ileus occurs but these were mostly drawn from anecdotal observations rather than scientific enquiry.

> *"I think ileus is the last big thing that we don't understand and don't have a great strategy to offset and anticipate in our patients" (Liz, Surgeon, Non-study site)*

Figure 4.2 – Final graphical map used to develop themes for health professional-participants



“I think there is um, a lack of understanding amongst er, ward nurses about exactly what postoperative ileus is…” (Maria, Specialist Nurse, Non-study site)

“In my experience, when you know patients have got what we think is a postop ileus, there is an element of waiting, sometimes a number of days just to hope, hope that it’s gonna rectify itself” (Dawn, Specialist Nurse, Non-study site)

“…there’s [sighs] obviously two types of ileus. You see the ileus where…you know not really a lot’s happening. And you get occasional patients who get an acute gastric distension who are looking really unwell”. (Scott, Surgeon, Non-study site)

Some participants felt disillusioned with previous efforts to reduce ileus and this impacted on their openness to consider new treatments, such as vagus nerve stimulation. They described how other novel treatments (such as chewing gum) had been explored extensively in the past but ultimately had lacked efficacy in practice. These participants tended to approach the idea of vagus nerve stimulation with scepticism, expressing a need for more information about its potential benefit and how this may be achieved in practice. Some participants (such as Scott; Surgeon) expressed how it would be important to provide pilot data to assure healthcare professionals that the treatment had a reasonable chance of benefit.

“I'm sure people mentioned to you before, the chewing gum extravaganza years, where everyone thought chewing the gum along with your high-calorie protein drinks would work…” (Liz, Surgeon, Non-study site)

“You’ll need to explain to me why picking up that vagus nerve there at that point affects the gut. So, that’s my first thought” (Liz, Surgeon, Non-study site)

“I'd guess you’d want some sort of pilot data, but I can only imagine how many numbers are going to be involved in a bit of pilot data for you to actually say that this is working” (Scott, Surgeon, Non-study site)

Overall, there were mixed views on the extent to which ileus is a problem in clinical practice, which impacted on participants’ perspectives of new treatments. Whilst some participants acknowledged its “debilitating” impact on patients and the health system, others expressed how the topic of ileus is commonly overlooked in place of other research priorities, such as cancer treatment and stigmatised complications such as anastomotic leak. In contrast to this opinion, some participants considered ileus to be a normal feature of recovery, occurring unavoidably after surgery and best managed with “supportive” treatment to reduce symptoms until it resolved. Interestingly, this perspective tended to accompany frustrations about the lack of efficacious treatments for ileus, suggesting that it was a product of prolonged attrition and futility.

“I’ve had patients in the past that say they’d rather die than have another ileus! So, you know they, it is really debilitating for them, and you know really painful; it makes them feel really unwell” (Dawn, Specialist Nurse, Non-study site)

“You still getting a feel a bit of a Cinderella problem. People are interested in [anastomotic] leaks. People are interested in long term cancer outcomes, but ileus doesn’t really get much traction does it”. (Scott, Surgeon, Non-study site)

“Everyone gets a temporary, you know halting of the bowel activity which is fairly transient” (Scott, Surgeon, Non-study site)

“The only treatment we do is a bridge to waiting for the body to start working (Matthew, Surgeon, Non-study site)

> *"I don't think we have any existing treatments and certainly nothing that has enough evidence behind it…" (Craig, Surgeon, Non-study site)*

4.3.4.2. Theme 2 – The challenge of implementing vagus nerve stimulation

Participants discussed several barriers to implementing vagus nerve stimulation in surgical practice. One of these was its perceived safety. The idea of stimulating the vagus nerve around the time of surgery provoked concerns about cardiovascular side-effects, particularly from surgeon participants. In particular, they were concerned that the device may increase the risk of faints and falls in the immediate postoperative setting, leading to avoidable injury. It was acknowledged by several participants that these concerns were likely the product of medical dogma about vagal physiology and that safety considerations should be guided by device-specific clinical evidence. A possible solution to overcome this dogma included setting clear safety nets, such as encouraging family members to be present during each stimulation at home or contacting patients at home to monitor their health whilst using the device.

> *"And of course, as soon as you say the vagal nerve stimulation, you can imagine some people might just get anxious about those two words. So again, it will be, you know just clarifying safety really, I think" (Scott, Surgeon, Non-study site)*

> *"Making sure that patients' family are there, and whether it's done together. So, I think it's just trying to get inbuilt safety". (Scott, Surgeon, Non-study site)*

> *"So, it's just all about showing there's a safety profile for these things. (Liz, Surgeon, Non-study site)*

Discordant views relating to stewardship and responsibility of the device was another barrier and arose mainly from considerations about safety. On one hand, some

nurse participants felt that the surgical team (doctors) were best place to manage the device owing to their overall position of responsibility in patient care. In contrast, surgeons often proposed that the specialist nurse team were best placed owing to their frequent contact and rapport with patients. Integrating the device into existing clinical frameworks, such as enhanced recovery protocols, emerged as a solution which involved the entire perioperative team.

> *"I think that the surgeons would be up for it…they're pretty keen to try anything that is going to um, improve patient outcomes…and I think if the surgeons are up for it, then the rest of the staff tend to be more motivated about change" (Maria, Specialist Nurse, Non-study site)*

> *"…the ideal people beyond any question of a doubt would be the colorectal nurse specialists". (Jonathan, Surgeon, Non-study site)*

> *"…[the device] could just go on the [Standard Operating Procedure] for ERAS" (Liz, Surgeon, Non-study site)*

Overall, participants acknowledged that a successful approach to implementing vagus nerve stimulation would need to consider multiple professional perspectives, including those of nurses, surgeons, and managers. These included considerations about device safety, treatment success, patient quality-of-life, and hospital finances/resources. Some participants held the view that implementing vagus nerve stimulation in this context would be challenging owing to conflicting priorities and resistance to change, particularly amongst surgeons. On the other hand, there was a strong view that implementation may be straight forward owing to non-invasive vagus nerve stimulation being a patient-administered treatment. This was considered to add positively to the patient experience

whilst avoiding additional burden on staff. It suggested that patient-partners and -champions may be essential in future strategies to implement this treatment into practice.

> *"The problem lies in the fact that hospitals are not functioning organic systems; they are siloed - 'That's my budget so, no'…" (Jonathan, Surgeon, Non-study site)*

> *"So, when you're thinking about change…there are certain people influenced by the financial side…there are people such as [specialist nurses], who look at the quality of life for the patient um… [surgeons] are driven by um, the patient being well after surgery. So, it's all relevant …". (Dawn, Specialist Nurse, Non-study site)*

> *"I think if, if it hasn't got the buy in of the surgeons, I don't think it would happen" (Maria, Specialist Nurse, Non-study site)*

> *"…you're not asking the surgeon to do anything…You're asking the patients to do something. The paradox is that it's a patient driven intervention, you might find implementation's better as it's in their vested interests". (Scott, Surgeon, Non-study site)*

4.3.4.3. Theme 3 – Putting patient empowerment into practice during recovery

In general, health professional participants were enthusiastic about patients self-administering the device since it empowered them to take ownership over a specific aspect of their care. It was felt that this may improve confidence with the wider recovery process. For some participants not involved in the feasibility study, there remained apprehensions about relinquishing responsibility to patients. One such apprehension was about patients' capacity to adhere to the treatment schedule after major surgery. Some found this lack of oversight to be uncomfortable, requiring a high level of "trust" in patients to administer the device correctly. It was also

considered to be a risk to the study method, putting the study at risk of flawed data if adherence could not be confirmed. Other participants described practical concerns relating to the device being lost or broken on the ward.

> *"…Putting patients in control is a strong point" (Scott, Surgeon, Non-study site)*

> *"There is an element that you have to trust the patient that they're going to be doing a certain management of their self-care" (Dawn, Specialist Nurse, Non-study site)*

> *"…you'll get a feel, there'll be patients [who] just won't be able to do it…the overwhelming issues of cancer and surgery are just too much" (Scott, Surgeon, Non-study site)*

> *"Erm, will we leave in on the bedside table? No. Because they get lost, they get broken, they get nicked". (Jonathan, Surgeon, Non-study site)*

In contrast, health professional participants who took part in the feasibility study described substantially more positive experiences. Their initial impressions included similar apprehensions, but these were alleviated during the course of the study. It was apparent that health professionals tended to underestimate the extent to which patients would engage with the device and their strong motivation to take part in recovery.

> *"They took, I suppose, a certain degree of ownership of it… I think it's-it's a real lesson in experience of patients…" (William, Research Nurse, Study site)*

> *"And you know they commented that it-it's great that I'm actually doing something for my recovery. It's putting like a bit of control back to them". (Louise, Specialist Nurse, Study site)*

> *"And nobody to my amazement has lost the device; they've all, when we've gone on [the ward], they've always got the device…" (Jen, Research Nurse, Study site)*

One participant described ways in which concerns about adherence could be addressed from the outset in a future definitive study. It was suggested that the device could be incorporated onto the prescription chart, with observation performed by the nursing team during medication rounds. This would provide more certainty that patients were administering the device correctly and at the appropriate time. It was also met with some concerns, however, from the nursing team who felt that it may increase staff burden.

> *"I wonder whether to give it a little bit more validity um, if it was prescribed as something that got checked, you know, have you used the device this morning. Have you used it this evening…" (William, Research Nurse, Study site)*

> *"I just think nurses, ward nurses are really, really busy, and it just would never be on the list of top priorities". (Maria, Specialist Nurse, Non-study site).*

4.3.4.4. Theme 4 – Overcoming barriers to recruitment

Health professionals acknowledged that recruiting patients with a new cancer diagnosis was a highly sensitive undertaking. They expressed concern about overburdening patients with information, particularly if recruitment to the study took place alongside emotionally demanding discussions about their diagnosis and treatment. Challenges included finding a private space for discussions, rationalising the volume of information, and managing patients' emotional frame of mind. Oftentimes, these challenges were compounded by the need to approach patients about multiple studies whose eligibility criteria overlapped. During the COVID-19 pandemic, most recruitment activities were converted to a telephone format which presented an opportunity to better manage the

information burden. Like patient participants, health professionals reported positive experiences of this since it enabled them to approach patients at mutually convenient times and to avoid intense periods of burden. Interestingly, healthcare professionals reported contrasting experiences of telephone consultations when training patients to use the device. In this case, it was felt to lack opportunities to build rapport.

> *"If you were to approach someone who had just received um, you know diagnostic news or something like that, that-that can be a difficult barrier" (William, Research Nurse, Study site).*

> *"…if it's a cancer diagnosis you've got to tread quite carefully, and like, not overburden them with too much information" (Jen, Research Nurse, Study site).*

> *"I quite like [telephone consent]. I think it's er, it's good because once they've done it over the um, over the phone and you've read out pointers they know what they're signing up to" (William, Research Nurse, Study site).*

> *"I think [telephone training] can work, but I would if I'm honest prefer face-to-face because I think sometimes that initial face-to-face you can build up a bit of a relationship with a patient" (Jen, Research Nurse, Study site).*

4.4. Discussion

4.4.1. Summary of findings

In summary, the results of this work provide important insights into the acceptability of non-invasive vagus nerve stimulation and the feasibility of a definitive study. For patients, recruitment to the study and compliance to the stimulation schedule were highly feasible, driven by their motivation to take control of recovery. Since the device

was unfamiliar to patients, it implicated a learning curve which varied between individuals. Some struggled to navigate this due to difficulties in locating the carotid pulse as a surface landmark and this led to challenges in self-administration. Blinding of the study treatment was not feasible in the most part and this was due to perceptible differences in the stimulation sensation between active and sham devices. Patients still remained compliant to the stimulation schedule owing to their investment in the scientific process and altruistic views about helping others. Amongst healthcare professionals, a detailed understanding of ileus was often missing, leading to uncertainties about its diagnosis and treatment. Healthcare professionals' motivation to explore new treatments was often guarded due to disappointing results from previous interventions which had led to feelings of disillusionment about the management of ileus. For vagus nerve stimulation specifically, individuals were apprehensive due to fears about side effects and cardiovascular events. Healthcare professionals who did not take part in the feasibility trial tended to underestimate patients' motivation to engage with the device. Those who did have a role in the feasibility work shared the same initial concerns but these were generally alleviated by the end of the study once the strength of patients' motivations had become apparent.

4.4.2. Interpretation

The interviews provided valuable information to explain and reflect on findings from the feasibility trial. Firstly, recruitment to the study was shown to be highly feasible despite the emotional burden of cancer treatment on patients and their families. Patients were driven to engage with the research because they felt it was a way to give back to the health service. Nevertheless, some patients declined to take part citing concerns about excessive treatment, information, and administrative burdens, particularly at the time of first approach. Previous literature exploring barriers to recruitment in cancer

research have explored the manner in which patients are recruited to studies. A study by Sygna and colleagues examined the performance of seven different types of recruitment strategies, including a mix of opt-in and opt-out approaches (219). The latter (including in-person recruitment in clinic and routine care letters with telephone follow up) performed best, compared to opt-in strategies such as flyers, newspaper adverts, and social media. In the present study, participants considered the timing and setting of in-person recruitment to be challenging since it was often done alongside emotionally demanding discussions about their diagnosis and treatment. Telephone recruitment was far more favourable to patients since it introduced greater flexibility in timing and was typically facilitated at distance in a comfortable environment such as their home. A potential future study should consider broad and flexible pathways for recruitment to ensure patients' preferences and circumstances can be accommodated.

Secondly, self-reported compliance to the study treatment was high but many patients struggled to position the device correctly using the carotid pulse as a landmark. This led participants to adapt the administration procedures and deviate away from how they had been trained. A common approach was to position the device visually using a mirror rather than using the carotid pulsation as a guide. Whilst this may have increased patients' confidence, it may also have led to a less targeted or inaccurate delivery of treatment. Previous research in the field of resuscitation medicine has explored the public's skill in identifying the carotid pulse. In one study of 449 volunteers, the average time to identify the pulse was 10 seconds, but it wasn't until 35 seconds had elapsed that 95% of all volunteers had successfully identified it (220). In another diagnostic accuracy study of 147 first responders, 66 (45%) did not identify a carotid pulse even though it was present (221). These findings demonstrate the challenge for lay people in identifying and using the carotid pulse as a reliable

landmark. As reported in the present study, possible solutions include face-to-face training with anatomical models to improve participants' ability and self-confidence.

Thirdly, whilst compliance to the stimulation schedule was good, the performance of blinding was shown to be poor. This was particularly true in study groups where participants switched between active and sham devices. Here, patients were able to compare devices and draw conclusions based on their experiences of the sensation, with stronger sensations considered to represent active treatment. Nevertheless, patients' attitude to engage with the device remained high, reflecting their desire to engage with the scientific process and help to drive improvement in care. The design of control groups and the robustness of blinding procedures is a frequently debated topic in neuromodulation studies. On one hand, control groups must be designed in such a way that blinding is maintained through close similarity of the sham and active interventions. On the other hand, caution is required as to whether sham interventions are capable of producing mild therapeutic effects either through their electrical stimulus or through tactile manipulation (222). Blinding was more robustly maintained in the study groups involving only one type of device. Although challenging, the use of blinding in neuromodulation studies is highly recommended and this will be an important consideration for the design of a future trial.

Finally, it was clear that patients sought opportunities to take control of their recovery and to be empowered during their care. This aligns with previous research showing that patients seek out opportunities to work in partnership with healthcare professionals during recovery in order to expedite their return to normal activities (197). In contrast, the results showed that healthcare professionals were hesitant to relinquish this control, instead preferring to maintain oversight of the entire recovery process. A key reason for this related to healthcare professionals' confidence in

patients to self-administer the device, particularly in the early postoperative period when patients may be feeling unwell. These concerns were most commonly expressed by healthcare professionals who had not been involved in the feasibility trial. For those who were involved in the feasibility trial, similar concerns were shared at the start but tended to reduce once patients were observed using the device. This suggests that healthcare professionals tend to underestimate patients' ability and motivation to take part in recovery and particularly to engage with self-administered interventions. Considering the themes that emerged from patient interviews, including those relating to confidence, it is likely that healthcare professionals form these attitudes according to initial impressions of individual patients, which may adapt over time. This suggests that a future trial would need to carefully consider how patient and professional perspectives can be handled concurrently. A mutually acceptable approach would provide patients and healthcare professionals with confidence in the safety of the device as well as avoiding unnecessary resistance to patent involvement.

4.4.3. Findings in context with theory

The topic content of interviews was informed by the Theoretical Framework of Acceptability (214). This is a multi-faceted construct used to explore the acceptability of healthcare interventions according to the following seven components: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy. The framework was selected here because it enabled an informed exploration of patients' and healthcare professionals' attitudes towards the device as well as an assessment of challenges and how these may be addressed. Burden and ethicality were key considerations when recruiting patients from emotional and challenging settings such as cancer clinics. In particular, the timing, location, and manner of approach impacted on patients' willingness to consider

the device and their willingness to enrol in the study. Coherence with the intervention was also important since this determined patients' ability to locate the carotid pulse and accurately self-administer the device. Confidence in this process enabled good self-efficacy whilst a lack of confidence led participants to struggle and make erroneous adaptations to the administration instructions. Overall, patients' attitude to the device was positive, as was their attitude to the scientific process. Their perspectives on whether the device was effective at reducing ileus seemed to have little impact on their engagement throughout the study. Instead, the opportunity to take part in research and contribute to possible improvements in clinical care emerged as a key incentive to take part.

4.4.4. Limitations

Limitations of this work are recognised. Firstly, although the study recruited a broad range of participants (including patients and healthcare professionals) it omitted other important stakeholders, such as hospital managers. It is likely that their perspectives will be important for more detailed considerations about costs and resources. Furthermore, younger patients (<50 years) and those with benign diseases were not represented in the interviews, possibly missing unique insights. This should be considered further to explore if any diverging view exist prior to a definitive trial. Secondly, it is acknowledged that interviews were undertaken solely over the phone which may have excluded some people from the study due to barriers of access and communication. This was necessary due to COVID-19 social distancing restrictions, which precluded face-to-face interviews in the patients' home or a communal area. Thirdly, resources for language translation were not available during this study which meant that all interviews were undertaken in English. In the future, it would be important to explore these considerations with a representative study population, enabled by expert translation

services at the time of approach and recruitment. Finally, it is acknowledged that the researcher who performed interviews (SC) had a clinical background with an interest in surgical recovery and postoperative ileus. This increases the risk of bias and should be considered when interpreting the analysis and results.

4.4.5. Further considerations

The results of the earlier feasibility trial along with the present qualitative data provide detailed insights about the feasibility of a definitive trial. Whilst some limitations are acknowledged, these data will enable an informed discussion surrounding the feasibility and progression outcomes, which will be discussed further in Chapter 6.

Chapter 5

Development of a core outcome set for studies of postoperative ileus after intestinal surgery

Preface

In this chapter, the development of a core outcome set for postoperative ileus after intestinal surgery is reported. This involves an iterative process of international, multi-stakeholder consensus, including patients and healthcare professionals as participants. The final outcome set will guide the selection of outcomes in a definitive trial of non-invasive vagus nerve stimulation, if shown to be feasible. More generally, it will provide a standardised framework for outcome selection in other clinical trials where the aim is to prevent, reduce, or curtail postoperative ileus. Ultimately, it is expected that this will reduce heterogeneity in outcome reporting, enabling higher quality evidence synthesis and faster implementation of research into practice.

5.1. Introduction

5.1.1 Defining and measuring postoperative ileus

Postoperative ileus is characterised by a temporary cessation of coordinated intestinal motility after surgery. This disrupts the normal transit of intestinal contents, leading to nausea, vomiting, abdominal distension, and a loss of defaecatory function. Despite being reported in as many as 10-15% of patients undergoing intestinal surgery, the terminology used to define and measure it is widely variable (18, 223). Terms such as “primary” and “secondary” ileus are commonly used to describe its aetiology, with primary ileus considered to be a response to surgical stress and secondary ileus considered to be a consequence of intra-abdominal sepsis. In other settings, “obligatory” ileus is used to describe a transient period of gut dysfunction that many consider to be a normal consequence of surgery, whereas “prolonged” ileus is protracted and associated with increased postoperative morbidity (224). Other terms include “physiological ileus”, “pathological ileus” and “adynamic ileus” (225).

The variation in how postoperative ileus is defined and measured has been explored previously. Vather and colleagues considered 47 studies within a systematic review and found that most reported definitions relating to the passage of flatus (83%), passage of stool (79%), and tolerance of oral diet (28%). The time point used to define prolonged postoperative ileus varied from 1 to 7 days, with a median across all studies of 4 days (225). Wolthuis and colleagues extended this by exploring how the type of definition for prolonged ileus impacted on its observed incidence. Across 17 RCTs, five definitions were described with incidences reported between 2.3% (absence of bowel function on postoperative day 3) and 61% (absence of bowel function on postoperative day 5 or reinsertion of nasogastric tube). Reinsertion of a

nasogastric tube was the most common (n=13) but the criteria for reinsertion were highly variable (16). This was similarly demonstrated in a study of patients undergoing cystectomy, where six definitions were retrospectively applied to 136 patients. The respective incidences ranged from 1% (no bowel movement or flatus on postoperative day 6) to 51% (inability to tolerate diet on postoperative day 5) (226).

To address this challenge, some studies have explored whether a standard definition for ileus can be agreed through consensus. In a Delphi study by Gero and colleagues, three statements were agreed amongst 35 surgeons, namely that ileus prevents adequate oral intake (97% agreement), occurs temporarily after surgery (86%), and is due to non-mechanical causes (89%). Abdominal pain, distension, and the absence of bowel sounds were considered to be the most important clinical features (71%) (15). In another study, Vather and colleagues surveyed 44 clinical experts and used the results to propose definitions for “normal” and “prolonged” ileus (Table 5.1). The majority of survey participants (56%) considered that ileus becomes prolonged on or after the fourth postoperative day but the range of responses varied between days 1 and 7 (225). In other studies, investigators have sought to develop instruments to measure the severity of ileus. For instance, Venara and colleagues produced a classification system to describe the clinical impact of ileus on recovery. This comprises five grades, ranging from minor impacts on the duration of hospital stay to profound impacts such as the need for critical care admission and death (Table 5.2) (227). Likewise, Alsharqawi and colleagues developed the I-FEED score, which stratifies patients into clinical pathways to guide subsequent management (228,229). The pathways include “normal function”, “gastrointestinal intolerance”, and “gastrointestinal dysfunction” and are determined according to the presence and/or

severity of postoperative intestinal symptoms (oral tolerance, severity of nausea, frequency of vomiting, examination findings, and duration of symptoms).

Table 5.1 – Definitions of "normal" and "prolonged" ileus from Vather at al. 2013 (225)

"Normal" postoperative ileus: Not meeting the following criteria before postoperative day 4: 1. Passage of flatus OR stool 2. Tolerance of an oral diet **"Prolonged" postoperative ileus**: Two or more of the following criteria on or after postoperative day 4 without prior resolution of "postoperative ileus" 1. Nausea or vomiting 2. Inability to tolerate an oral diet over last 24 h 3. Absence of flatus over last 24 h 4. Abdominal distension 5. Radiologic confirmation

Table 5.2 – Classification framework for postoperative from Venara at al. 2017 (227)

Grade A	No consequence of POI apart from an increase in the length of stay
Grade B	Need for symptomatic measures or diagnostic examinations (such as laxatives, prokinetic drugs, antispasmodic drugs, antiemetic drugs)
Grade C	Need for nasogastric tube intake or hospital re-admission after discharge
Grade D	Severe consequences, including D1: general complications (such as ionic imbalance, pneumopathy; and D2: need for critical care or further surgery.
Grade E	Death

Despite previous efforts to standardise the definition and measurement of ileus, the findings from these previous studies suggest that a high degree of heterogeneity persists. This is a major challenge for designing robust clinical trials and comparing the efficacy of competing treatments in practice. The development of a core outcome set (COS) for postoperative ileus may represent an alternative solution and has not been defined in previous literature. The principles of a COS and its potential role for improving research on postoperative ileus are herein described.

5.1.2 Core outcome sets in healthcare research

A COS is an agreed set of outcomes that should be reported as standard by all trials within a defined scope of research (230). The aim of a COS is not to restrict the selection of outcomes in clinical research but to prioritise a minimum set to enable between-study comparability. To date, over 100 COS have been developed across health research and another 200 are in development (231). Their role is recognised by funders such as the NIHR, guideline developers such as NICE, and other groups such as the Cochrane Collaboration and European Medicines Agency (232).

The value of a COS depends on several factors, including its need, the method by which it is developed, and the extent to which it is adopted by investigators. The Core Outcome Measures in Effectiveness Trials (COMET) initiative exists to facilitate these and to provide a central, open-access repository to support dissemination (231). A growing body of evidence exists to optimise how a COS should be developed, including work exploring methods of outcome scoring, the nature of feedback presented to participants, the impact of attrition between consensus rounds, and how consensus should be defined (233). In contrast, relatively little evidence exists to describe how adoption amongst investigators can be maximised. This is a challenge

for COS developers since the benefits of a COS can only be realised following wide community adoption. A systematic review by Hughes and colleagues noted that the uptake of COS in future relevant RCTs is widely variable (0-82%), with a key reason being a lack of understanding about their role in clinical research (234).

There are a number of benefits to incorporating a COS within the design of a clinical trial. Firstly, a COS reduces heterogeneity in outcome reporting by encouraging investigators to measure the same outcomes. This facilitates faster and more robust evidence synthesis leading to earlier implementation of appropriate research findings in to practice. Secondly, a COS helps to reduce reporting bias arising from the selective reporting of favourable results. By pre-specifying a COS during the design of a clinical trial, the selection of outcomes is transparent and the risk of bias is reduced. Lastly, a COS ensures that all relevant and important outcomes are measured. This is a product of the COS development process, which seeks to engage all key stakeholder groups, such as patients, carers, and healthcare professionals in a process of collective consensus. It ensures that the most relevant outcomes to the health service, its users, and professionals are prioritised (235).

5.1.3. A core outcome set for postoperative ileus

The assessment of postoperative ileus in clinical trials is complex. Most previously reported definitions focus on the return of bowel function, the need for NGT reinsertion, or the duration of hospital stay (16). This likely reflects the perspectives of clinicians as to which outcomes are considered most important. In contrast, evidence exists that patients prioritise different outcomes during their recovery, such as freedom from pain, nausea, and vomiting (236). It is unclear what outcomes are important to other healthcare professionals, such as nurses and dietitians, but they

also have a key role in facilitating recovery after surgery. There is a need for a core outcome set in this setting to prioritise the selection of outcomes through mutual consensus as well as to reduce heterogeneity between studies. This does not replace the perspectives drawn from earlier consensus exercises on the definition of postoperative ileus or the work done to produce assessment tools. Instead, it aims to complement them by providing a pragmatic framework for outcome assessment.

5.1.4. Aims and objectives

The aim of this work is to develop an agreed core outcome set for postoperative ileus after intestinal surgery that is generalisable across healthcare settings.

The objectives of this work are as follows:

1. To generate a comprehensive list of outcomes used to describe postoperative ileus in previous literature from the results of a systematic review
2. To supplement the list of outcomes identified from existing literature with others identified from consultation groups with key stakeholders
3. To explore whether consensus can be reached between key stakeholders about what outcomes to include in a COS for postoperative ileus and to ratify it for dissemination

5.2. Methods

5.2.1. Overview of methods

The development of this COS was undertaken according to the Core Outcome Set-STAndards for Development framework (COS-STAD) (237). This outlines the minimum standards to be considered whilst developing a COS and applying it

robustly to health research. The first step involves setting the scope of the COS, including details of the setting in which it should be used, the health condition, the patient population, and the range of applicable healthcare interventions. The second step involves identifying 'panels' of key stakeholders, including those who will use the COS (such as clinical investigators), healthcare professionals, and patients who are affected by it. The third step involves an iterative process of seeking consensus across key stakeholder panels to identify, prioritise, and agree a series of core outcomes. In the present study, this comprised three sequential stages, including a systematic review with consultation exercise, a Delphi prioritisation process, and a final stakeholder consensus meeting. The final output is an agreed COS, ratified for immediate dissemination and for adoption in future applicable research.

5.2.2. Ethics and governance

As a study involving the recruitment of healthcare workers and members of the public from non-NHS settings, consideration by a university REC was sought. Approval was confirmed by the University of Sheffield REC (Ref: 029907) on 27th September 2019. A full outline of necessary amendments to the final approval during the course of the study is provided in Appendix A-5.1. The study protocol was published prospectively following external peer review and the COS was registered with the COMET initiative prior to the start of its development (238, 239). To ensure full transparency, the report described herein is reported in line with the Core Outcome Set-Standards for Reporting (COS-STAR) guidance (240).

5.2.3. Scope

The scope of the COS was defined according to the COS-STAD framework, as follows:

Setting: The COS will be applicable in academic health settings, such as during the development and reporting of clinical studies. This includes randomised and non-randomised studies which involve a healthcare intervention.

- *Health Condition:* The COS will be applicable to postoperative ileus, a condition characterised by intestinal dysfunction in the days after surgery. Specifically, postoperative ileus exists in the absence of an obstructive cause (such as mechanical bowel obstruction), which is beyond the remit of this COS.
- *Patient Population:* The COS will be applicable to adult patients undergoing intestinal surgery. Adults are defined as individuals aged ≥18 years and intestinal surgery is considered to represent any intra-abdominal procedure on the intestinal tract (sub-diaphragmatic oesophagus to anus) with or without the formation of a stoma. The scope extends across international settings.
- *Healthcare Interventions:* The COS will be applicable to clinical studies evaluating the effectiveness of an intervention for which the purpose is to prevent, reduce, or curtail the impact of postoperative ileus. This includes any medicinal or non-medicinal intervention, including medical devices.

5.2.4. Stakeholders

Three stakeholder panels were prospectively defined. All panels were considered to hold unique perspectives capable of guiding the development process, including:

- *Patients:* This panel comprised adult members of the public with previous experience of undergoing intestinal surgery.
- *Medical professionals:* This panel comprised surgeons and physicians who are responsible for delivering patient care. Perspectives from both consultant/attending and trainee professionals were considered to be relevant.

- *Allied healthcare professionals (AHP):* This panel comprised nurses and dietitians who are responsible for delivering patient care. Perspectives from all nursing roles including specialist nurses were considered to be relevant.

To ensure that the development process remained applicable to all stakeholder groups, a multi-disciplinary steering committee was convened. This included international representation from Asia, Australasia, Europe, and North America, and included patient, medical, and allied healthcare investigators. A full outline of the committee and their contributions to the study are provided in Appendix A-5.2.

5.2.5. Patient and public involvement

A pro-active approach to patient and public involvement was used throughout to ensure that the patient voice remained prominent at all stages. Two public representatives joined the Steering Committee, each with extensive experience of patient and public involvement activities in the past. They advised on the study protocol, assisted with recruitment across public networks, assisted with the development of participant-facing materials such as the provision of plain English summaries, and contributed to management decisions throughout the study. Their role will continue during future dissemination and implementation of the COS in practice.

5.2.6. Recruitment and consent

Patients, medical professionals, and AHPs were eligible to take part in each stage of the study if they had experience of undergoing or caring for people after intestinal surgery, respectively. No other exclusion criteria were applied. Medical professionals and AHPs were approached via multiple routes, including social media, professional mailing lists, and charity distribution channels. Patients were approached via social

media and patient and public involvement networks. For the consultation exercise, individuals were invited to express an interest in taking part and participants were selected purposively according to their stakeholder panel and country of residence. For the Delphi process, individuals were invited to self-select themselves for participation after confirming the study eligibility criteria. For the consensus meeting, participants were selected purposively (stakeholder panel and country of residence) from those who had expressed an interest during the earlier Delphi process. At all stages, basic characteristic data were collected, including those required to confirm eligibility. Informed consent was confirmed using an online form hosted by the Research Electronic Data Capture (REDCap) platform. Written versions of the participant information material and consent forms can be found in Appendix A-5.3.

5.2.7. Longlisting of candidate outcomes

A longlist of candidate outcomes was generated using two sequential approaches. The first involved extraction of outcomes from an existing systematic review and the second involved a stakeholder consultation exercise.

5.2.7.1. Systematic review of outcomes used in previous research

An initial longlist was generated from the results of a systematic review published in 2018 in preparation for this development process (241). This was a registered review of published literature (PROSPERO: CRD42017082351) involving searches of MEDLINE, EMBASE, and CINAHL databases, as well as all ‘Primary Registries’ included on the World Health Organisation (WHO) Registry Network. All RCTs published or registered between 1990 and 2017 involving adult patients undergoing intestinal surgery and reporting at least one outcome relating to bowel function were included. Outcomes were presented according to a series of conceptual outcome

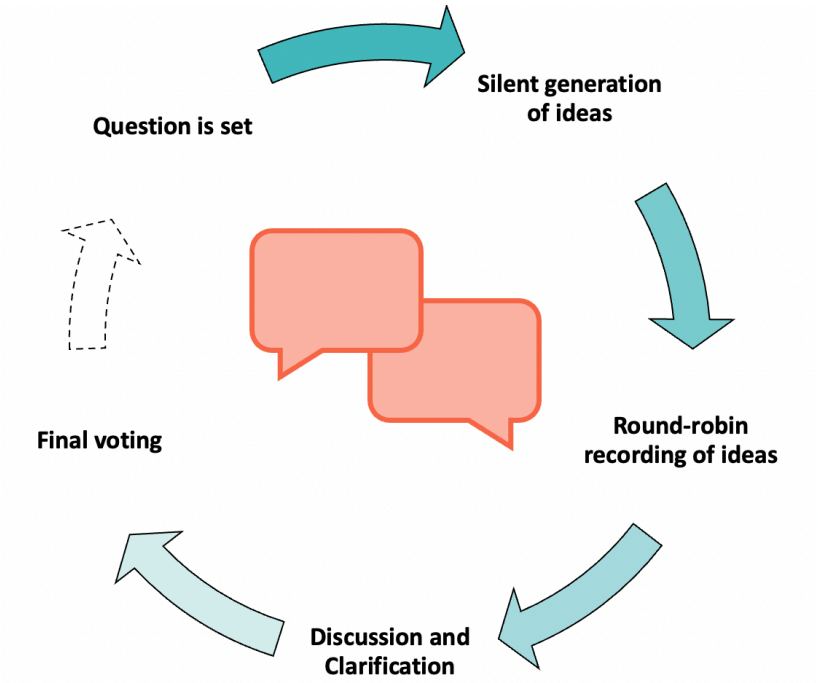
domains, including “Life Impact”, “Pathological Manifestations”, and “Resource Use”, as recommended by the Outcome Measures in Rheumatology (OMERACT) Framework which is widely applied elsewhere (242). For the purpose of longlisting, all outcomes that were reported in the review and their respective conceptual domain were extracted by a single investigator and catalogued verbatim.

5.2.7.2. Stakeholder consultation to identify supplementary outcomes

To explore whether outcomes existed that had not been identified from the systematic review of literature, consultation groups with key stakeholders were convened via video-conference. A nominal group technique (NGT) approach was used to identify and agree additional outcomes to be added to the longlist. The NGT approach was selected for its ability to facilitate new, unrestricted, idea-generation amongst participants. This differs from focus groups as it involves setting a single question for discussion followed by four stages: silent generation of ideas; round robin of new suggestions; clarification of ideas; and final voting (Figure 5.1) (243).

During each group, a working longlist was presented alongside the question: “Should any other outcomes be added to the list”. This was followed by 10 minutes of reflection (‘silent generation of ideas’), followed by an invitation to suggest new outcomes in a ‘round robin’ fashion. This continued until no new suggestions were forthcoming. Groups discussed each new outcome, including possible amendments (‘clarification’), and then voted on whether to include it in a revised longlist (‘voting’). The threshold for acceptance was a majority between participants of each group.

Figure 5.1 – Summary of Nominal Group Technique



5.2.7.3. Ratification of the outcome longlist

The working longlist was reviewed by the Steering Committee. In cases of composite outcomes, these were broken down to produce discrete constructs. Duplicated outcomes arising as a result of this process were consolidated to avoid repetition. A small number of additional outcomes were added by the committee where this was considered to improve breadth and international applicability. The final longlist was agreed and ratified by all members of the Steering Committee.

5.2.8. Delphi survey to prioritise outcomes

The final longlist was used to populate a Delphi survey. The Delphi technique was selected for its ability to gather opinions from a large number of stakeholders followed

by cross-panel feedback (243). This facilitates an iterative process of prioritisation, leading to a final stakeholder consensus meeting.

5.2.8.1. Survey development

The Delphi survey was facilitated using the Google Forms platform (Google, Mountain View, CA). All outcomes were presented in a random order alongside a nine-point integer numerical rating scale (NRS), as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) group (244). Higher ratings indicated greater importance, with 9 representing an outcome that was “important” and 1 representing an outcome that was “not important”. Each outcome was accompanied by a plain English summary, developed with close public input (Appendix A-5.4). The survey was piloted by the Steering Committee, who provided feedback relating to its structure and clarity of technical and plain English language. This was used to refine the survey prior to dissemination to participants.

5.2.8.2. Survey dissemination

The Delphi survey was disseminated across three rounds. During Round 1, participants were invited to rate all longlisted outcomes using the NRS scale. Any outcome that fulfilled one of two pre-defined thresholds was carried forward to the consensus meeting (Table 5.3). The first threshold required at least 70% of participants from each panel to provide a response between 7 and 9 (“cross-panel criteria”). The second required at least 90% of participants from any single panel to provide a response between 7 and 9 (“single panel criteria”). At the end of Round 1, participants were invited to propose additional outcomes to be considered during future rounds. These were reviewed by members of the Steering Committee for possible inclusion in subsequent rounds according to uniqueness and scope.

Only participants who took part in Round 1 were invited to Round 2 and in turn only those who took part in Round 2 were invited to Round 3. Personalised feedback was provided to participants prior to each subsequent round (see 5.2.8.3. S*urvey feedback and analysis*). Outcomes that had not achieved one of the pre-defined thresholds to be carried forward were presented again for a second and third round of voting, respectively. The same thresholds were applied across all rounds and no further opportunities for participants to propose new outcomes were provided.

5.2.8.3. Survey feedback and analysis

Prior to completing Round 2 and Round 3, participants were shown a personalised summary of their responses from the earlier round along with an aggregated summary of responses for each stakeholder panel. The aggregated summaries were expressed descriptively using the median NRS response for each outcome. The feedback was presented numerically (example shown in Appendix A-5.5). Participants were asked to consider this feedback prior to completing each subsequent round.

Table 5.3 – Delphi and consensus meeting thresholds for consensus

Delphi Prioritisation Process

Consensus was achieved if at least one of the following criteria were met

- ≥70% of participants from each stakeholder group rated an outcome between 7-9
- ≥90% of participants from a single stakeholder group rated an outcome between 7-9

An extended threshold was set for consideration of “extended-threshold” outcomes:

- ≥65% of participants from each stakeholder group rated an outcome between 7-9 on the numerical rating scale during Round 3 of the Delphi Process

Consensus Meeting

Motions for consideration of consensus were ratified if:

- ≥80% of participants voted in favour of the proposed consensus statement

5.2.8.4. Variations to protocol

After careful consideration by the Steering Committee, it was decided to re-consider some outcomes that had fallen short of the pre-defined thresholds. The first reason was due to strong advocacy from public representatives who felt that some patient-centric outcomes had been narrowly excluded during the Delphi process. To facilitate this, an extended threshold was set requiring at least 65% of participants from each panel to provide an NRS response between 7 and 9 (Table 5.3). The second reason was due to erratic response patterns observed for a single outcome ('time to tolerate fluid intake') between rounds. These outcomes (herein referred to as "extended-threshold outcomes') were carried forward for detailed discussion during the consensus meeting and were considered separately from those that had been prioritised per-protocol.

5.2.9. Consensus meeting to agree the final core outcome set

An online consultation meeting was facilitated via video-conference using the online Blackboard Collaborate platform (Blackboard Inc., Reston, VA) on 6th March 2021. Participants were provided with the list of prioritised outcomes from the Delphi survey (including plain English summaries) prior to the meeting. A pre-meeting briefing took place to familiarise participants with the online platform and the house rules (Appendix A-5.6). An independent Chairperson with expertise in COS development co-facilitated the meeting. Diverging views were actively sought throughout and the Chairperson ensured that all participants had the opportunity to contribute to the discussion.

The first part of the meeting focussed on the content of the COS. Participants were invited to ratify or object to the outcomes that had been carried forward from the Delphi survey per-protocol. It was not possible to exclude these after being prioritised

by the wider participant population, but clarifications to the wording were permitted where these were felt to improve clarity. The extended-threshold outcomes were discussed in turn, with each being subject to a final vote on whether to include in the final set. The second part of the meeting focussed on the presentation of the COS, including clustering of outcomes into domains. Throughout the meeting, motions for consideration of consensus were generated through discussion and presented for final voting by the Chairperson. Participants cast their votes anonymously via the online *Polling* feature using the responses “Yes”, “No”, or “Abstain”. A motion was accepted if at least 80% of non-abstaining participants voted in favour.

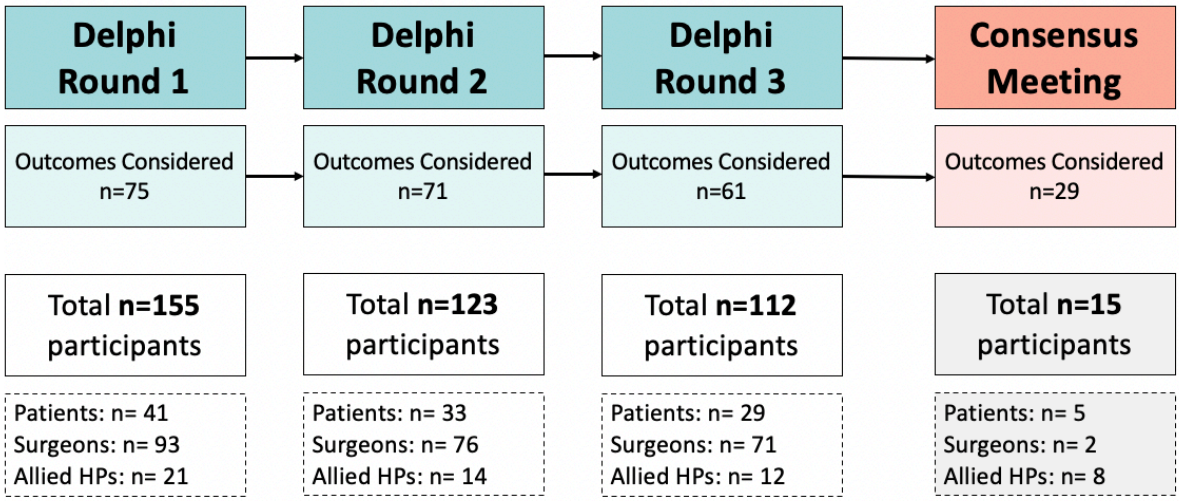
5.2.10. Statistical analysis

All data were expressed descriptively as rates (%) or averages (medians with IQR). Additional analyses were performed to explore the potential for attrition bias between Delphi rounds and the potential for sampling bias during the consensus meeting. To determine if between-round attrition may have introduced bias, the distribution of NRS responses submitted across all outcomes were compared between each round (245). Distributions were explored visually using histograms and statistically using tests of normality (Shapiro-Wilk for <50 participants and Kolmogorov-Smirnov for ≥50 participants). Unpaired t-tests or Mann-Whitney U-Tests were then used to compare distributions, with significant differences between rounds considered to represent significant attrition bias. Sampling bias was similarly explored by comparing the distribution of NRS responses submitted in Round 3 for participants who were and were not sampled to take part in the consensus meeting. For all analyses, the level of statistical significance was set at $P<0.05$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) v26 (IBM Corp., Armonk, NY).

5.3. Results

An overview of the COS development process, including an outline of the flow of candidate outcomes at each stage, is shown in Figure 5.2.

Figure 5.2 – Overview of COS development process



5.3.1. Participant characteristics

For the consultation exercise, participants were purposively sampled. A total of 26 individuals expressed an interest in taking part and 14 were recruited. These were allocated to panel-specific groups, including one patient group (n=3), two medical professional groups (n=5 and n=3), and one AHP group (n=3).

For the Delphi process, 155 individuals consented and participated in Round 1 of the survey. After completing Round 1, 123 took part in Round 2 (n=123/155; 79.4%) and 112 took part in Round 3 (n=112/123; 91.1%). The final responses received during Round 3 included 29 patients (29/112; 25.9%), 71 medical professionals (71/112; 63.4%), and 12 AHPs (12/112; 10.7%).

For the consensus meeting, participants were purposively sampled from those who had expressed an interest during the Delphi process. A total of 27 submitted an expression of interest and 14 were recruited. This included five patients (n=5/15; 33.3%), eight medical professionals (8/15; 53.3%), and two AHPs (n=2/15; 13.3%). A full outline of participant characteristics for each stage are shown in Table 5.4.

Table 5.4 – Participant characteristics during development of the COS

	Consultation (n=14)	R1 Delphi (n=155)	R2 Delphi (n=123)	R3 Delphi (n=112)	Consensus (n=15)
Stakeholder Group					
Patients	3 (21.4%)	41 (26.5%)	33 (26.8%)	29 (25.9%)	5 (33.3%)
AHPs	3 (21.4%)	21 (13.5%)	14 (11.4%)	12 (10.7%)	2 (13.3%)
Medical Professionals	8 (57.1%)	93 (60.0%)	76 (61.8%)	71 (63.4%)	8 (53.3%)
Location					
Asia	0 (0.0%)	3 (1.9%)	3 (2.4%)	3 (2.7%)	1 (6.7%)
Africa	0 (0.0%)	2 (1.3%)	2 (1.6%)	1 (0.9%)	0 (0.0%)
Australasia	0 (0.0%)	24 (15.5%)	14 (11.4%)	13 (11.6%)	3 (20.0%)
Europe (Non-UK)	6 (42.9%)	20 (12.9%)	16 (13.0%)	16 (14.3%)	2 (13.3%)
North America	0 (0.0%)	1 (0.6%)	1 (0.8%)	1 (0.9%)	0 (0.0%)
United Kingdom (UK)	8 (57.1%)	105 (67.7%)	87 (70.7%)	78 (69.6%)	9 (60.0%)

AHPs: Allied Healthcare Professionals; UK: United Kingdom; R: Round

5.3.2. Longlisting of outcomes

5.3.2.1. Summary of existing systematic review

The systematic review comprised 217 published RCTs and 96 trial registry records (210). The majority of published RCTs were reported between 2010-2017 (49.3%) and from a wide range of geographical settings, including Asia (37.8%), Europe (32.3%), and North America (20.3%). Seventy-three outcomes were extracted from the systematic review verbatim. These included 27 outcomes which were relevant to “Life Impact”, 21 relevant to “Pathological Manifestation”, 23 relevant to both “Life Impact” and “Pathological Manifestation”, and 2 relevant to “Resource Use” domains.

5.3.2.2. Stakeholder consultation exercise

All 73 outcomes extracted from the systematic review were presented to participants of the consultation exercise. In total, six new outcomes were proposed across all consultation groups. This included two from the patient group, two from the AHP group, and one from each of the medical professional groups. Following clarification and discussion, six were added to the longlist by majority agreement. A full list of proposed outcomes and voting patterns is provided in Table 5.5.

Table 5.5 – Proposed outcomes during nominal groups

Consultation Group	Proposed Outcome(s)	Final Decision	Voting responses
Patient Group 1 (n=3)	*"Anxiety"*	Added to longlist	In favour n=3/3
	"Vomiting with nasogastric tube in situ"	Added to longlist	In favour n=3/3
AHP Group 1 (n=3)	*"Overall fluid balance"*	Added to longlist	In favour n=3/3
	"Mobility"	Added to longlist	In favour n=3/3
Medical Professional Group 1 (n=3)	*"Postoperative inflammatory response"*	Added to longlist	In favour n=3/3
Medical Professional Group 2 (n=5)	*"Radiological intestinal dilatation"*	Added to longlist	In favour n=4/5

AHPs: Allied Healthcare Professionals

5.3.2.3. Ratification of the outcome longlist

All outcomes extracted from the systematic review (n=73) as well as those generated from the consultation exercise (n=6) were considered by the Steering Committee. After careful consideration, 11 composite outcomes were deconstructed to form 22 single constructs; twenty duplicated outcomes were subsequently removed; and 12 closely related outcomes were rationalised to form 4 summary outcomes. A further 13 outcomes were added by the Steering Committee. Overall, this produced 75 unique outcomes used to populate Round 1 of the Delphi process.

5.3.3. Delphi prioritisation process

All 75 longlisted outcomes were presented to participants (n=155) during Round 1. Thirteen reached a threshold to be carried forward to the consensus meeting, including 10 via the cross-panel criteria (≥70%) and three via the single panel criteria (≥90%). Of the latter, one was due to prioritisation by AHPs and two were due to prioritisation by patients. Twenty-six new outcomes were proposed by participants and eight were accepted for presentation in later rounds (Appendix A-5.7).

During Round 2, seventy outcomes were presented to participants (n=123). This included 62 existing outcomes that had not been carried forward to the consensus meeting and eight new proposals that had been accepted from Round 1. A further nine outcomes reached a threshold to be carried forward, including two via the cross-panel criteria and seven via the single panel criteria. Four of the latter were due to prioritisation by AHPs and three due to prioritisation by patients.

During Round 3, sixty-one outcomes that had not achieved one of the pre-defined thresholds to be carried forward were re-presented (n=112). One outcome was carried forward to the consensus meeting via the single panel criteria due to prioritisation by patients. Following consideration by the Steering Committee, it was agreed to carry forward six extended-threshold outcomes that had marginally missed the pre-defined thresholds.

In total, 29 out of 75 outcomes were carried forward across all three Delphi rounds, with the remaining 46 subsequently discarded from the process. A full outline of outcomes and panel-specific scoring patterns for each round is shown in Table 5.6.

Table 5.6 – Results of the Delphi prioritisation process

Outcome	Medical Professionals			Allied Healthcare Professionals			Patients		
	R1 (7-9) (n=93)	R2 (7-9) (n=76)	R3 (7-9) (n=71)	R1 (7-9) (n=21)	R2 (7-9) (n=14)	R3 (7-9) (n=12)	R1 (7-9) (n=41)	R2 (7-9) (n=33)	R3 (7-9) (n=29)
Outcomes prioritised and considered at the consensus meeting									
Incidence of readmission due to postoperative ileus	88.17%	NR	NR	90.48%	NR	NR	87.80%	NR	NR
A measure of gastrointestinal recovery using a validated tool	78.49%	NR	NR	76.19%	NR	NR	82.93%	NR	NR
Need for parenteral nutrition	81.72%	NR	NR	95.24%	NR	NR	63.41%	NR	NR
Time to first stoma output	78.49%	NR	NR	90.48%	NR	NR	75.61%	NR	NR
Need for nasogastric tube placement	84.95%	NR	NR	90.48%	NR	NR	70.73%	NR	NR
Severity of abdominal pain	40.86%	NR	NR	57.14%	NR	NR	92.68%	NR	NR
Incidence of postoperative ileus	87.10%	NR	NR	90.48%	NR	NR	85.37%	NR	NR
Duration of postoperative ileus	86.02%	NR	NR	95.24%	NR	NR	82.93%	NR	NR
Incidence of prolonged postoperative ileus	92.47%	NR	NR	95.24%	NR	NR	85.37%	NR	NR
Incidence of morbidity due to postoperative ileus	82.80%	NR	NR	100.00%	NR	NR	87.80%	NR	NR
Complications: Anastomotic leak	83.87%	NR	NR	85.71%	NR	NR	90.24%	NR	NR
Readiness for discharge based on gastrointestinal function	70.97%	NR	NR	76.19%	NR	NR	80.49%	NR	NR
Complications: Enterotomy	58.06%	NR	NR	66.67%	NR	NR	90.24%	NR	NR
Nutritional status	67.74%	73.68%	NR	71.43%	92.86%	NR	65.85%	63.64%	NR
Volume of nasogastric tube aspirate	53.76%	64.47%	NR	85.71%	92.86%	NR	53.66%	75.76%	NR
Duration of vomiting	63.44%	64.47%	NR	71.43%	92.86%	NR	70.73%	72.73%	NR
Complications: Abdominal infection	60.22%	69.74%	NR	57.14%	64.29%	NR	82.93%	93.94%	NR
Incidence of nausea	53.76%	56.58%	NR	76.19%	92.86%	NR	63.41%	54.55%	NR
Complications: Peritonitis	65.59%	76.32%	NR	66.67%	71.43%	NR	70.73%	72.73%	NR
Complications: Sepsis	62.37%	72.37%	NR	66.67%	71.43%	NR	87.80%	90.91%	NR
Need for intensive care unit admission*	NR	63.16%	NR	NR	71.43%	NR	NR	96.97%	NR

Time without adequate nutritional intake*	NR	71.05%	NR	NR	85.71%	NR	NR	75.76%	NR
Complications: Organ injury or failure	67.74%	67.11%	70.42%	66.67%	71.43%	58.33%	80.49%	87.88%	93.10%
Extended-threshold outcomes considered at the consensus meeting									
Incidence of vomiting	74.19%	72.37%	76.06%	71.43%	78.57%	66.67%	68.29%	66.67%	65.52%
Incidence of nasogastric tube aspirate > 500 ml per day	58.06%	65.79%	67.61%	71.43%	78.57%	66.67%	58.54%	72.73%	65.52%
Time to tolerate normal diet	69.89%	64.47%	66.20%	71.43%	71.43%	75.00%	48.78%	57.58%	65.52%
Time to first passage of stool	64.52%	64.47%	64.79%	85.71%	71.43%	83.33%	73.17%	75.76%	68.97%
Gastrointestinal-related quality of life	63.44%	69.74%	69.01%	57.14%	64.29%	75.00%	78.05%	69.70%	72.41%
Time to tolerate fluid intake	72.04%	67.11%	60.56%	71.43%	85.71%	75.00%	68.29%	69.70%	62.07%
Outcomes not considered at the consensus meeting									
Frequency of bowel sounds	15.05%	13.16%	11.27%	61.90%	42.86%	33.33%	43.90%	39.39%	34.48%
Complications: Renal	45.16%	44.74%	38.03%	42.86%	42.86%	25.00%	73.17%	69.70%	72.41%
Gastric emptying	31.18%	28.95%	16.90%	61.90%	57.14%	41.67%	60.98%	45.45%	27.59%
Mobility	60.22%	55.26%	60.56%	52.38%	64.29%	50.00%	68.29%	66.67%	68.97%
Incidence of abdominal pain	45.16%	42.11%	47.89%	52.38%	50.00%	50.00%	85.37%	69.70%	62.07%
Radiological intestinal dilatation	31.18%	26.32%	30.99%	71.43%	64.29%	58.33%	58.54%	63.64%	31.03%
Anxiety	23.66%	17.11%	14.08%	52.38%	42.86%	25.00%	58.54%	45.45%	41.38%
Need for laxative medication	27.96%	19.74%	9.86%	52.38%	57.14%	41.67%	41.46%	45.45%	24.14%
Quantification of bowel gas	17.20%	9.21%	12.68%	47.62%	42.86%	25.00%	43.90%	33.33%	31.03%
Time to first postoperative abdominal peristalsis	25.81%	26.32%	29.58%	57.14%	50.00%	50.00%	63.41%	66.67%	58.62%
Incidence of satiety	20.43%	15.79%	8.45%	42.86%	42.86%	8.33%	29.27%	30.30%	10.34%
Complications: Urinary	22.58%	27.63%	18.31%	42.86%	28.57%	25.00%	75.61%	75.76%	62.07%
Complications: Pneumonia	58.06%	56.58%	60.56%	38.10%	50.00%	41.67%	63.41%	78.79%	75.86%
Vomiting after nasogastric tube removal	68.82%	59.21%	59.15%	71.43%	78.57%	75.00%	53.66%	66.67%	62.07%
Time to first solid intake	60.22%	55.26%	53.52%	76.19%	85.71%	33.33%	58.54%	39.39%	58.62%
Time to return of appetite	47.31%	34.21%	21.13%	61.90%	71.43%	50.00%	41.46%	39.39%	37.93%
Overall fluid balance	54.84%	59.21%	50.70%	76.19%	78.57%	75.00%	70.73%	69.70%	65.52%

Postoperative inflammatory response	50.54%	47.37%	39.44%	66.67%	35.71%	41.67%	73.17%	72.73%	65.52%
Duration of parenteral nutrition	75.27%	78.95%	80.28%	80.95%	78.57%	66.67%	63.41%	66.67%	58.62%
Time to first passage of flatus	70.97%	60.53%	64.79%	80.95%	64.29%	66.67%	53.66%	63.64%	51.72%
Extent of satiety	21.51%	17.11%	9.86%	47.62%	35.71%	8.33%	41.46%	30.30%	17.24%
Duration of belching	20.43%	14.47%	11.27%	47.62%	50.00%	16.67%	29.27%	15.15%	13.79%
Amount of food intake per meal	26.88%	25.00%	18.31%	52.38%	42.86%	16.67%	36.59%	30.30%	24.14%
Time to second passage of flatus	30.11%	19.74%	16.90%	66.67%	71.43%	33.33%	46.34%	33.33%	27.59%
Cumulative frequency of flatus	34.41%	23.68%	16.90%	66.67%	42.86%	41.67%	39.02%	45.45%	20.69%
Complications: Thrombosis or embolism	43.01%	40.79%	39.44%	38.10%	28.57%	25.00%	75.61%	84.85%	75.86%
Time to detect bowel sounds	21.51%	13.16%	16.90%	61.90%	35.71%	16.67%	51.22%	42.42%	37.93%
Need for antiemetic medication	41.94%	35.53%	35.21%	61.90%	50.00%	41.67%	56.10%	57.58%	44.83%
Complications: Cardiac	41.94%	40.79%	40.85%	38.10%	28.57%	25.00%	70.73%	78.79%	86.21%
Duration of nasogastric tube placement	67.74%	65.79%	69.01%	80.95%	85.71%	58.33%	65.85%	75.76%	75.86%
Consistency of stool	17.20%	11.84%	12.68%	47.62%	42.86%	8.33%	46.34%	39.39%	34.48%
Extent of hunger	30.11%	22.37%	18.31%	33.33%	64.29%	50.00%	26.83%	24.24%	24.14%
Time to first soft food	40.86%	34.21%	36.62%	71.43%	57.14%	50.00%	46.34%	57.58%	55.17%
Frequency of stool	23.66%	25.00%	21.13%	57.14%	57.14%	58.33%	60.98%	63.64%	62.07%
Vomiting with nasogastric tube in situ	48.39%	53.95%	54.93%	61.90%	85.71%	83.33%	75.61%	78.79%	72.41%
Incidence of abdominal swelling/distension	40.86%	40.79%	26.76%	71.43%	78.57%	66.67%	56.10%	48.48%	48.28%
Duration of nausea	48.39%	42.11%	43.66%	66.67%	64.29%	50.00%	73.17%	60.61%	48.28%
Complications: Respiratory	51.61%	55.26%	57.75%	42.86%	50.00%	41.67	70.73%	81.82%	72.41%
Complications: Wound infection	60.22%	40.79%	42.25%	42.86%	42.86%	41.67%	82.93%	78.79%	82.76%
Incidence of hiccups	38.71%	30.26%	22.54%	52.38%	57.14%	41.67%	24.39%	27.27%	10.34%
Severity of abdominal swelling/distension	43.01%	39.47%	38.03%	76.19%	85.71%	50.00%	65.85%	66.67%	68.97%
Time to tolerate solid intake	65.59%	55.26%	66.20%	66.67%	78.57%	75.00%	51.22%	66.67%	58.62%
Time to tolerate low-residue diet	47.31%	34.21%	28.17%	57.14%	71.43%	41.67%	56.10%	54.55%	37.93%
Incidence of belching	25.81%	23.68%	18.31%	42.86%	50.00%	41.67%	31.71%	24.24%	13.79%

Gastrointestinal motility	35.48%	28.95%	29.58%	61.90%	50.00%	41.67%	51.22%	57.58%	44.83%
Time to intake of > 1000 ml fluids per day	41.94%	38.16%	45.07%	57.14%	42.86%	41.67%	60.98%	51.52%	48.28%
Gastrointestinal transit	37.63%	39.47%	32.39%	61.90%	57.14%	41.67%	56.10%	54.55%	44.83%
Time to first fluid intake	50.54%	55.26%	46.48%	71.43%	64.29%	58.33%	65.85%	51.52%	55.17%
Length of hospital stay*	NR	71.05%	66.20%	NR	64.29%	41.67%	NR	63.64%	55.17%
Mental well-being*	NR	38.16%	45.07%	NR	64.29%	66.67%	NR	69.70%	72.41%
Weight loss*	NR	47.37%	38.03%	NR	50.00%	33.33%	NR	39.39%	41.38%
Incidence of hypokalaemia*	NR	46.05%	38.03%	NR	57.14%	41.67%	NR	48.48%	44.83%
Cost of admission*	NR	55.26%	39.44%	NR	35.71%	41.67%	NR	27.27%	20.69%
Need for readmission (for any reason)*	NR	71.05%	69.01%	NR	64.29%	50.00%	NR	84.85%	89.66%

As per the Methods, participants were invited to propose new outcomes at the end of Round 1. Proposals considered by the Steering Committee and subsequently presented to participants during Round 2 are marked by an asterisk (*); Outcomes reaching the pre-defined criteria for consensus during each round were taken forward to the consensus meeting and not scored again in subsequent rounds. Others were re-presented in later rounds for further consideration; NR: Not rated (i.e. due to reaching consensus in earlier rounds); R: Round

5.3.4. Consensus meeting

The first part of the consensus meeting (n=15 participants) considered 23 prioritised and 6 extended-threshold outcomes for possible inclusion in the COS. There were no objections to the inclusion of all prioritised outcomes carried froward from the Delphi process and these were ratified for inclusion. The extended threshold outcomes were then discussed in turn. Agreement was reached to include the outcome “incidence of vomiting” (n=12/14, 85.7%; 1 abstention). Four other outcomes, including “time to first passage of stool” (n=4/13, 30.8%; 2 abstentions), “time to tolerate normal diet” (n=6/13, 46.2%; 2 abstentions), “time to tolerate fluid intake” (n=4/12, 33.3%; 3 abstentions), and “incidence of nasogastric tube aspirate >500ml/day” (n=2/11, 18.2%; 4 abstentions) did not achieve sufficient agreement and were discarded. The remaining outcome “gastrointestinal related quality-of-life” was felt to lack sufficient clarity for voting. Some participants felt that “quality-of-life” had connotations with longer-term well-being, which was beyond the defined scope of this COS. Consensus was achieved to re-phrase this outcome to “patient-reported perception of ileus” (n=12/14, 85.7%; 1 abstention). Participants then voted on whether to include it in the COS and this was agreed (n=12/14, 85.7%; 1 abstention).

The second part of the consensus meeting considered how the final COS should be presented for optimal clarity. One participant (Patient Panel) challenged whether the prioritised outcomes “incidence of postoperative ileus” and “incidence of prolonged postoperative ileus” were sufficiently unique to be included as independent items. Since defining these terms was beyond the scope of developing a COS, agreement was achieved to rationalise both to a single outcome “incidence of postoperative ileus” (n=12/13, 92.3%; 2 abstentions). Another participant (Medical Professional Panel) noted that four prioritised outcomes (“abdominal infection”; “anastomotic leak”,

“peritonitis”, and “enterotomy”) were akin to risk factors, rather than outcomes, for the development of ileus. Since these had been prioritised during the Delphi process, it was considered neither appropriate or desirable to exclude them from the COS. Instead, after thorough discussion, agreement was reached to retain them as a supplementary component of the COS to reflect essential contextual information to be reported alongside all other outcomes (12/12, 100%; 3 abstentions).

A final COS comprising of 20 outcomes, alongside 4 contextual items, was ratified by all participants (Table 5.7). Outcomes were clustered into domains to assist investigators when operationalising the COS. This was done through consensus, leading to six grouped domains and three outcomes which remained as standalone items. Agreed domains were: “Incidence and duration of ileus” including 2 outcomes (n=13/13, 100%; 2 abstentions); “Vomiting and gastric decompression” including 5 outcomes (n=11/12, 91.7%; 3 abstentions); “Nutritional factors” including 3 outcomes (n=12/12, 100%; 3 abstentions), “Return of gut function” including 3 outcomes (n=11/12, 91.7%; 3 abstentions); “Complications arising from ileus” including 4 outcomes (n=12/12, 100%; 3 abstentions); and “Pre-disposing factors for ileus” including four contextual items (n=12/12 100%; 3 abstentions).

5.3.5. Additional analyses

The rate of attrition between Round 1 (n=155 responses) and Round 2 (n=123 responses) was 20.6%. This was greatest in the AHP panel (33.3%), followed by the Patient (19.5%) and Medical Professional (18.3%) panels. The average Round 1 NRS response of participants who were lost to follow up (median: 7; IQR: 6-7) and who remained in the study (median 7; IQR: 6-7) was not significantly different (P=0.891), suggesting an absence of attrition bias between Rounds 1 and 2.

Table 5.7 – Final agreed COS

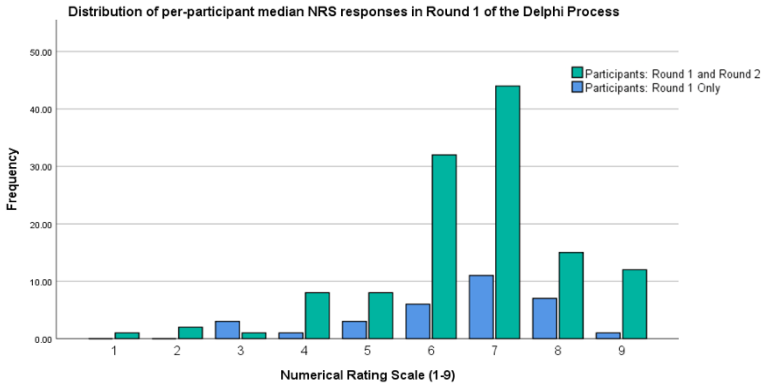
Domain	Core Outcome
Incidence and duration of ileus	Incidence of ileus Duration of ileus
Vomiting and gastric decompression	Incidence of nausea Incidence of vomiting Duration of vomiting Need for nasogastric tube placement Volume of nasogastric tube aspirate
Abdominal pain	Severity of abdominal pain
Nutritional factors	Nutritional status Time without adequate nutritional intake Need for parenteral nutrition
Return of gut function	A measure of gastrointestinal recovery using a validated tool Time to first stoma output Readiness for discharge based on gastrointestinal function
Patient experience	Patient-reported perception of ileus
Complications arising from ileus	Morbidity Septic complications Admission to intensive care Organ injury or failure
Readmission	Readmission
Pre-disposing factors for ileus	Abdominal infection Anastomotic leak Peritonitis Enterotomy

The rate of attrition between Round 2 (n=123 responses) and Round 3 (n=112 responses) was 8.9%. This was also greatest in the AHP panel (14.3%), followed by the Patient (12.1%) and Medical Professional (6.6%) panels. The average Round 2 NRS response of participants who were lost to follow up (median: 7; IQR: 6-8) and who remained in the study (median 7; IQR: 6-7) was not significantly different (P=0.385), suggesting an absence of attrition bias between Rounds 2 and 3.

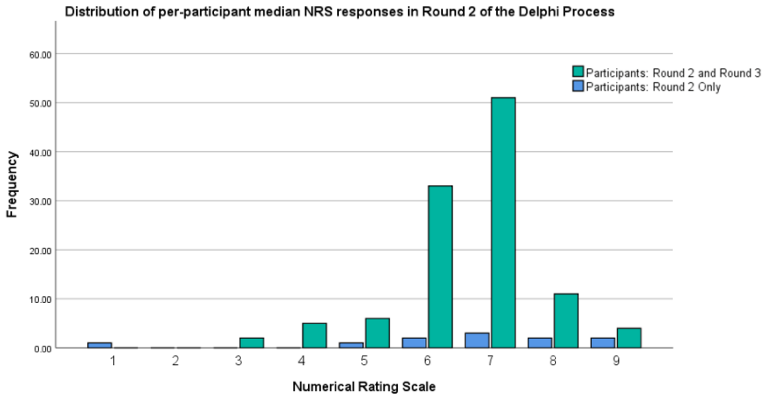
Participants of the consensus meeting were sampled purposively to ensure broad representation across stakeholder panels. The average Round 3 NRS response of participants who were sampled (median: 6; IQR: 6-7) and not sampled (median 6; IQR: 5-7) to take part in the meeting was not significantly different (P=0.385), suggesting an absence of sampling bias in the consensus meeting (Figure 5.3).

Figure 5.3. Graphical representation to explore attrition and sampling bias

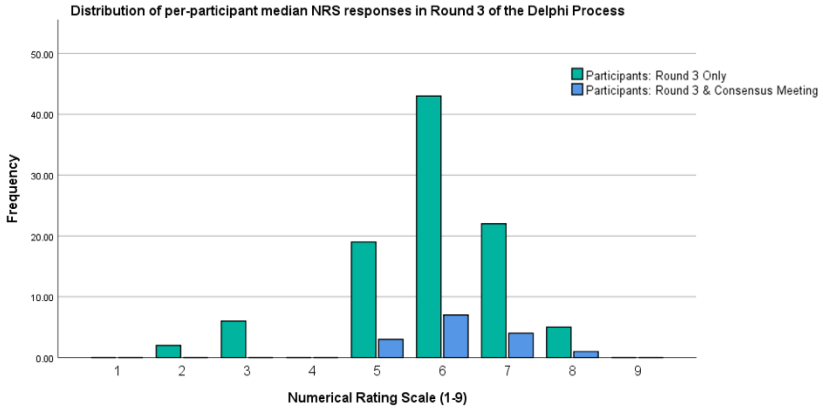
A



B



C



A: Distribution of median NRS responses of participants who were lost to follow up after Round 1 and participants who remained in the study at Round 2; B: Distribution of median NRS responses of participants who were lost to follow up after Round 2 and participants who remained in the study at Round 3; C: A: Distribution of median NRS responses of participants who were purposively sampled to take part in the consensus meeting and those who were not sampled. NRS: Numerical Rating Scale.

5.4. Discussion

5.4.1. Summary of main findings

A COS for postoperative ileus in adult patients undergoing intestinal surgery has been agreed through a systematic process of consensus. This was developed with close input from key stakeholders, including patients and healthcare professionals. The recruitment of participants on an international scale means that the content of the COS is applicable across broad healthcare settings, as is the challenge of postoperative ileus. It is the recommendation of this work that all future clinical trials exploring approaches to prevent, reduce, or curtail the impact of postoperative ileus should use this COS as a framework for selecting outcomes. This does not restrict the range of outcomes that are available to investigators, but instead it represents a minimum set of outcomes that have been prioritised for use in future research.

5.4.2. Context of existing literature

As far as can be determined from existing literature and from information contained on the COMET Database, no other COS relevant to postoperative ileus in adult patients has been previously agreed. Notably, the development of a COS for studies of postoperative ileus in children (<18 Years) is currently in development. This is an important study since postoperative ileus is common after paediatric surgery and there is evidence to suggest that important differences in prioritised outcomes may exist. When the results of this work become available, it is expected to complement the present COS and will ensure that an agreed framework for outcome selection exists across the full coverage of ages groups (246).

Earlier consensus processes have sought to define a standard definition for postoperative ileus (Table 5.1) (225). Exploring agreement on the most appropriate definition was beyond the scope of this work since a COS seeks only to define what outcomes are most important. A clear definition is important, however, particularly so that investigators can apply the agreed outcome “incidence of postoperative ileus” and measure it consistently. The work by Vather and colleagues is therefore considered complimentary and should be considered in parallel when operationalising the COS.

Over the next two years, ongoing work by Lee and colleagues will aim to develop a patient-reported outcome measure (PROM) for intestinal recovery after surgery (247). The expected final output is a PROM that is applicable to any type of intra-abdominal surgery, including patients undergoing intestinal surgery. This work is also considered complimentary to the present COS since it will provide an evidence-based approach to measure the agreed outcome “Patient-reported perception ileus”.

5.4.3. Considerations for reaching consensus

The Delphi method is commonly used to obtain input from a range of experts with the aim of seeking consensus. Key challenges include the selection of participants, managing strict timeframes, the possibility of a low response rate, and inadvertently guiding user feedback (248). Another key challenge is the approach to defining consensus and using this as an indication of when to close the process. A methodological review of Delphi studies in 2014 showed that 11 approaches to defining consensus were used across a sample of 98 published reports, with the most common approach based on percent agreement (median threshold 75%). Whilst the authors acknowledged that there is no way to show the validity of any

specific approach, they proposed that these decisions should be justified prospectively and reported transparently (249). In the present work, it was decided that consensus should be considered across all stakeholder groups but also with consideration to strongly held views of specific groups (such as patients). This led to the use of two prospectively chosen definitions for consensus, namely the “cross-panel” and “single-panel” criteria. The selection of 70% and 90% thresholds, respectively, was informed by previous evidence supporting consensus thresholds of approximately 75% as a mechanism to facilitate the convergence of opinions (250).

5.4.4. Strengths and limitations

This study has a number of strengths. Input from the public and other stakeholders was prominent throughout the development process, including in the recruitment strategy and the expert steering group. The impact of this involvement was pivotal and led to important decisions such as the handling of “extended threshold outcomes”, which ultimately shaped the final COS. Similarly, the international scope of recruitment and diverse representation within the Steering Committee helped to ensure that the final COS became globally inclusive. This will help to facilitate its adoption across the international community.

Limitations of the study are also recognised. Firstly, whilst the rate of participant attrition between Delphi rounds was in line with previous COS development work, there was a disproportionate attrition of AHP participants (251, 252). The reasons for this are unclear but it may suggest that this group felt less engaged or invested in the process compared to patients and medical professionals. The impact of this was mitigated by ensuring fair representation of AHPs at the final consensus meeting. There was also no evidence of significant attrition bias between rounds, suggesting

that the impact of attrition was minimal. Secondly, the majority of study activities were facilitated exclusively online using teleconference and survey platforms. It is possible that this excluded some potential participants, such as those who lacked computer literacy or who do not have access to the internet. This was mitigated by the diverse Steering Committee, who provided guidance throughout the process and offered insight whilst finalising the final longlist of outcomes. Lastly, due to budgetary, constraints all stages of the study were facilitated in English. This may have excluded some potential participants due to language barriers, but an attempt to mitigate this was made through the use of plain English recruitment and study materials. Public representatives were closely involved in the development of these resources to ensure that they were effective and appropriately pitched.

5.4.5. Implementation in practice

Patients, healthcare professionals, and society will only benefit from this COS if it is widely adopted in future trials. Previous literature has demonstrated that the uptake of COS instruments is variable, with common barriers including a lack of appreciation about their role in clinical research or a lack of knowledge amongst investigators that they exist (231).To address this, it is important that this COS is disseminated widely through multiple channels and with careful attention to guidance and education. The COS has already been disseminated as a peer reviewed publication with open-access, as well as via presentations at national and international conferences (253). Ongoing and future strategies include social media campaigns, engagement with learned societies and public advocacy groups, and community engagement with experts in the field. Another challenge with some COS instruments is managing the number of agreed outcomes and the practical implications of operationalising them in

future trials. This raises practical implications for the collection of research data, particularly around costs, logistics, and researcher and participant burden. The present work produced a COS comprising 20 outcomes and 4 contextual items, which will require dedicated resources to integrate into future trials. Importantly, however, this represents the product of wide community consensus, developed through a rigorous and systematic process. Abbreviations of the COS or selective reporting would eliminate its potential benefit, serving only to exacerbate the variation in outcome reporting. Within the dissemination strategy, it will be important to build confidence in the method of developing this COS, as well as the necessity for universal adoption. Possible approaches include education campaigns and positive reinforcement by funders and journal editors. An assessment of adoption will be planned in the future to explore the effectiveness of these strategies and the need for further efforts. As recommended by the COMET handbook, this will also include consideration of whether iterative adaptations to the content of the COS are required in light of new research, community attitudes, or clinical practice guidelines (245).

5.4.6. Future work

The role of a COS is to provide an agreed framework to guide the selection of outcomes. It does not, however, guide the selection of measurement instruments or the definition used for event outcomes. To ensure consistency in how these are measured, future work should consider the development of a core measurement set. This involves a process of systematically identifying existing instruments for each prioritised outcome, followed by assessments of quality and a consensus process to agree a single instrument or definition for each outcome. This process is guided by published guidance from the COSMIN Group (Consensus-based Standards for the

Selection of Health Measurement Instruments) (230). Additionally, future work on vagus nerve stimulation and ileus should consider the extent to which some outcomes may be directly impacted by the therapy itself and how this would affect the interpretation of results. For instance, the role of vagus nerve stimulation in reducing nausea through other vagal mechanisms, rather than the anti-inflammatory mechanism associated with intestinal recovery.

Chapter 6

Overall discussion

Preface

In this final chapter, the findings of the thesis are summarised according to the overall aim and objectives. A critical assessment of feasibility is discussed in relation to the progression criteria and recommendations for future work are made. An appraisal of the strengths and weaknesses of the research are explored along with a description of its anticipated impacts. The chapter ends with a final conclusion describing the feasibility of non-invasive vagus nerve stimulation to reduce ileus after colorectal surgery and the steps required to enable a definitive trial in the future.

6.1. Summary of findings

This thesis describes an assessment of feasibility for a definitive evaluation of non-invasive vagus nerve stimulation to reduce ileus after colorectal surgery. Central to this are principles set out by the IDEAL Collaboration on the iterative assessment of novel surgical technology and innovation (Table 6.1) (254). The findings presented here do not give a final answer as to whether non-invasive vagus nerve stimulation is clinically or economically beneficial for patients and health systems. Rather, it provides an assessment of whether future definitive work is appropriate, feasible in the clinical context, and optimally designed with respect to methodological challenges.

Table 6.1 – IDEAL Collaboration Framework for Surgical Innovation

Stage of Innovation	Methodological Descriptor	Purpose
Stage 0: Pre-clinical	Basic science and pre-clinical animal studies	To explore safety and technical consistency prior to human testing
Stage 1: Idea	First in human	Proof of concept in a small and selected patient population
Stage 2a: Development	Single-centre observational studies	Development of intervention and technical parameters
Stage 2b: Exploration	Pilot and feasibility assessments in readiness for a robust RCT	Assessment of feasibility and refinement of a definitive study
Stage 3: Assessment	Definitive evaluations of clinical and cost effectiveness	Comparative assessment of clinical and economic benefit
Stage 4: Monitoring	Registries or routine databases to monitor safety and outcomes	Long-term surveillance

The clinical problem of postoperative ileus was described in Chapter 1. Uncertainty about its pathophysiology, targets for intervention, and a lack of consensus about how

to define it in clinical trials have meant that ileus continues to be an unmet clinical challenge, even in the era of enhanced recovery (4). Over the last 20 years, numerous clinical interventions have been evaluated with the aim of curtailing the impact of ileus, but many of these have failed to show any significant clinical or economic benefit (26). Vagus nerve stimulation has emerged as a new candidate treatment, involving electrical stimulation of the vagus nerve or one of its branches (115). Existing approaches to stimulate the vagus nerve, however, are invasive and likely not acceptable to patients or clinicians. Non-invasive approaches may enable its widespread use in clinical practice but require a clear argument for efficacy and assessments of feasibility prior to progressing to a definitive evaluation of clinical effectiveness.

In Chapter 2, the scientific mechanisms of vagus nerve stimulation were explored in a systematic scoping review of pre-clinical evidence (IDEAL Stage 0). It was shown that the vagus nerve contributes to maintaining normal intestinal homeostasis through a vago-vagal anti-inflammatory reflex. This involves a feedback loop of vagal afferent and efferent nerve fibres which inhibit the release of inflammatory mediators from intestinal macrophages via interactions with the enteric nervous system (9). This mechanism can be therapeutically exploited by stimulating the vagus nerve exogenously, either invasively (abdominal vagus nerve) or non-invasively (cervical or auricular vagus nerves). In rodents, this was previously shown to reduce intestinal inflammation and in turn ameliorate intestinal dysfunction after surgery (154). It was then translated to first-in-human studies (IDEAL Stage 1) as well as early clinical studies (IDEAL Stage 2a), demonstrating the safety of vagus nerve stimulation in surgical practice (96, 97, 160).

Drawing on this early evidence, a non-invasive device that can be self-administered by patients was considered to be the most clinically suitable approach to stimulate the

vagus nerve. This would circumvent the need for an invasive procedure and enable administration before surgery (at home) and after surgery (in hospital). In Chapter 3, a feasibility RCT was performed to explore key methodological uncertainties for a future definitive trial of non-invasive vagus nerve stimulation using the gammaCore device (IDEAL Stage 2b). This showed that participant recruitment was readily feasible, as was the collection of a series of clinical outcome data with minimal loss to follow up. Compliance to self-administration was high and was shown to be feasible according to the prospective progression criteria. This tended to decrease after surgery, however, suggesting that specific postoperative barriers may exist to achieving full compliance. The approach to blinding was challenging, with evidence of frequent unblinding, particularly amongst participants exposed to both types of devices (active and sham).

In Chapter 4, qualitative insights from trial participants and healthcare professionals were gathered to explore reasons for these barriers and possible solutions. Participants were highly compliant to the device because they keenly sought opportunities to participate in their recovery. For others, the device was a distraction from the burden and stress of treatment. The trend of reduced compliance after surgery was a result of low self-esteem, a lack of motivation, and physical challenges related to recovery after surgery. Solutions appeared to centre around assistance from healthcare professionals during these times of challenge whilst still enabling patients' impetus to self-participate. Unexpectedly, insights emerged to suggest that the fidelity of self-administration was unsatisfactory, despite an apparent high level of compliance. Participants found it challenging to position the device on the neck with accuracy, with some resorting to guessing the position and erroneously adapting the administration process. Solutions centred around offering flexible methods of training, particularly face-to-face approaches which made use of practical cues. The problem of unblinding was most prominent in

treatment groups comprising of both types of devices and was a result of participants being able to compare differences in the tactile sensation. Insights from healthcare professionals showed that there was some level of scepticism about non-invasive vagus nerve stimulation. This was a result of concerns about its safety as well as a lack of positive results from previous candidate treatments, creating a sense of futility. A clear argument for its efficacy was considered essential to address these concerns.

Finally, to ensure that a future definitive RCT would assess the most appropriate clinical outcomes, an internationally agreed COS was developed in Chapter 5 (253). This was the product of an iterative process of consensus between multiple stakeholder groups, including patients, surgeons, and allied healthcare professionals. A final COS comprising of 20 outcomes, alongside 4 contextual items, was ratified. As well as being directly applicable to a definitive RCT of vagus nerve stimulation, the COS represents the community consensus for preferred outcome assessment in all interventional studies of ileus after abdominal surgery

6.2. Interpretation of feasibility

A series of feasibility questions were set at the beginning of this research, each exploring a key methodological uncertainty about the conduct of a definitive RCT. Criteria for progression were determined prospectively (“Stop”: not feasible; “Modify”: likely feasible with change(s); and “Progress”: feasible without change) according to realistic targets agreed by clinical, methodological, and patient representatives. The criteria were supplemented by qualitative insights to explore reasons for barriers and possible solutions. “Modify” outcomes were considered using the ADepT framework, a systematic approach for decision-making in feasibility studies involving the identification, appraisal, and agreement of changes to the study design to enable feasibility (193).

6.2.1. Proportion of eligible patients identified from screening logs

Across both study sites, the proportion of patients who were eligible to be recruited surpassed the threshold of feasibility in all but one month of recruitment. This showed that an acceptable volume of potential participants existed to facilitate recruitment in a future definitive trial. Since this represented a “Progress” feasibility outcome, no further changes to the study method were necessary. Insights from healthcare professionals during interviews identified some concerns about the potential physiological side effects of vagus nerve stimulation (such as cardiac arrythmias) and highlighted the importance of justifying safety within the eligibility criteria. A previous proof-of-concept study of the gammaCore device, as well as data presented in this research, demonstrated a comparable safety profile of active treatment with other control and sham treatment groups (97). The device should therefore be considered safe to enter further evaluative studies alongside ongoing surveillance of safety.

6.2.2. Number of eligible patients randomised over 24 months

The recruitment of participants was impacted by the COVID-19 pandemic due to obligatory suspensions in recruitment at both study sites. Assessments of feasibility were undertaken with consideration to these circumstances, acknowledging that suspensions are disruptive, often leading to loss of site engagement, reduced enrolment, and loss to follow up (255). At SJUH, the trial was paused for 3 out of 24 months. During months of open recruitment, the rate of enrolment frequently exceeded the threshold of feasibility. This was considered to represent a “Progress” feasibility outcome, requiring no changes to the study method. At BRI, the trial was paused for a total of ten months across two discrete periods of time. This led to significant disruption, with the rate of enrolment only gaining traction in the latter ten months of uninterrupted

recruitment. This was considered to represent a “Modify” feasibility outcome. The lack of continuity in open recruitment was the key barrier but was not considered to be modifiable owing to the exceptional circumstances in which it occurred. Instead, strategies to mitigate disruption could offer a realistic solution if similar circumstances were to occur in the future. Examples include clear communication between sites, engaging with patient representatives throughout, and iterative review and refinement of risk assessments and mitigation strategies in light of changing circumstances (255).

6.2.3. Adequacy of participant blinding

Participant blinding was shown to be challenging, with unblinding occurring across all treatment groups but most prominently in groups exposed to both types of devices. This led to unexpected comparisons between active and sham devices, revealing differences in the character and strength of the stimulation sensation. Participants described how some devices had more “power” than others, raising suspicions that a stronger sensation was related to an active device. Unblinding was less profound in groups where participants were exposed to the same type of device throughout and where comparisons were not possible. Participants in these groups were more likely to remain oblivious to the treatment allocation but an unexpected lack of sensation relating to sham devices was still sufficient to cause unblinding of some participants. Overall, this represented a “Stop” feasibility outcome, indicating that participant blinding was not feasible in the current study design. Upon further appraisal, it was considered that blinding in treatment groups that exposed participants to only one type of device may be feasible with modification. This was supported by sub-analyses of the progression criteria for these treatment groups, which represented a “Modify” outcome. Modification may involve adjustments to the sham stimulation parameters or changes to how the

user experience is explained to patients. Either way, a focussed re-assessment of feasibility in light of modifications will be essential prior to a definitive trial with blinding.

6.2.4. Average compliance to the study treatment schedule

Compliance to the study treatment was high across all treatment groups, demonstrating participants' commitment to the study processes. This represented a "Progress" feasibility outcome, suggesting that no further changes to the methods were necessary. In contrast, a number of important insights were shared during interviews with patient- and healthcare professional-participants which warranted further consideration. Firstly, whilst compliance to the study treatment before surgery was good, there was a trend for this to decline in the early postoperative period. Insights from interviews suggested that this was due to emotional and physical burdens of recovery precluding the same high level of motivation observed before surgery. According to patients, solutions to address this included greater involvement from ward staff, such as assistance with administering the device or verbal prompts. According to healthcare professionals, there were concerns that assisted administration would lead to excessive work burden, increasing the daily demands on staff. On balance, pre-scheduled prompts linked to the medication chart were considered to be a reasonable solution to support compliance whilst avoiding staff burden. It was also considered that this may address healthcare professionals' concerns about maintaining oversight of adherence. It is unlikely that this change would require dedicated feasibility testing, but it would be important to engage appropriate stakeholders (such as nurses, surgeons, and patients) in the design of these refined study processes. The refinements could also be assessed during an internal pilot phase of a definitive trial prior to wider roll out of recruitment.

Secondly, it became evident from interviews with patients that the fidelity of self-administration was unsatisfactory at times. Patients expressed how they found it difficult to identify the carotid pulse and position the device on the neck, leading to a lack of confidence as well as erroneous adaptations to the administration process. This was an unexpected observation and was in contrast to the high level of self-reported compliance observed during the trial. The approach to telephone training was considered to be a key factor contributing to this, which was necessary due to COVID-19 related restrictions. Patients found it difficult to fully grasp the process of identifying the pulse when trained remotely and healthcare professionals similarly found it difficult to build rapport. Accordingly, face-to-face training was proposed as a key solution, enabling more clearer and more engaging explanations with the use of visual adjuncts. Overall, despite good levels of self-reported compliance, it will be important to revisit the approach to training using a face-to-face format. An assessment of fidelity should be undertaken to ensure that the refined approach is effective at imparting the correct process of administration.

6.2.5. Proportion of randomised patients lost to follow up

Throughout the trial, only one participant was lost to follow up. This was due to cancellation of surgery which was not re-scheduled until after the trial had closed and the final planned analysis had been undertaken. In contrast to the challenges of device training, interviews with patients revealed that they were supportive of remote consultations for routine study processes. This helped to reduce cost, travel, and time burdens related to making dedicated trips to the hospital. Overall, these findings represented a “Progress” feasibility outcome, suggesting that no further changes to the study methods are necessary to optimise loss to follow up in a definitive trial.

6.2.6. Proportion of missing clinical outcome data

There were no missing data across a series of candidate clinical outcomes. In particular, this was true for a number of outcomes that were prioritised by the COS, including time to gastrointestinal recovery using a validated tool (such as GI-2) and need for nasogastric tube insertion. Since these findings represented a “Progress” feasibility outcome, no further changes to the existing methods are necessary. Of note, there were several outcomes that were prioritised by the COS but were not assessed during the feasibility trial. These included outcomes such as: Readiness for discharge based on gastrointestinal function, time for adequate nutrition, and severity of abdominal pain. Whilst there are no specific concerns about the feasibility of collecting these outcome data, this should be confirmed in a future internal pilot study.

6.2.7. Incidence of complications or serious complications

Insights from interviews with healthcare professional-participants indicated that safety was a key factor in determining their acceptability of vagus nerve stimulation. This was due to long-held concerns about potential cardiac side-effects and the possibility that these may lead to avoidable harm in the postoperative period. In the present study, the rates of complications were similar across all treatment groups, indicating that there was no increase in complications associated with stimulation of the vagus nerve. This represented a “Progress” feasibility outcome, suggesting that no further changes to the study methods would be required prior to progressing to a definitive trial. These findings join those of other studies demonstrating an acceptable safety profile of non-invasive vagus nerve stimulation after surgery (97,160). Future evaluative studies should continue to monitor the incidence and type of complications within a programme of surveillance.

6.3. Findings in context

The present study provides the only known data on the feasibility of non-invasive vagus nerve stimulation in the setting of abdominal surgery. This adds to a small body of previous evidence describing its clinical efficacy for reducing ileus in humans. Hong and colleagues showed that stimulating the auricular vagus nerve once for 10 minutes during surgery (frequency 25Hz; current 10mA) led to significant changes in gastric muscle activity, specifically a reduction in the frequency of pyloric action potentials and an increase in their amplitude. Along with increased levels of serum gastrin (a surrogate for vagus nerve activation), this supported the authors' hypothesis that vagus nerve stimulation improves gastric propulsion (96). In a recent RCT of 134 patients undergoing laparoscopic surgery, Ru and colleagues similarly demonstrated a reduction in the incidence of ileus (6.25% vs. 20.0%; P=0.022) in patients receiving auricular vagus nerve stimulation. In this study, stimulation was performed once for 20 minutes prior to anaesthesia (frequency 25Hz; current 10mA) (98). In a small study by Chapman and colleagues, stimulation of the cervical vagus nerve was performed twice daily (2 minutes bilaterally) for a total of five days before and after surgery using the gammaCore device (frequency 25Hz; maximum current 60mA). This was associated with improvements in the time to first passage of flatus (1.65 $\pm$ 0.81 vs. 2.35 $\pm$ 1.32 days) and stool (1.75 $\pm$ 0.91 vs. 2.18 $\pm$ 2.21 days) (97). None of these studies were powered to definitively evaluate the effect of vagus nerve stimulation on intestinal function but their findings provided early signals of efficacy. In contrast, the findings of the present study did not show a signal towards efficacy, contradicting observations from earlier work. One possible reason may be due to poor fidelity with the process of self-administration, leading to ineffective stimulation and a lack of observed clinical benefit. Another possible reason may be due to small sample sizes in the earlier studies, increasing the risk of spuriously

positive results. Taken together, the evidence for non-invasive vagus nerve stimulation remains uncertain but early data provide a generally positive signal, justifying further dedicated assessments of efficacy. Although the fidelity of self-administration was lower than expected in the present study, it is a target for future modification in a refined programme of training. Indeed, a previous study of healthy volunteers showed that administration of gammaCore with the same stimulation parameters increased vagal tone and reduced serum TNFα, confirming that the device stimulates the vagus nerve and elicits an anti-inflammatory effect when delivered as planned (170).

The challenges and implications of the COVID-19 pandemic are also important when interpreting the results. Social distancing restrictions meant that face-to-face training could not take place as planned in the present study, instead requiring participants to take part in remote training sessions via telephone. This emerged as a key barrier to feasibility, leading to a lack of confidence in the process of self-administration. This has not been reported in previous studies evaluating the gammaCore device. Its use in other clinical contexts, such as migraine and gastroparesis, is usually accompanied by face-to-face training, dedicated support structures, and established relationships with healthcare professionals (174, 176, 177). It is likely that all of these were disrupted during this study owing to unfamiliar changes in care pathways and unprecedented pressures on healthcare staff. It is also possible that these challenges were exacerbated by the acute clinical context of this study, comprising patients undergoing major surgery in hospital as opposed to chronic conditions managed predominantly at home. The lessons drawn from this study provide valuable information on how existing study processes can be adapted, ensuring that a future definitive trial is more resilient.

6.4. Strengths

As an overall programme of research, several key strengths are recognised which enabled a robust assessment of feasibility. Firstly, the conduct of interviews alongside the feasibility trial provided valuable information to enable contextualisation and appraisal of the findings. In some cases, insights drawn from interviews revealed weaknesses in the study method which were not appreciated by the rigid progression criteria of the trial. It was important to consider these insights in order to fully appreciate reasons, solutions, and implications of the findings when put in context. In addition, interviews with patients and healthcare professionals enabled an assessment of diverging and converging perspectives. This was important to ensure that modifications to the study method or other decisions based on the feasibility data were compatible with the expectations of all stakeholders. Secondly, the study benefited from dedicated patient and public involvement in the form of a patient advisory group. This was composed of a diverse range of individuals with a history of colorectal surgery, comprising different ages, sex, and backgrounds. Their role in the research was essential, particularly when addressing the operational challenges of COVID-19 and navigating social distancing restrictions. Their input helped to ensure that realistic and balanced changes to the study processes were implemented to enable its successful completion. One of these included the approach to telephone consent, which was readily supported by participants and contributed to a successful feasibility outcome for recruitment during highly difficult circumstances. Finally, underpinning this research were principles of the IDEAL Collaboration framework for surgical innovation. This begun with an assessment of pre-clinical and early proof-of-concept data during the scoping review (IDEAL Stage 0 and 1) leading to an assessment of treatment and study feasibility (IDEAL Stage 2b) (254). This iterative approach ensured that the appropriateness of future work was considered

systematically. In particular, the ongoing assessment of safety at multiple stages of assessment will help to address long-held concerns of adverse events, which were raised prominently during interviews with healthcare professionals. Overall, it is important to acknowledge that surgical devices are complex interventions requiring an evidence-based approach to assessment and this should continue during future work.

6.5. Limitations

Limitations of this research are also recognised and should be considered when interpreting the results. Firstly, the study was limited to assessing the feasibility of a single device. The gammaCore device is unique to other available transcutaneous stimulator devices in that it is designed specifically for self-administration and targets the cervical vagus nerve rather than its auricular branches in the ear. Whilst some feasibility considerations may be generalisable, such as patients' attitudes to stimulating the vagus nerve, other factors relating to patients' experience of the device may differ. If alternative devices were considered in this setting, it may be necessary to consider further focussed assessments of feasibility prior to progressing to evaluative studies. Secondly, although the conduct of interviews was a strength of the present work, the sampling frame was limited to nurses, surgeons, and patients. It is important to note that many other healthcare professionals have a role in recovery after surgery, including anaesthetists, dietitians, physiotherapists, pharmacists, and occupational therapists, as well as service managers. The interviews were not able to provide information on whether any broader clinical or hospital-level barriers existed to the implementation of non-invasive vagus nerve stimulation. In the design of future work, it would be important to mitigate this by involving a diverse range of professional stakeholders to ensure that all perspectives are considered and addressed. Finally, the fidelity of self-administration

emerged as an unexpected challenge. Despite good self-reported compliance with the administration schedule, patients struggled to correctly position the device on the neck, leading them to adapt the self-administration process. Based on data from interviews, many of these adaptations were erroneous and likely not effective in stimulating the vagus nerve. They were considered to be a consequence of remote training, which was not widely supported. It was not possible to refine this or to formally re-assess fidelity during the present work because the challenge of device positioning was not anticipated in advance. Instead, it will be important to undertake further assessments of feasibility with attention to training and fidelity prior to progressing to a definitive trial.

6.6. Impact

The purpose of feasibility research is to explore whether a future study can be undertaken successfully and how the methods and processes should be refined (256). The feasibility trial here showed that many aspects of a future RCT are feasible, including recruitment, data collection, and retention of participants. On the other hand, it identified some areas that were not feasible in the present form and would require modification before progressing to a definitive trial. These findings are highly valuable for researchers and clinicians who are interested in the role of vagus nerve stimulation around the time of major surgery. Whilst pre-clinical and early clinical data show proof-of-concept and early signals of efficacy, the present data show that further refinements are required before committing extensive resources to a final evaluation of clinical and cost effectiveness. This will help to ensure that a future study is capable of providing a definitive final answer whilst at the same time reducing the risk of research waste (17).

The qualitative work provided key insights about feasibility but also raised other transferable considerations. Interviews with patients highlighted their strong enthusiasm

to contribute to medical research, even when unblinded to the study treatment. This is important since it highlights the complexity of factors which determine compliance to healthcare interventions. Previous research has explored these at length, including the role of education, relationships with healthcare providers, and cultural considerations (257). The findings here are notable since they demonstrate the role of patients' personal values as well as knowledge of the device allocation. This should inform future feasibility studies since it suggests that universal feasibility criteria used in isolation may oversimply compliance, leading to erroneous and unrepresentative findings.

Finally, the agreed COS provides valuable information to inform the methods of a future definitive trial. It also represents the agreed community consensus on outcome assessment for ileus after abdominal surgery (253). According to the COMET initiative, this should be considered as the minimum set of outcomes to be reported in all eligible studies focussing on ileus after abdominal surgery (245). The impact is to standardise the reporting of agreed outcomes, making it easier for the results of future studies to be compared, contrasted, and combined within systematic reviews and meta-analyses. Ultimately, this should lead to faster realisation of research findings in clinical practice.

6.7. Future work

The present work highlighted areas requiring additional feasibility assessment. Areas requiring modification and re-assessment include the development of a refined face-to-face training programme, an assessment of fidelity of the self-administration process, and device-related considerations related to blinding. Areas requiring clarification in a future internal pilot and unlikely requiring substantial refinement include the completeness of additional outcome data in light of the COS as well as processes to encourage and record daily self-administration. An outline of these proposals is shown in Table 6.2.

Table 6.2 – Proposals for future feasibility work

Further dedicated feasibility work		Clarification in a future internal pilot	
Training	**Deficiency**: evidence of sub-optimal training **Solution:** Development of face-to-face training. The programme should be co-developed with patients, nurses, and surgeons	Data	**Deficiency**: Completeness of data collection for unassessed outcomes **Solution:** Assessment of data completeness within future internal pilot
Intervention fidelity	**Deficiency**: Incorrect self-positioning of device **Solution:** Assessment of fidelity in light of new programme of training	Device compliance	**Deficiency**: Evidence of lower compliance after surgery (postoperative) **Solution:** Prompts during nursing drug rounds. Assessment of practicality within future internal pilot
Blinding	**Deficiency**: Participant unblinding **Solution:** Consideration of refined sham intervention (adjustment of parameters vs. alternative positioning) Re-assessment of blinding with new sham in the context of a parallel-group study (i.e. Active vs Sham)	-	-

Owing to conflicting signals of efficacy from this and earlier work, further research to explore the case for efficacy is required prior to a definitive trial of clinical and cost effectiveness. This should consider the role of cervical and auricular vagus nerve stimulation and the adequacy of their respective stimulation parameters. Whilst previous studies in humans have demonstrated positive signals of efficacy with short stimulation cycles (such as single doses of 10-20 minutes during surgery), greater certainty about the therapeutic mechanism of non-invasive vagus nerve stimulation is required before progressing the work forward. After addressing the described feasibility deficiencies, a dedicated trial of clinical efficacy should explore the extent to which non-invasive

stimulation successfully stimulates the vagus nerve in the context of abdominal surgery and the parameters required to elicit an anti-inflammatory response.

6.8. Conclusions

Non-invasive vagus nerve stimulation has emerged as a new candidate treatment to reduce ileus after abdominal surgery. The data presented here show that many aspects of a definitive trial of non-invasive vagus nerve stimulation using the gammaCore device are feasible. In contrast, some aspects such as device training, fidelity of self-administration, and participant blinding require modification followed by re-assessments of feasibility. Proposals for this additional work are proposed. Whilst early studies exploring the role of cervical and auricular vagus nerve stimulation provide positive signals of efficacy, this was not echoed by the present study. As such, the next step should include a dedicated assessment of clinical efficacy to confirm or refute whether non-invasive vagus nerve stimulation has the mechanistic potential for benefit. Ultimately, this will guide the progression to a definitive trial of clinical and cost-effectiveness.

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Appendices

Chapter 2 Appendix (A-2)

A-2.1. Data charting template

Characteristics:	
Title of manuscript	
Year	
Authors	
Background and aims:	**Methodology and outcome measures/experiments:**
Important results	

Characteristics:	
Title of manuscript	
Year	
Authors	
Background and aims:	**Methodology and outcome measures/experiments:**
Important results	

A-2.2. Concept table for key search terms

Concept	Key terms
Bowel Function	Ileus Function Motility Dysmotility Transit Gastric emptying Peristalsis Obstruction
Surgery	Surgery Procedure Operation
Intestine	Intestine Bowel Colon Ileum Jejunum Duodenum Stomach Rectum Gastrointestinal tract Intestinal tract
Vagus nerve	Vagus Vagal

Chapter 3 Appendix (A-3)

A-3.1. Summary of amendments to ethics approval

Amendment 1 7th Oct 2019 HRA Category A; Approval: 15th Nov 2019	1) Clarifications to the study eligibility criteria were made. Specifically, it was clarified that for patients to be eligible, an intestinal anastomosis must be pre-planned. 2) Planned data points were amended. A small number of data points which were initially planned will not be collected and were removed from the protocol. 3) The possible settings for qualitative interviews to take place were expanded to include the hospital, participants' home, or via telephone. 4) Approval was confirmed for a member of staff to assist with interview transcription. 5) It was clarified that the randomisation service would be accessible using an online portal with authorised investigators provided with a unique login.
Amendment 2 19th Feb 2020 HRA Category A; Approval: 16th Mar 2020	1) The protocol for participant withdrawal was clarified. Specifically, it was clarified that cessation of treatment would not necessarily implicate withdrawal from the study.
Amendment 3 21st Feb 2020 HRA Category C (COVID); Approval: 23rd Jun 2020	In light of the COVID-19 pandemic and social distancing requirements: 1) Approval was confirmed for patients to be approached with information about the study by telephone. This would follow a virtual clinic with their treating clinician, where verbal permission to approach would be sought. Study information would be sent to patients by post. 2) Approval was confirmed for patients to provide informed consent for the main trial by telephone. The new process included an initial audio recording of verbal consent, with data handled according to the existing data management plan. Upon admission to hospital patients were asked to provide written confirmation of consent using the existing consent form. 3) Approval was confirmed for the study device will be posted to patients. This replaced the need for a dedicated study visit. All devices would be sent using a recorded postal service. 4) Approval was confirmed for verbal training to be delivered by videocall or telephone. This replaced the need for a dedicated visit. A written instruction guide would accompany the device. It was confirmed that patients would have an allocated contact. 5) An additional information sheet and a summary postcard were produced. These items supplemented the information provided on the existing Patient Information Sheet and provided details on COVID-related changes to the study.
Amendment 4 8th September 2020 HRA Category C (COVID); Approval: 23rd Jun 2020	1) Typographic corrections were made to the protocol
Amendment 5 31st January 2021 HRA Category A Approval: 22nd February 2021	1) Approval was confirmed to add an additional planned component of the qualitative work This would recruit a maximum of twenty clinicians from around the UK to explore possible barriers to a definitive clinical trial and implementation. Specifically, the following were added: – A clinician participant information sheet was produced (v1.0; 13th December 2020) – A clinician consent form was produced (v1.0; 13th December 2020) – A clinician interview topic guide was produced (v1.0; 13th December 2020)

Amendment 6 21st July 2021 HRA Category A Approval: 23rd July 2021	1. Approval was confirmed to expand the sampling frame of the clinician qualitative sub-study. The existing protocol recruited clinicians from external study sites to explore their perspectives on future implementation of the study treatment. The new protocol widened this to include clinicians from study sites who already had experience of the study device.
Amendment 7 6th November 2021 HRA Category C Approval: 6th November 2021	1. This amendment clarified the procedure for withdrawal of treatment in circumstances where participants become ineligible during the course of the study. 2. The sampling framework for clinician interviews was expanded in light of emerging data. This now included any healthcare professional who had a role in looking after colorectal surgery patients (previously included only surgeons and nurses).

A-3.2. Study recruitment materials

A-3.2.1. Feasibility trial participant information sheet

The Leeds Teaching Hospitals NHS Trust

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Vagus nerve stimulation to improve bowel function after surgery

We invite you to take part in a research study

- Before you decide, it is important for you to understand why the research is being done and what it involves.
- This information sheet is designed to help you decide if you would like to take part. Please read the information carefully and discuss it with friends & relatives. We suggest that you take this information home and consider it further.
- Taking part in this research study is entirely voluntary. If you choose not to take part, it will not affect the normal care you receive from your doctors.
- Please feel free to ask us any questions about the study, or if you would like more information.

Thank you for reading this information. If you decide to take part, you will be asked to sign a consent form. This will be provided by a member of the study team.

Contents:

Please read this document carefully

About Us

The study is run by a team of clinical and academic doctors at your hospital and University of Leeds.

For any questions on the study please contact the Principle Researcher (details at the end of this document), or feel free to ask any member of your clinical team.

The Leeds Teaching Hospitals NHS Trust

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Why are we doing this study?

Surgery on the bowel often causes "ileus". This is where the bowel temporarily stops working and *goes to sleep*. It takes several days for the bowel to start working again, which can cause unpleasant symptoms such as bloating, vomiting, and cramps. Patients who have had bowel surgery in the past have asked us to improve this.

What does the study involve?

A new treatment called "vagus nerve stimulation" may help to prevent ileus. This is done using a small, hand-held device called GammaCore® which stimulates the nerves that supply the bowel. It is self-administered at home and in hospital by applying it gently beneath the chin. The device produces a gentle electrical stimulation for two minutes which feels like a gentle "tingling" sensation. The device should not affect your bowels before your operation.

We will ask you to use the GammaCore® device twice daily for five days before and five days after your operation. Some people will receive a "dummy"/placebo device which looks and feels identical. This will help us to decide if the real device works.

The type of device you receive will be chosen at random and kept secret until after the study finishes. This helps to ensure a "fair" comparison. When in hospital, we may ask you to switch the type of device to help us make further comparisons.

During the study, we will ask you to keep a diary of using the GammaCore® device. We will also ask you about your bowel function whilst in hospital (such as number of toilet visits and dietary habits). Before discharge from hospital, we will ask you which device (active or placebo) you think you received, and after you go home, we will call you to ask about your recovery.

If you are having your operation at **St. James's Hospital in Leeds**, we will ask your permission to do some simple tests. These are optional. They will help us to understand why the device works. They will include some blood tests – one before, one during, and two just after your operation. We will try our best to do these at the same time as your routine hospital blood tests. We will also take two samples of abdominal fluid during the operation. This is taken routinely, but is usually thrown away at the end of surgery.

Participant Information Sheet – Main Trial v1.0 IRAS Study ID: 262904 22nd May 2019

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Why have I been chosen, and do I have to take part?

We have approached you as a potential participant of this study because you are having a bowel operation. Taking part is entirely voluntary and you are free to stop at any time. All other aspects of your care will remain the same. If you decide not to take part, your decision will be respected fully and will not impact on the care you receive.

What are the possible advantages of taking part?

We hope that this new treatment will help to prevent ileus after surgery. However, this is not certain and is the reason we are doing the study. The research may not directly benefit you but it will help us to improve the recovery of bowel function in the future.

What are the possible disadvantages of taking part?

As you are having an extra treatment, there is a small chance of extra side effects. These are considered mild and infrequent. If they do occur, they typically resolve soon after using the device. Possible effects are:

- Mild "lip twitch" during use (due to stimulation of small nearby muscles)
- Facial tingling (the stimulation strength can be adjusted to your comfort)
- Mild irritation of the skin/application site

How do I confirm my interest?

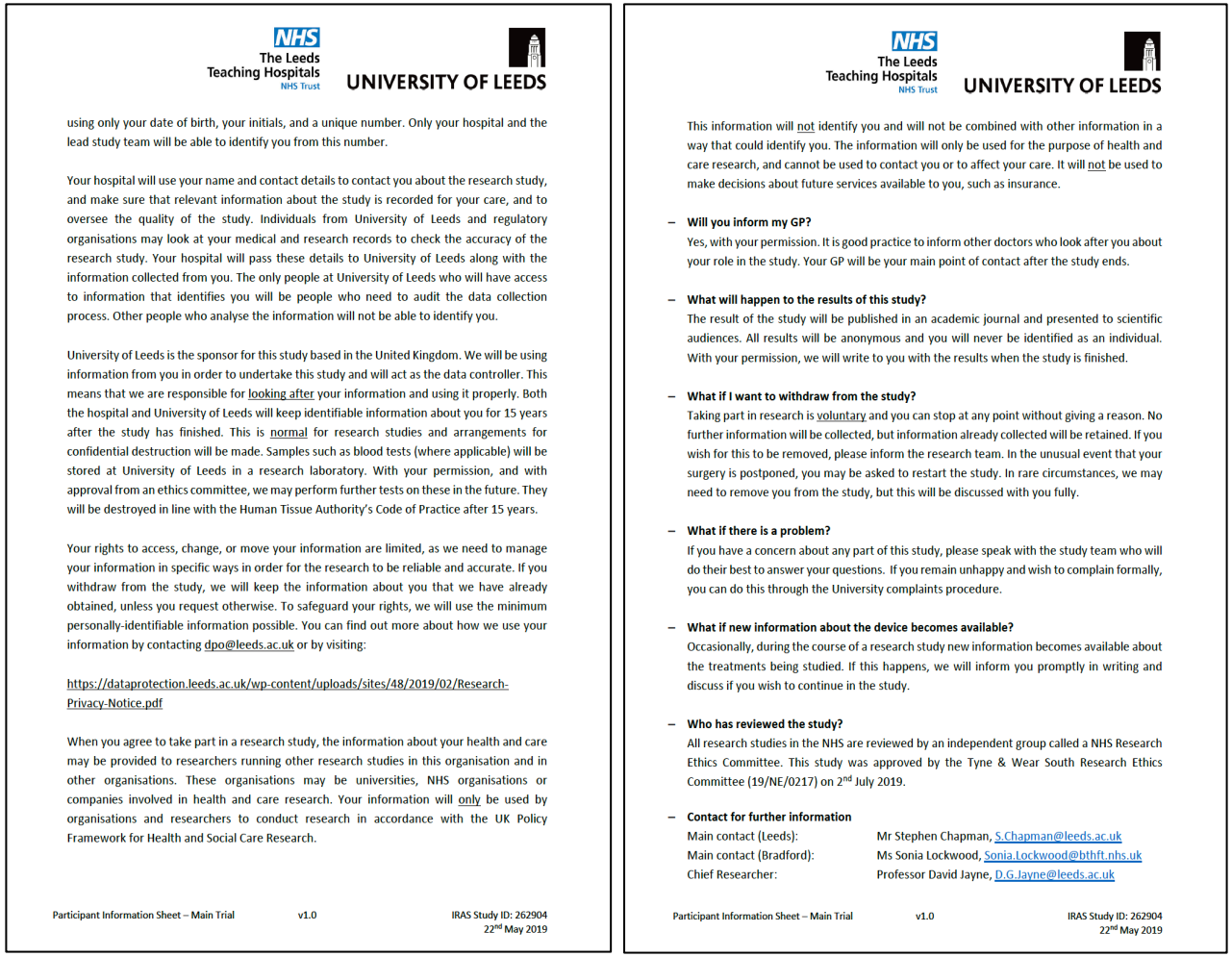
If you are interested, you may wish to take this information home and consider it further. With your permission, we will contact you by phone to ask about your decision. If you do take part, we will arrange a time to give you the device and show you how to use it. We will also ask you to sign a consent form.

More information and frequent questions

– **Who is organising and funding the research?**
The study is organised by a team of doctors at University of Leeds. It is being funded by the research arm of the NHS, and supported by the device manufacturer.

– **Confidentiality**
Information needed for the study will be collected on paper forms and stored at your hospital. Once all information has been collected, copies of these forms will be sent from your hospital to the lead study team at University of Leeds using Royal Mail postal service. Your full name will be included on the consent form but on other forms you will be identified

Participant Information Sheet – Main Trial v1.0 IRAS Study ID: 262904 22nd May 2019



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using only your date of birth, your initials, and a unique number. Only your hospital and the lead study team will be able to identify you from this number.

Your hospital will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from University of Leeds and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Your hospital will pass these details to University of Leeds along with the information collected from you. The only people at University of Leeds who will have access to information that identifies you will be people who need to audit the data collection process. Other people who analyse the information will not be able to identify you.

University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller. This means that we are responsible for looking after your information and using it properly. Both the hospital and University of Leeds will keep identifiable information about you for 15 years after the study has finished. This is normal for research studies and arrangements for confidential destruction will be made. Samples such as blood tests (where applicable) will be stored at University of Leeds in a research laboratory. With your permission, and with approval from an ethics committee, we may perform further tests on these in the future. They will be destroyed in line with the Human Tissue Authority's Code of Practice after 15 years.

Your rights to access, change, or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained, unless you request otherwise. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information by contacting dpo@leeds.ac.uk or by visiting:

https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/02/Research-Privacy-Notice.pdf

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

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This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

- **Will you inform my GP?**
  Yes, with your permission. It is good practice to inform other doctors who look after you about your role in the study. Your GP will be your main point of contact after the study ends.

- **What will happen to the results of this study?**
  The result of the study will be published in an academic journal and presented to scientific audiences. All results will be anonymous and you will never be identified as an individual. With your permission, we will write to you with the results when the study is finished.

- **What if I want to withdraw from the study?**
  Taking part in research is voluntary and you can stop at any point without giving a reason. No further information will be collected, but information already collected will be retained. If you wish for this to be removed, please inform the research team. In the unusual event that your surgery is postponed, you may be asked to restart the study. In rare circumstances, we may need to remove you from the study, but this will be discussed with you fully.

- **What if there is a problem?**
  If you have a concern about any part of this study, please speak with the study team who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the University complaints procedure.

- **What if new information about the device becomes available?**
  Occasionally, during the course of a research study new information becomes available about the treatments being studied. If this happens, we will inform you promptly in writing and discuss if you wish to continue in the study.

- **Who has reviewed the study?**
  All research studies in the NHS are reviewed by an independent group called a NHS Research Ethics Committee. This study was approved by the Tyne & Wear South Research Ethics Committee (19/NE/0217) on 2nd July 2019.

- **Contact for further information**

Main contact (Leeds):	Mr Stephen Chapman, S.Chapman@leeds.ac.uk
Main contact (Bradford):	Ms Sonia Lockwood, Sonia.Lockwood@bthft.nhs.uk
Chief Researcher:	Professor David Jayne, D.G.Jayne@leeds.ac.uk

Participant Information Sheet – Main Trial v1.0 IRAS Study ID: 262904
22nd May 2019

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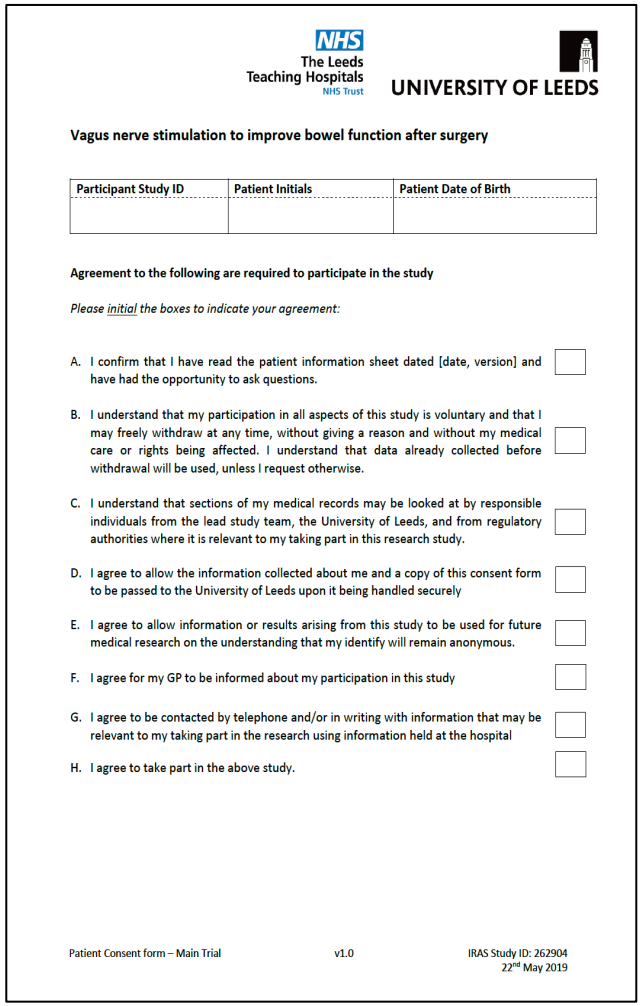
A-3.2.2. Feasibility trial consent form



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Vagus nerve stimulation to improve bowel function after surgery

Participant Study ID	Patient Initials	Patient Date of Birth

Agreement to the following are required to participate in the study

Please initial the boxes to indicate your agreement:

A. I confirm that I have read the patient information sheet dated [date, version] and have had the opportunity to ask questions. ☐

B. I understand that my participation in all aspects of this study is voluntary and that I may freely withdraw at any time, without giving a reason and without my medical care or rights being affected. I understand that data already collected before withdrawal will be used, unless I request otherwise. ☐

C. I understand that sections of my medical records may be looked at by responsible individuals from the lead study team, the University of Leeds, and from regulatory authorities where it is relevant to my taking part in this research study. ☐

D. I agree to allow the information collected about me and a copy of this consent form to be passed to the University of Leeds upon it being handled securely ☐

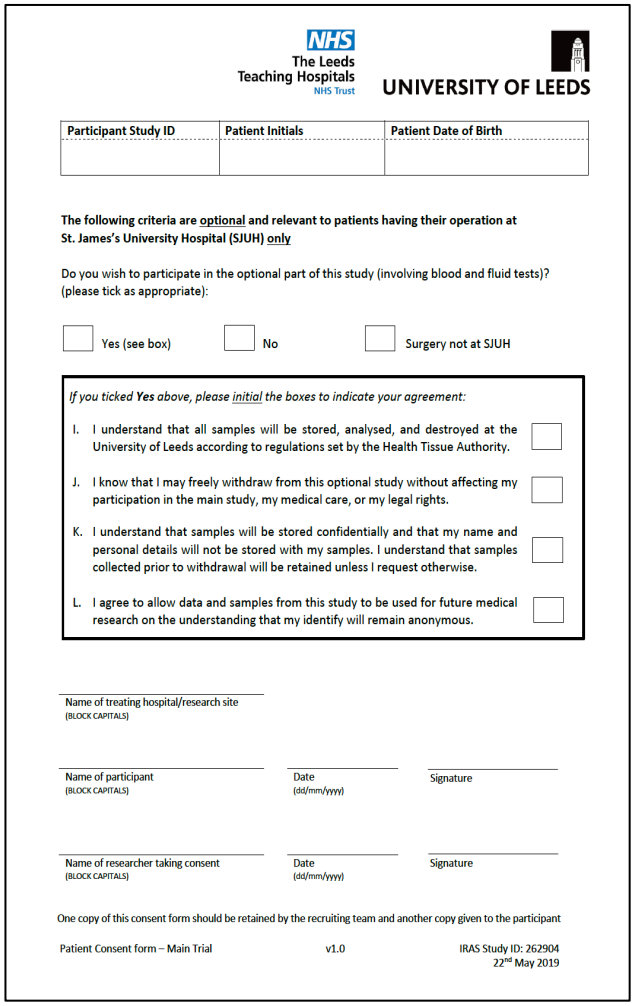
E. I agree to allow information or results arising from this study to be used for future medical research on the understanding that my identify will remain anonymous. ☐

F. I agree for my GP to be informed about my participation in this study ☐

G. I agree to be contacted by telephone and/or in writing with information that may be relevant to my taking part in the research using information held at the hospital ☐

H. I agree to take part in the above study. ☐

Patient Consent form – Main Trial v1.0 IRAS Study ID: 262904
22nd May 2019



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Participant Study ID	Patient Initials	Patient Date of Birth

The following criteria are optional and relevant to patients having their operation at St. James's University Hospital (SJUH) only

Do you wish to participate in the optional part of this study (involving blood and fluid tests)? (please tick as appropriate):

☐ Yes (see box) ☐ No ☐ Surgery not at SJUH

*If you ticked **Yes** above, please initial the boxes to indicate your agreement:*

I. I understand that all samples will be stored, analysed, and destroyed at the University of Leeds according to regulations set by the Health Tissue Authority. ☐

J. I know that I may freely withdraw from this optional study without affecting my participation in the main study, my medical care, or my legal rights. ☐

K. I understand that samples will be stored confidentially and that my name and personal details will not be stored with my samples. I understand that samples collected prior to withdrawal will be retained unless I request otherwise. ☐

L. I agree to allow data and samples from this study to be used for future medical research on the understanding that my identify will remain anonymous. ☐

Name of treating hospital/research site (BLOCK CAPITALS)

Name of participant (BLOCK CAPITALS) | Date (dd/mm/yyyy) | Signature

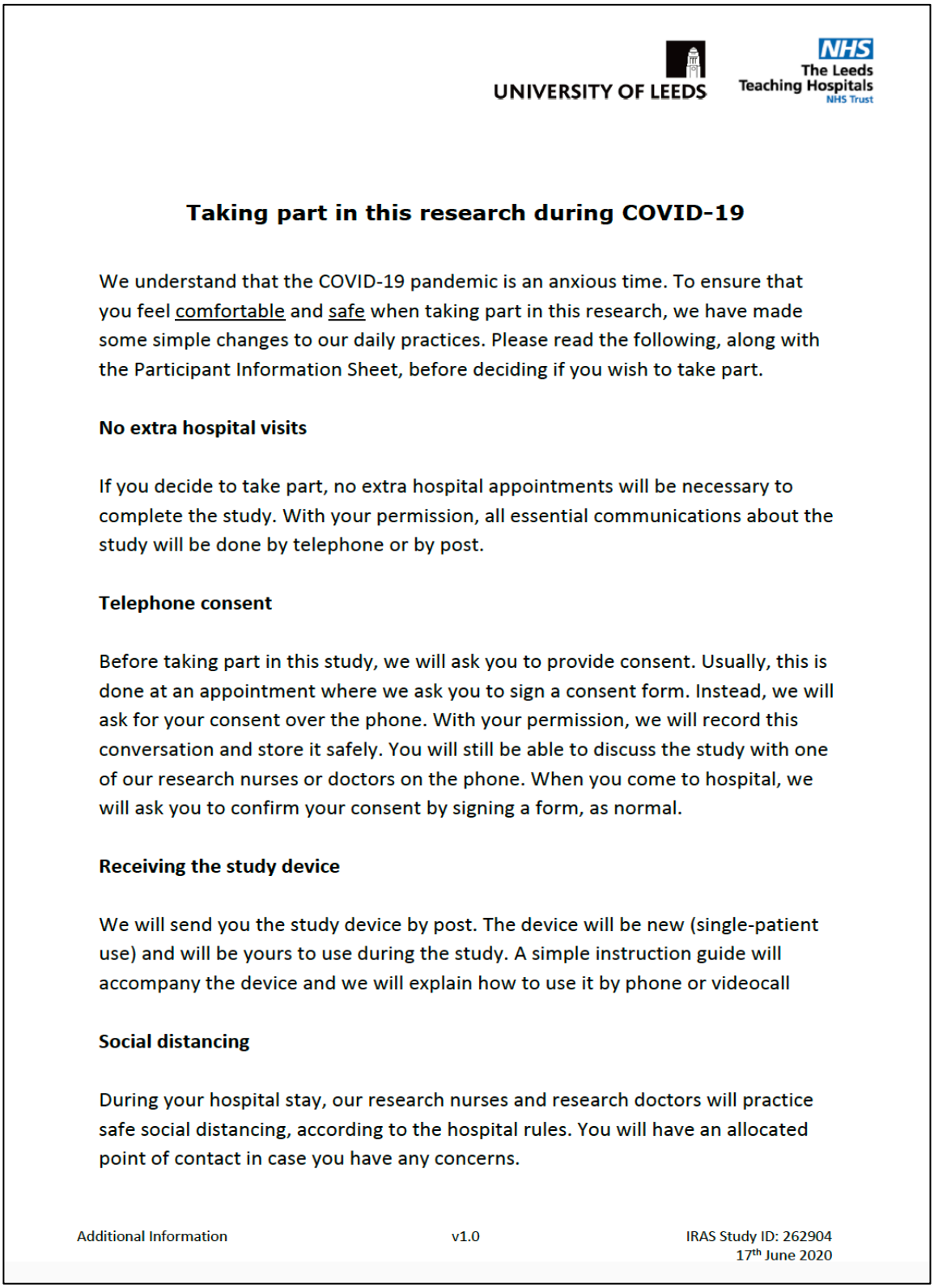
Name of researcher taking consent (BLOCK CAPITALS) | Date (dd/mm/yyyy) | Signature

One copy of this consent form should be retained by the recruiting team and another copy given to the participant

Patient Consent form – Main Trial v1.0 IRAS Study ID: 262904
22nd May 2019

Variant shown (including NHS Trust logo) is for St. James's University Hospital site

A-3.2.3. Additional COVID-19 study recruitment information



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Taking part in this research during COVID-19

We understand that the COVID-19 pandemic is an anxious time. To ensure that you feel comfortable and safe when taking part in this research, we have made some simple changes to our daily practices. Please read the following, along with the Participant Information Sheet, before deciding if you wish to take part.

No extra hospital visits

If you decide to take part, no extra hospital appointments will be necessary to complete the study. With your permission, all essential communications about the study will be done by telephone or by post.

Telephone consent

Before taking part in this study, we will ask you to provide consent. Usually, this is done at an appointment where we ask you to sign a consent form. Instead, we will ask for your consent over the phone. With your permission, we will record this conversation and store it safely. You will still be able to discuss the study with one of our research nurses or doctors on the phone. When you come to hospital, we will ask you to confirm your consent by signing a form, as normal.

Receiving the study device

We will send you the study device by post. The device will be new (single-patient use) and will be yours to use during the study. A simple instruction guide will accompany the device and we will explain how to use it by phone or videocall

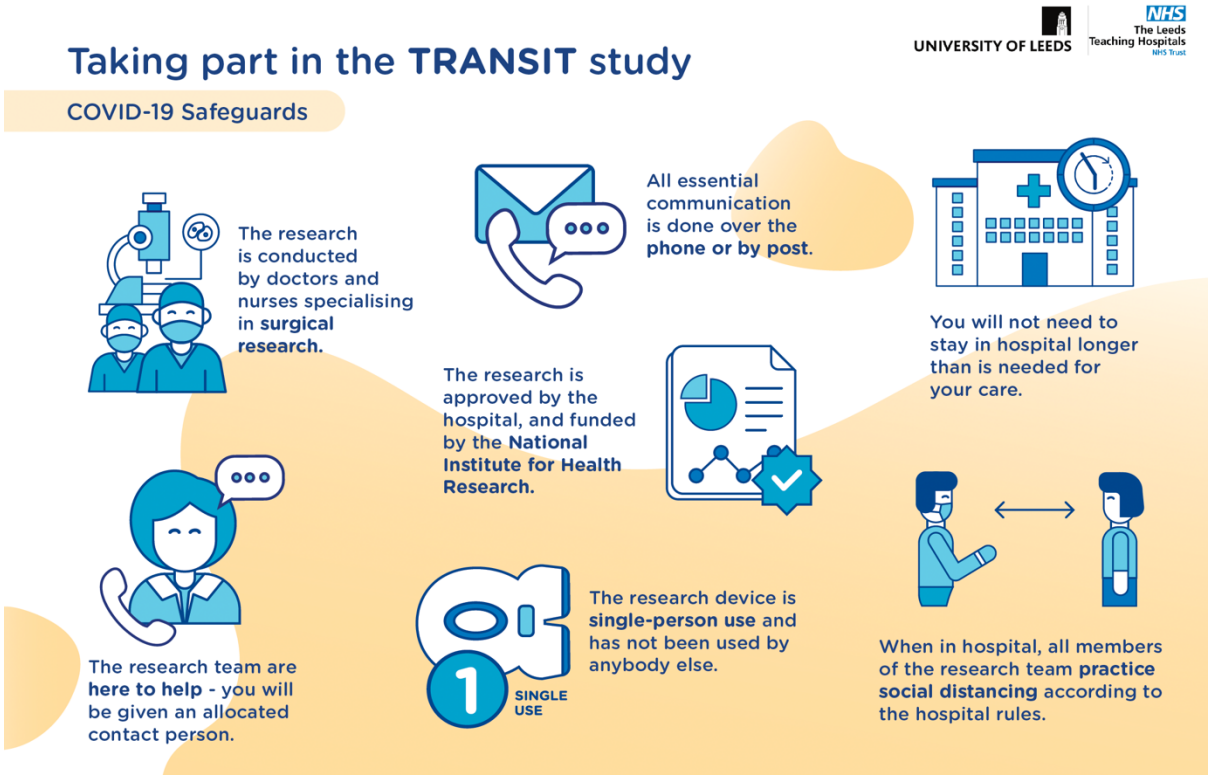
Social distancing

During your hospital stay, our research nurses and research doctors will practice safe social distancing, according to the hospital rules. You will have an allocated point of contact in case you have any concerns.

Additional Information v1.0 IRAS Study ID: 262904
17th June 2020

Variant shown (including NHS Trust logo) is for St. James's University Hospital site

A-3.2.4. Additional COVID-19 study recruitment postcard



Variant shown (including NHS Trust logo) is for St. James's University Hospital site

A-3.3. Standard operating procedure for study device training

1. Introduce yourself to the participant and explain the purpose of training

2. Provide participants with a description of the device, including the digital display, handset buttons and their function, stimulation surfaces/caps, and conducting gel

3. Provide participants with a demonstration using a test device, including all steps as follows:

    a. Locate carotid pulse with fingers
    b. Apply a minimal amount of gel (pea-sized)
    c. Switch on device switch but do not advance the intensity until device in situ.
    d. Apply with gentle pressure to underside of jaw. Minimal pressure against neck; only enough to ensure stimulation surfaces contact skin
    e. Advance intensity until sensation becomes uncomfortable or painful then reduce. It should be uncomfortable without being painful
    f. At the conclusion of stimulation, the device will beep but it must be turned off before terminating treatment or beginning a second stimulation
    g. Use a clean soft cloth to remove the gel from the stimulation surfaces.
    h. Remove gel from neck with a damp cloth. Residual gel can prove irritating to some individuals
    i. Store gammaCore where it will remain dry at room temperature. Ensure the device will not be switched on by mistake
    j. Confirm understanding and answer any remaining questions
    k. Be sure to leave patient with the device and the instruction guide

4. Invite participants to self-administer the device using the steps above under direct supervision. Provide feedback on their performance and re-educate if necessary

5. Invite questions about the study and provide answers until participant feels confident and comfortable to use the device independently.

6. Provide participants with the study “Quick Guide”, comprising of a step-by-step guide on how to administer the device. Show participants the integrated diary, to be used to record their usage and stimulation setting.

7. Participants to be provided with contact details to the local research delivery team in case of further questions or uncertainties after the training session.

8. Local investigators can seek further support from the study team if unanswered questions or uncertainties persist.

A-3.4. Study device “Quick-Guide” and participant diary

FUNDED BY
NIHR | National Institute for Health Research

NHS

Vagal nerve stimulation to improve bowel function after surgery

Diary and quick instruction guide

Working together in partnership
Leeds Teaching Hospitals NHS Trust and
Bradford Teaching Hospitals NHS Foundation Trust

Top Tips

- When using the device, ensure that you are comfortable and sat down.
- For the first few times, practice in front of a mirror.
- Have some paper towels or tissues nearby to wipe off the gel.
- You can adjust the stimulation strength to a level that suits you.

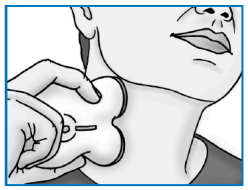
Step 1: Locate the correct position

- Gently place your first two fingers on your neck to find your pulse.
- If you cannot find your pulse, feel for the soft part of your neck beneath your chin
- This is the correct position when using the device.

Step 2: Prepare the device

- Remove the plastic caps from the stimulation surfaces.
- Apply a small (pea-sized) amount of gel on both surfaces.
- Turn on the device by pressing and holding the top (+) button. You will hear it beep and a green light will appear.
- Press the top (+) button repeatedly to increase the setting. You will see a number on the digital display (1-40). You should use a setting that is comfortable. If needed, decrease the setting by pressing the bottom (-) button repeatedly.

Step 3: Use the device



- Place the device gently on your neck at the same location where you found your pulse.
- Ensure that both stimulation surfaces are resting gently and flush to your skin.
- Continue to hold the device in place until the device beeps and stops delivering the stimulation
- Clean the gel off the device and your neck using paper towels.

Repeat all the above steps on the opposite side of your neck. You will need to start again from Step 1.

Your diary for before surgery

	5 days before surgery	4 days before surgery	3 days before surgery	2 days before surgery	1 day before surgery
Morning stimulation performed today?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Morning stimulation setting	..... (1-40)	..... (1-40)	..... (1-40)	..... (1-40)	..... (1-40)
Evening stimulation performed today?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Evening stimulation setting	..... (1-40)	..... (1-40)	..... (1-40)	..... (1-40)	..... (1-40)

Your diary for after surgery

	1 day after surgery	2 days after surgery	3 days after surgery	4 days after surgery	5 days after surgery
Morning stimulation performed today?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Morning stimulation setting	..... (1-40)	..... (1-40)	..... (1-40)	..... (1-40)	..... (1-40)
Evening stimulation performed today?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Evening stimulation setting	..... (1-40)	..... (1-40)	..... (1-40)	..... (1-40)	..... (1-40)

Please remember to bring this diary back with you on your day of surgery.

Researcher and main contact: **Stephen Chapman, s.chapman@leeds.ac.uk**

Publication date
04/2019

A-3.5. Definitions of clinical outcomes

Complication	Definition
Acute kidney injury (37)	Increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hours; or Increase in SCr to ≥ 1.5 times baseline, which is known; or Urine volume <0.5 ml/kg/h for 6 hours
Anastomotic leak (38)	Confirmed defect of the intestinal wall at the anastomotic site (including suture and staple lines leading to a communication between intra- and extra-luminal compartments. The diagnosis can be made on cross-sectional imaging or at time of re-operation
Pneumonia (40)	Chest radiography evidence of new or progressive and persistent infiltrates, consolidation, or cavitation AND one of: • Fever (>38C with no other recognised cause) • Leucopenia (WCC<4 x 10^9/L) or Leucocytosis (WCC>12 x 10^9/L) • Age > 70 years AND altered mental status (with no other cause) OR two of: • New onset purulent sputum or change in character of sputum • Increased respiratory secretions • Bronchial breath sounds • New onset sough, dyspnoea or tachypnoea • Worsening gas exchange (hypoxaemia, increased O_2 demand)
Surgical site infection (SSI) (41)	Infection (superficial/deep) occurs within 30 days after the operation and involves at least one of the following: • Purulent drainage with or without laboratory confirmation • Organisms isolated from an aseptically obtained culture • At least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative • Diagnosis of infection made by a surgeon or attending physician

A-3.6. Summary of participant characteristics by randomised strata: type of surgery

	Group 1: Stim/Stim n=9	Group 2: Stim/Sham n=10	Group 3: Sham/Stim n=12	Group 4: Sham/Sham n=12	Total n=43
Right sided Surgery					
Sex					
Male	6 (66.7%)	2 (20.0%)	9 (75.0%)	5 (41.7%)	22 (51.2%)
Female	3 (33.3%)	8 (80.0%)	3 (25.0%)	7 (58.3%)	21 (48.8%)
Age (years)	69.0 (7.8)	65.2 (11.6)	66.9 (7.3)	68.3 (8.1)	67.0 (8.6)
BMI (kg/m^2)	31.6 (10.1)	26.6 (4.5)	27.9 (4.5)	27.8 (4.9)	28.0 (6.2)
Current smoker	1 (11.1%)	2 (20.0%)	0 (0.0%)	0 (0.0%)	3 (7.0%)
Prior abdominal surgery	0 (0.0%)	3 (30.0%)	4 (33.3%)	3 (25.0%)	10 (23.3%)
Ischaemic heart disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diabetes mellitus	1 (11.1%)	1 (10.0%)	2 (16.7%)	0 (0.0%)	4 (9.3%)
Chronic kidney disease	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (2.3%)
COPD	0 (0.0%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	2 (4.7%)
PVD	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	1 (2.3%)
Regular opioid use	0 (0.0%)	1 (10.0%)	2 (16.7%)	0 (0.0%)	3 (7.0%)
Baseline Hb (g/L)	128.9 (17.8)	126.6 (18.6)	132.5 (18.4)	127.3 (17.9)	128.9 (17.6)
Baseline albumin (g/L)	36.1 (3.8)	38.7 (2.8)	37.1 (3.2)	38.5 (2.9)	37.6 (3.2)
Baseline eGFR*	76.6 (9.2)	78.2 (13.4)	81.7 (14.1)	77.9 (10.1)	78.8 (11.7)

	Group 1: Stim/Stim n=15	Group 2: Stim/Sham n=14	Group 3: Sham/Stim n=12	Group 4: Sham/Sham n=13	Total n=54
Left sided Surgery					
Sex					
Male	10 (66.7%)	3 (21.4%)	9 (75.0%)	7 (53.8%)	29 (53.7%)
Female	5 (33.3%)	11 (78.6%)	3 (25.0%)	6 (46.2%)	25 (46.3%)
Age (years)	63.5 (6.0)	63.6 (12.8)	67.6 (7.4)	63.2 (10.7)	64.4 (9.5)
BMI (kg/m^2)	29.1 (6.0)	28.8 (5.6)	29.9 (5.6)	29.4 (8.9)	29.3 (6.5)
Current smoker	1 (6.7%)	0 (0.0%)	2 (16.7%)	1 (7.7%)	4 (7.4%)
Prior abdominal surgery	6 (40.0%)	6 (42.9%)	7 (58.3%)	8 (61.5%)	27 (50.0%)
Ischaemic heart disease	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	2 (3.7%)
Diabetes mellitus	2 (13.3%)	0 (0.0%)	1 (8.3%)	1 (7.7%)	4 (7.4%)
Chronic kidney disease	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)
COPD	1 (6.7%)	1 (7.1%)	2 (16.7%)	1 (7.7%)	5 (9.3%)
PVD	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (1.9%)
Regular opioid use	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Baseline Hb (g/L)	150.5 (11.2)	137.9 (18.1)	142.5 (8.6)	136.2 (13.4)	141.9 (14.3)
Baseline albumin (g/L)	43.0 (10.1)	38.3 (2.9)	38.3 (4.0)	38.4 (3.8)	39.5 (6.0)
Baseline eGFR*	78.0 (15.7)	82.5 (8.9)	84.7 (8.9)	84.7 (13.9)	82.2 (12.4)

** Units are ml/min/1.73 m^2; Categorical variables expressed as rates (%); continuous variables expressed as mean (standard deviation); BMI: Body Mass Index; eGFR: estimated glomerular filtration rate; COPD: chronic obstructive pulmonary disease; Hb: haemoglobin; PVD: peripheral vascular disease*

A-3.7. Summary of participant characteristics by randomised strata: clinical site

	Group 1: Stim/Stim n=21	Group 2: Stim/Sham n=21	Group 3: Sham/Stim n=22	Group 4: Sham/Sham n=21	Total n=85
St. James's University Hospital, Leeds					
Sex					
Male	14 (66.7%)	5 (23.8%)	16 (72.7%)	10 (47.6%)	45 (52.9%)
Female	7 (33.3%)	16 (76.2%)	6 (27.3%)	11 (52.4%)	40 (47.1%)
Age (years)	66.3 (7.0)	65.9 (11.8)	66.4 (6.9)	64.7 (10.2)	65.8 (9.1)
BMI (kg/m2)	29.9 (7.8)	27.9 (4.9)	28.2 (4.5)	27.7 (7.2)	28.4 (6.2)
Current smoker	2 (9.5%)	1 (4.8%)	2 (9.1%)	1 (4.8%)	6 (7.1%)
Prior abdominal surgery	5 (23.8%)	9 (42.9%)	10 (45.5%)	10 (47.6%)	34 (40.0%)
Ischaemic heart disease	1 (4.8%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	2 (2.4%)
Diabetes mellitus	2 (9.5%)	0 (0.0%)	3 (13.6%)	1 (4.8%)	6 (7.1%)
Chronic kidney disease	1 (4.8%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	2 (2.4%)
COPD	1 (4.8%)	1 (4.8%)	4 (18.2%)	1 (4.8%)	7 (8.2%)
PVD	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (4.8%)	2 (2.4%)
Regular opioid use	0 (0.0%)	1 (4.8%)	2 (9.1%)	0 (0.0%)	3 (3.5%)
Baseline Hb (g/L)	142.1 (18.1)	135.0 (18.7)	136.3 (15.1)	132.0 (17.2)	136 (17.6)
Baseline albumin (g/L)	40.1 (9.2)	38.5 (2.9)	37.5 (3.5)	38.4 (3.5)	38.5 (5.3)
Baseline eGFR*	76.5 (14.3)	79.8 (11.4)	83.3 (12.1)	82.5 (12.3)	80.4 (12.7)

	Group 1: Stim/Stim n=3	Group 2: Stim/Sham n=3	Group 3: Sham/Stim n=2	Group 4: Sham/Sham n=4	Total n=12
Bradford Royal Infirmary, Bradford					
Sex					
Male	2 (66.7%)	0 (0.0%)	2 (100.0%)	2 (50.0%)	6 (50.0%)
Female	1 (33.3%)	3 (100.0%)	0 (0.0%)	2 (50.0%)	6 (50.0%)
Age (years)	60.3 (6.7)	53.3 (9.0)	76.5 (0.7)	70.8 (4.0)	64.8 (10.3)
BMI (kg/m2)	30.9 (8.1)	27.8 (8.5)	36.5 (6.3)	33.4 (5.7)	31.9 (6.8)
Current smoker	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Prior abdominal surgery	1 (33.3%)	0 (0.0%)	1 (50.0%)	1 (25.0%)	3 (25.0%)
Ischaemic heart disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diabetes mellitus	1 (33.3%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	2 (16.7%)
Chronic kidney disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
COPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PVD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Regular opioid use	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Baseline Hb (g/L)	146.0 (12.3)	123.3 (19.0)	149.5 (0.7)	131.3 (4.7)	136.5 (15.1)
Baseline albumin (g/L)	40.5 (2.1)	38.0 (1.4)	40.0 (0.0)	39.0 (3.0)	39.3 (2.1)
Baseline eGFR	83.7 (7.1)	86.0 (6.9)	83.0 (2.8)	74.3 (13.6)	81.6 (9.0)

** Units are ml/min/1.73 m^2; Categorical variables expressed as rates (%); continuous variables expressed as mean (sta deviation); BMI: Body Mass Index; eGFR: estimated glomerular filtration rate; COPD: chronic obstructive pulmonary dise Hb: haemoglobin; PVD: peripheral vascular disease*

A-3.8 – Rates of missing data

Data Variable		Expected data availability	Actual data availability	Missing data
Predefined clinical outcome data				
	Time to tolerate oral intake	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Time to first passage of flatus	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Time to first passage of stool	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Time to GI-2 outcome*	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Need for insertion of nasogastric tube	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Total length of inpatient hospital stay	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
Other clinical outcome data				
	30-day postoperative complications$^{\Psi}$	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	30-day planned critical care$^{\Psi}$	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	30-day unplanned critical care$^{\Psi}$	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	30-day treatment-related AEs$^{\Psi}$	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	30-day hospital readmission $^{\Psi}$	n=96/97 (99.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	30-day mortality$^{\Psi}$	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
Other clinical variables				
	Sex	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	Age	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	Height	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	Weight	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	Smoking status	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	History of previous surgery	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	History of chronic kidney disease	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	History of COPD	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	History of ischaemic heart disease	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	History of peripheral vascular disease	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	History of diabetes mellitus	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	History of preoperative opioid use	n=97/97 (100.0%)	n=97/97 (100.0%)	n=0/97 (0.0%)
	Baseline serum haemoglobin$^{\Omega}$	n=97/97 (100.0%)	n=90/97 (92.8%)	n=7/97 (7.2%)
	Baseline serum albumin$^{\Omega}$	n=97/97 (100.0%)	n=75/97 (77.3%)	n=22/97 (22.7%)
	Baseline eGFR$^{\Omega}$	n=97/97 (100.0%)	n=86/97 (88.7%)	n=11/97 (11.3%)
	ASA Classification	n=96/97 (99.0%)	n=95/96 (99.0%)	n=1/96 (1.0%)
	Operative approach	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Need for operative conversion	n=94/97 (97.9%)	n=94/94 (100.0%)	n=0/94 (0.0%)
	Procedure type	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Creation of anastomosis	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Creation of unplanned stoma	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Operative duration	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Administration of spinal analgesia	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Placement of intra-operative NGT	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Postoperative C-Reactive Protein	n=96/97 (99.0%)	n=91/96 (94.8%)	n=0/96 (0.0%)
	Need for red blood cell transfusion	n=96/97 (99.0%)	n=96/96 (100.0%)	n=0/96 (0.0%)
	Neoadjuvant treatment	n=87/97 (89.7%)	n=87/87 (100.0%)	n=0/87 (0.0%)
	Postoperative histology (T-Stage)	n=87/97 (89.7%)	n=87/87 (100.0%)	n=0/87 (0.0%)
	Postoperative histology (N-Stage)	n=87/97 (89.7%)	n=87/87 (100.0%)	n=0/87 (0.0%)
	Postoperative histology (M-Stage)	n=87/97 (89.7%)	n=87/87 (100.0%)	n=0/87 (0.0%)

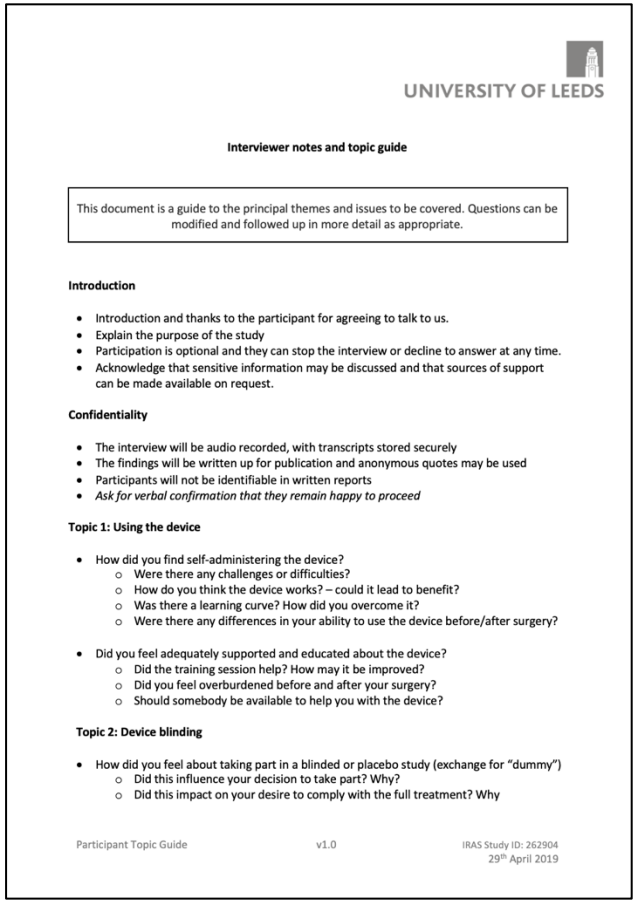
AE: Adverse event; ASA: American Society of Anesthesiologists Physical Status Classification System; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated glomerular filtration rate; NGT: nasogastric tube

** GI-2: A composite outcome comprising time to first tolerance of oral intake and passage of first stool*
Ψ Outcomes measured within 30 days of initial planned surgery; Ω Measurements no more than 30 days prior to surgery

Chapter 4 Appendix (A-4)

A-4.1. Topic guides

A-4.1.1 Final topic guide for trial participants



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Interviewer notes and topic guide

This document is a guide to the principal themes and issues to be covered. Questions can be modified and followed up in more detail as appropriate.

Introduction

- Introduction and thanks to the participant for agreeing to talk to us.
- Explain the purpose of the study
- Participation is optional and they can stop the interview or decline to answer at any time.
- Acknowledge that sensitive information may be discussed and that sources of support can be made available on request.

Confidentiality

- The interview will be audio recorded, with transcripts stored securely
- The findings will be written up for publication and anonymous quotes may be used
- Participants will not be identifiable in written reports
- *Ask for verbal confirmation that they remain happy to proceed*

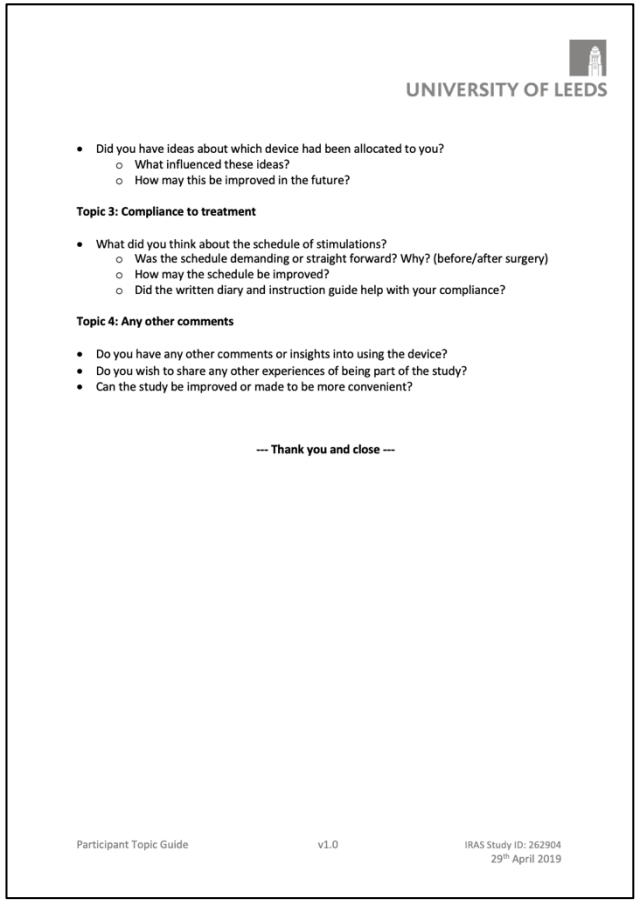
Topic 1: Using the device

- How did you find self-administering the device?
  - Were there any challenges or difficulties?
  - How do you think the device works? – could it lead to benefit?
  - Was there a learning curve? How did you overcome it?
  - Were there any differences in your ability to use the device before/after surgery?
- Did you feel adequately supported and educated about the device?
  - Did the training session help? How may it be improved?
  - Did you feel overburdened before and after your surgery?
  - Should somebody be available to help you with the device?

Topic 2: Device blinding

- How did you feel about taking part in a blinded or placebo study (exchange for "dummy")
  - Did this influence your decision to take part? Why?
  - Did this impact on your desire to comply with the full treatment? Why

Participant Topic Guide v1.0 IRAS Study ID: 262904 29th April 2019



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- Did you have ideas about which device had been allocated to you?
  - What influenced these ideas?
  - How may this be improved in the future?

Topic 3: Compliance to treatment

- What did you think about the schedule of stimulations?
  - Was the schedule demanding or straight forward? Why? (before/after surgery)
  - How may the schedule be improved?
  - Did the written diary and instruction guide help with your compliance?

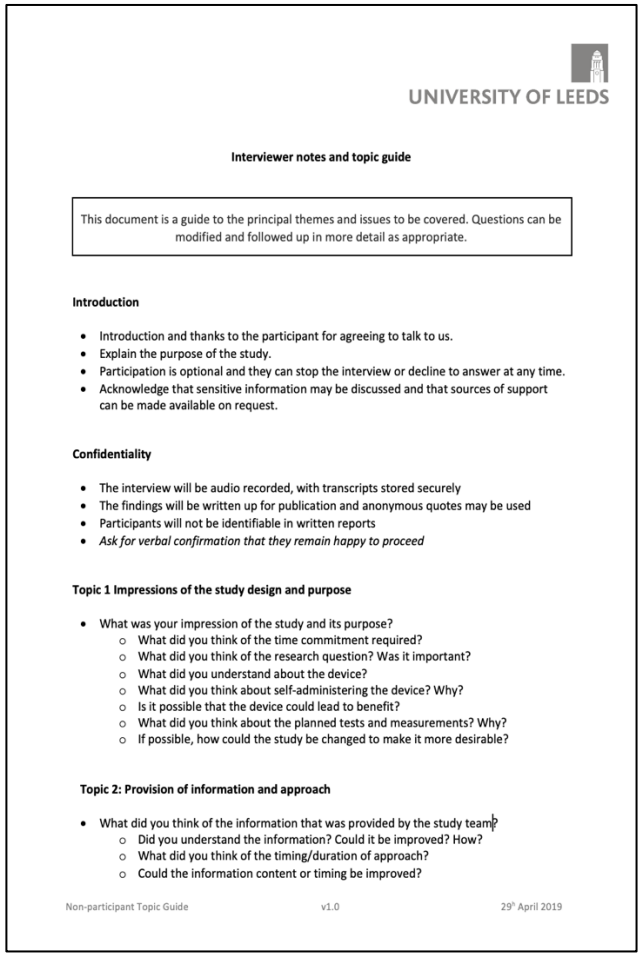
Topic 4: Any other comments

- Do you have any other comments or insights into using the device?
- Do you wish to share any other experiences of being part of the study?
- Can the study be improved or made to be more convenient?

--- Thank you and close ---

Participant Topic Guide v1.0 IRAS Study ID: 262904 29th April 2019

A-4.1.2 Final topic guide for trial non-participants



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Interviewer notes and topic guide

This document is a guide to the principal themes and issues to be covered. Questions can be modified and followed up in more detail as appropriate.

Introduction

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Confidentiality

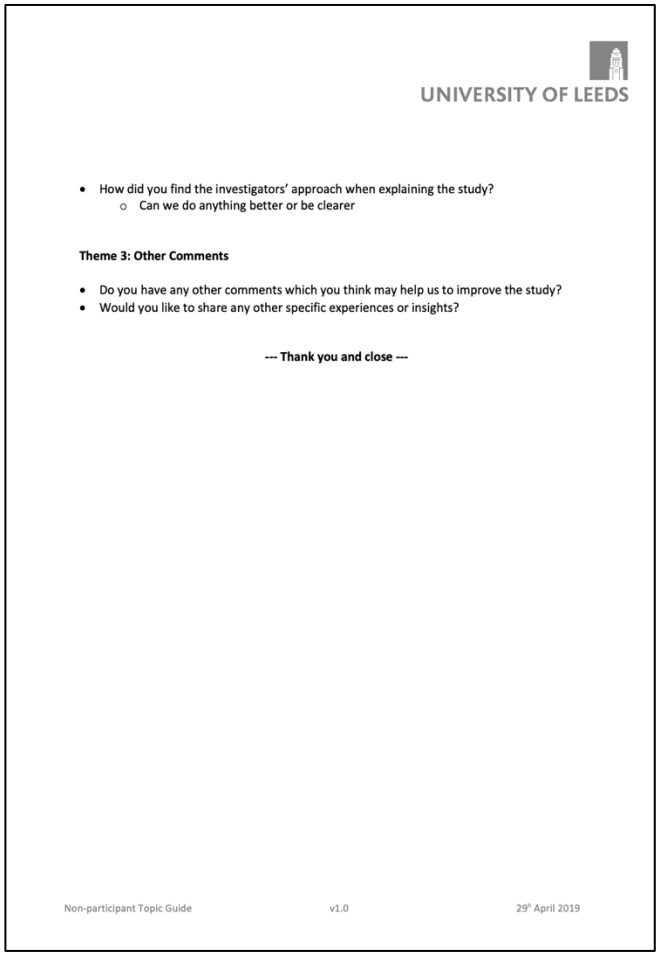
- The interview will be audio recorded, with transcripts stored securely
- The findings will be written up for publication and anonymous quotes may be used
- Participants will not be identifiable in written reports
- *Ask for verbal confirmation that they remain happy to proceed*

Topic 1 Impressions of the study design and purpose

- What was your impression of the study and its purpose?
  - What did you think of the time commitment required?
  - What did you think of the research question? Was it important?
  - What did you understand about the device?
  - What did you think about self-administering the device? Why?
  - Is it possible that the device could lead to benefit?
  - What did you think about the planned tests and measurements? Why?
  - If possible, how could the study be changed to make it more desirable?

Topic 2: Provision of information and approach

- What did you think of the information that was provided by the study team?
  - Did you understand the information? Could it be improved? How?
  - What did you think of the timing/duration of approach?
  - Could the information content or timing be improved?



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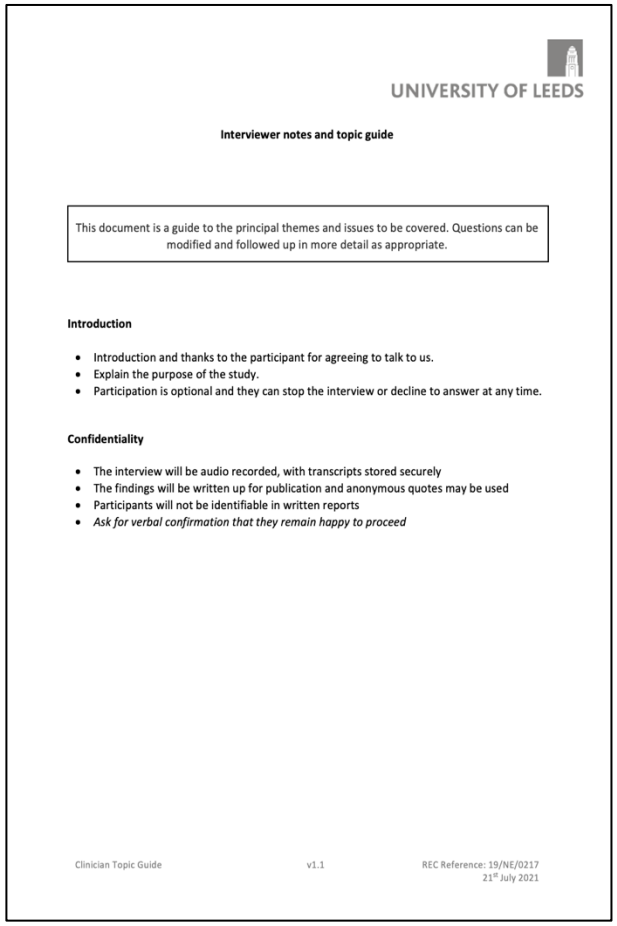
- How did you find the investigators' approach when explaining the study?
  - Can we do anything better or be clearer

Theme 3: Other Comments

- Do you have any other comments which you think may help us to improve the study?
- Would you like to share any other specific experiences or insights?

--- Thank you and close ---

A-4.1.3 Final topic guide for health professional participants



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Interviewer notes and topic guide

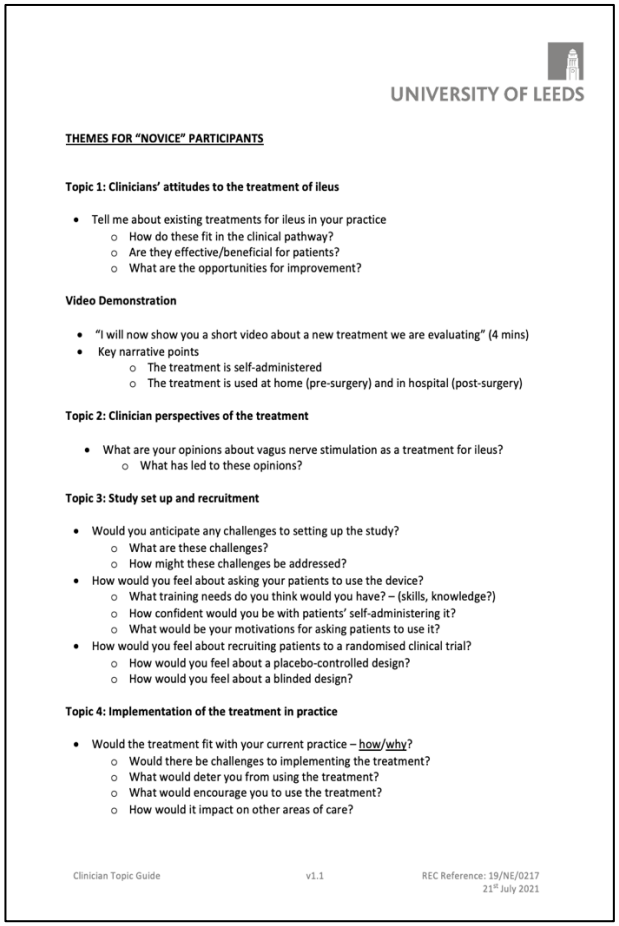
This document is a guide to the principal themes and issues to be covered. Questions can be modified and followed up in more detail as appropriate.

Introduction

- Introduction and thanks to the participant for agreeing to talk to us.
- Explain the purpose of the study.
- Participation is optional and they can stop the interview or decline to answer at any time.

Confidentiality

- The interview will be audio recorded, with transcripts stored securely
- The findings will be written up for publication and anonymous quotes may be used
- Participants will not be identifiable in written reports
- *Ask for verbal confirmation that they remain happy to proceed*



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THEMES FOR "NOVICE" PARTICIPANTS

Topic 1: Clinicians' attitudes to the treatment of ileus

- Tell me about existing treatments for ileus in your practice
  - How do these fit in the clinical pathway?
  - Are they effective/beneficial for patients?
  - What are the opportunities for improvement?

Video Demonstration

- "I will now show you a short video about a new treatment we are evaluating" (4 mins)
- Key narrative points
  - The treatment is self-administered
  - The treatment is used at home (pre-surgery) and in hospital (post-surgery)

Topic 2: Clinician perspectives of the treatment

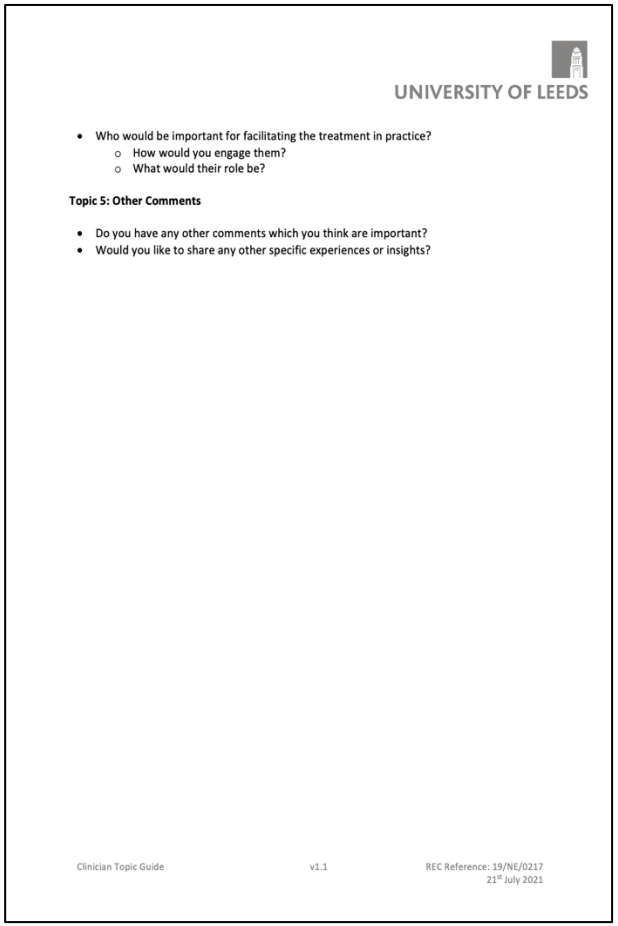
- What are your opinions about vagus nerve stimulation as a treatment for ileus?
  - What has led to these opinions?

Topic 3: Study set up and recruitment

- Would you anticipate any challenges to setting up the study?
  - What are these challenges?
  - How might these challenges be addressed?
- How would you feel about asking your patients to use the device?
  - What training needs do you think would you have? – (skills, knowledge?)
  - How confident would you be with patients' self-administering it?
  - What would be your motivations for asking patients to use it?
- How would you feel about recruiting patients to a randomised clinical trial?
  - How would you feel about a placebo-controlled design?
  - How would you feel about a blinded design?

Topic 4: Implementation of the treatment in practice

- Would the treatment fit with your current practice – how/why?
  - Would there be challenges to implementing the treatment?
  - What would deter you from using the treatment?
  - What would encourage you to use the treatment?
  - How would it impact on other areas of care?



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- Who would be important for facilitating the treatment in practice?
  - How would you engage them?
  - What would their role be?

Topic 5: Other Comments

- Do you have any other comments which you think are important?
- Would you like to share any other specific experiences or insights?

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TOPICS FOR "STUDY SITE" PARTICIPANTS

Topic 1: Clinicians' attitudes to the treatment of ileus

- Tell me about existing treatments for ileus in your practice
  - How do these fit in the clinical pathway?
  - Are they effective/beneficial for patients?
  - What are the opportunities for improvement?

Topic 2: Clinician perspectives of the treatment

- What are your opinions about vagus nerve stimulation as a treatment for ileus?
  - What has led to these opinions?

Topic 3: Study set up and recruitment

- How did you find the process of setting up the study at your site?
  - What challenges (if any) existed?
  - What lessons did you learn which may help us in the future?
  - Who did you engage to set up the study?
- What training needs did you have at the beginning of the study?
  - Can and how might training be improved?
  - What further support (if any) would be useful?
- How did you approach patients for the study?
  - What barriers (if any) to approaching patients existed?
  - How did you explain/demonstrate the device?
  - In what ways did you adapt your approach over time?
- How did you consent patients for the study?
  - What barriers (if any) to consenting patients existed
  - How did the timing of consent fit with the clinical pathway?
  - In what ways did you adapt your approach over time?

Topic 4: Implementation of the treatment in practice

- How did you find delivering the study according to the agreed protocol?
  - Which parts worked well/which parts were challenging?
  - How might these issues be addressed?
- To what extent did the study treatment integrate into normal care?
  - Were there any unexpected consequences?
  - How did other staff/ward members react to the treatment?
- Who was important for facilitating the treatment in practice?
  - How did you engage them?
  - What was their role?

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Topic 5: Other Comments

- Do you have any other comments which you think are important?
- Would you like to share any other specific experiences or insights?

A-4.2. Study recruitment materials

A-4.2.1. Qualitative study participant information sheet (trial participants)

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Vagus nerve stimulation to improve bowel function after surgery

Optional interview study

We invite you to take part in an optional study. Please read this information sheet alongside the main study information.

Why are we doing this optional study?

We are interested in your experiences of using the GammaCore® device at home and in hospital. We hope to understand what you liked and did not like about the device. This will help us to improve the treatment in the future.

What does the study involve?

We will ask you to take part in an informal interview (30-45 minutes) with the researcher. This will take place after discharge. We will try our best to coordinate the interview with your existing hospital visits, or if you prefer, the interview can take place at your home or by phone. If an extra visit to the hospital is required, we will happily reimburse your travel and parking expenses. The interview will be voice recorded, but your personal details will never be identified.

Why have I been chosen, and do I have to take part?

We have approached you for this optional study because you are due to have a bowel operation. Taking part is voluntary. You do not have to participate in this optional study in order to still take part in the main study.

What are the possible advantages of taking part?

The interview may not necessarily lead to advantages to you as an individual, but it is a chance for you to tell us what you thought of the GammaCore® device. We value your opinions as these will help us to improve the treatment in the future.

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What are the possible disadvantages of taking part?

There are no serious disadvantages of taking part. We know that discussing your experiences can bring back memories which may be sensitive. You can pause or stop the interview at any point. We can also tell you about sources of support. We will try our best to make the interview convenient by coordinating it with your existing hospital visits. If this is not possible, we will happily reimburse your travel and parking expenses.

How do I confirm my interest in this study?

You do not need to decide right now; we will ask about your decision during your hospital visit. If you do decide to take part, we will ask you to sign an extra consent form and arrange a time for the interview. If you do not decide to take part, this will not affect your involvement in the main study or your clinical care.

More information *about this optional study*

- **Confidentiality**
  All information will be stored confidentially at University of Leeds. The electronic voice recordings will be sent securely to a trusted external service for transcription, with personal details censored to ensure anonymity. They will only store these recordings for as long as is necessary and will agree to keep all audio content confidential. The recordings will then be stored securely by University of Leeds for 15 years, before being permanently deleted.

- **Will my GP be informed of my role in this study?**
  Yes, with your permission, we will inform your GP of your involvement in the interview.

- **What will happen to the results of this study?**
  The results will be published in an academic journal and presented to scientific audiences. Anonymous quotes may be used, but you will never be identified as an individual.

- **What if I want to withdraw from the optional study?**
  You are free to withdraw from the study up to 7 days after the interview. After this time, transcriptions will be anonymised and it may not be possible to identify you. It is possible to withdraw from the optional study and continue in the main study if you wish.

- **Who has reviewed the study?**
  As with the main study, this optional study was approved by the Tyne & Wear South Research Ethics Committee (19/NE/0217) on 2nd July 2019.

- **Contact for further information**
  Researcher and main contact: Mr Stephen Chapman; S.Chapman@leeds.ac.uk
  Supervising Researcher: Ms Carolyn Czoski Murray; C.J.CzoskiMurray@leeds.ac.uk

Participant Information Sheet – Interview Study v1.1 IRAS Study ID: 262904
22nd September 2019

A-4.2.2. Qualitative study participant information sheet (trial non-participants)

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Vagus nerve stimulation to improve bowel function after surgery

Non-participant interview study

We invite you to take part in a short interview after your operation.

Why are we doing this study?

As researchers, we are interested in how research can be improved in the future. We understand that taking part in research studies is a personal choice and we are interested in what factors may encourage or deter people from taking part. We would like to discuss what influenced your decision to decline participation in this specific study. This will help us to improve our research in the future.

What does the study involve?

We will ask you to take part in a 30-minute interview with the researcher. This will take place after discharge. We will try our best to coordinate the interview with your existing hospital visits, or if you prefer, the interview can take place at your home or via telephone. If an extra visit to the hospital is required, we will happily reimburse your travel and parking expenses. The interview will be voice recorded, but your personal details will never be identified in any transcripts.

Why have I been chosen, and do I have to take part?

We have approached you for this study because you are due to have a bowel operation and have decided not to take part in the main study. The interview represents a standalone research study and taking part is entirely voluntary.

What are the possible advantages of taking part?

The interview may not necessarily lead to advantages to you as an individual, but it is a chance for you to tell us what you thought about our proposed study. We value your opinions as these will help us to improve in the future.

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What are the possible disadvantages of taking part?

There are no serious disadvantages of taking part. We know that discussing your experiences can bring back memories which may be sensitive. You can pause or stop the interview at any point. We can also tell you about sources of support. We will try our best to make the interview convenient by coordinating it with your existing hospital visits. If this is not possible, we will happily reimburse your travel and parking expenses.

How do I confirm my interest in this optional study?

You do not need to decide right now; we will ask about your decision during your hospital visit. If you do decide to take part, we will ask you to sign an extra consent form and arrange a time for the interview. If you do not decide to take part, this will not affect your clinical care.

More information *about this optional study*

- **Confidentiality**
  All information will be stored confidentially at the University of Leeds. The electronic voice recordings will be sent securely to a trusted external service for transcription, with personal details censored to ensure anonymity. They will only store these recordings for as long as is necessary and will agree to keep all audio content confidential. The recordings will then be stored securely by University of Leeds for 15 years, before being permanently deleted.

  Your hospital will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from University of Leeds and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Your hospital will pass these details to University of Leeds along with the information collected from you. The only people at University of Leeds who will have access to information that identifies you will be people who need to audit the data collection process. People who analyse the information will not be able to identify you.

  University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller. This means that we are responsible for looking after your information and using it properly. University of Leeds will keep identifiable information about you for 15 years after this study has finished. This is normal for research studies and arrangements for confidential destruction will be made. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and

Non-participant interview information Sheet v1.1 IRAS Study ID: 262904 22nd September 2019

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accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information by contacting dpo@leeds.ac.uk or by visiting:

https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/02/Research-Privacy-Notice.pdf

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

- **Will my GP be informed of my role in this study?**
  Yes, with your permission, we will inform your GP of your involvement in the interview.

- **What will happen to the results of this study?**
  The result will be published in an academic journal and presented to scientific audiences. Anonymous quotes may be used, but you will never be identified as an individual.

- **What if I want to withdraw from the optional study?**
  You are free to withdraw from the study up to 7 days after the interview. After this time, transcriptions will be anonymised and it may not be possible to identify you. It is possible to withdraw from the optional study and continue in the main study if you wish.

- **Who has reviewed the study?**
  As with the main study, this optional study was approved by the Tyne & Wear South Research Ethics Committee (19/NE/0217) on 2nd July 2019.

- **Contact for further information**
  Researcher and main contact: Mr Stephen Chapman; S.Chapman@leeds.ac.uk
  Supervising Researcher: Ms Carolyn Czoski Murray; C.J.CzoskiMurray@leeds.ac.uk

Non-participant interview information Sheet v1.1 IRAS Study ID: 262904 22nd September 2019

A-4.2.3. Qualitative study participant information sheet (health professionals)

UNIVERSITY OF LEEDS

Vagus nerve stimulation to improve bowel function after surgery

Clinician interview study

We invite you to take part in a short interview.

Why are we doing this study?

Non-invasive vagus nerve stimulation is a plausible new treatment to reduce ileus after colorectal surgery. Previous studies have confirmed its proof of concept. We would like to explore the perceptions of this treatment amongst the colorectal community in preparation for future research. Specifically, we are interested in whether you would support the treatment in a randomised clinical trial and whether you would consider using it in mainstream practice if shown to be effective.

What does the study involve?

We will ask you to take part in a 30-minute telephone interview with the researcher. With your permission, this will take place outside of your NHS working hours to ensure it does not clash with your other clinical commitments. Before taking part in the study, we will ask you to sign and return a consent via email.

Why have I been chosen, and do I have to take part?

We have approached you for this study because you are a healthcare professional who looks after patients having colorectal surgery. Taking part is entirely voluntary. If you have any questions about the study, the researchers will be delighted to discuss these via email or telephone.

What are the possible advantages of taking part?

The interview may not necessarily lead to advantages to you as an individual, but it is a chance for you to tell us what you think of the proposed treatment. We value your opinions as these will help us to make important decisions about future research.

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What are the possible disadvantages of taking part?

There are no disadvantages of taking part. The interviews will be performed by a doctoral researcher who has experience of facilitating interviews, under the supervision of an experienced academic. You can pause or stop the interview at any point. We will try our best to make the interview as convenient as possible.

How do I confirm my interest in this study?

If you decide to take part, we will ask you to sign and return a consent form via email. We will then arrange a time and date for the interview via telephone. Your contact details will be stored for up to one year after the study finishes and will then be permanently removed from our records.

More information about this study

- **Confidentiality**
  All information collected during this study will be stored confidentially at the University of Leeds. Voice recordings of the interview will be transcribed by a trusted external service, with all identifying information censored. Audio data from the interview will then be deleted. The only people at the University of Leeds who will have access to information that identifies you will be the researchers and people who need to audit the study.

  University of Leeds is the sponsor for this study. We will use information collected from you to undertake this study and will act as the data controller. This means that we are responsible for looking after your information and using it properly. University of Leeds will keep identifiable information for 15 years after this study has finished. This is normal for research studies and arrangements for confidential destruction will be made. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information by contacting dpo@leeds.ac.uk or by visiting:

  https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/02/Research-Privacy-Notice.pdf

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When you agree to take part in a research study, the information collected may be provided to researchers running other research studies in the same organisation and other organisations. These may be universities, the NHS, or companies involved in health and care research. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research. The information provided will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you for other purposes.

- **What will happen to the results of this study?**
  The result will be published in an academic journal and presented to scientific audiences. Anonymous quotes may be used, but you will never be identified as an individual.

- **What if I want to withdraw from the study?**
  You are free to withdraw from the study up to 7 days after the interview. After this time, transcriptions will be analysed and it may not be possible to identify you.

- **Who has reviewed the study?**
  This study was approved by the Tyne & Wear South Research Ethics Committee (19/NE/0217) as a substantial amendment on 22nd February 2021.

- **Contact for further information**
  Researcher and main contact: Mr Stephen Chapman; S.Chapman@leeds.ac.uk
  Supervisor: Ms Carolyn Czoski Murray; C.J.CzoskiMurray@leeds.ac.uk

A-4.2.4. Qualitative study participant consent form (trial participants)

NHS
The Leeds Teaching Hospitals
NHS Trust

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Vagus nerve stimulation to improve bowel function after surgery:

Optional interview study

Participant Study ID	Patient Initials	Patient Date of Birth

Agreement to the following additional items are required to participate in the optional study

Please initial the boxes to indicate your agreement:

A. I have read the optional interview study patient information sheet dated [date, version] and have had the opportunity to ask questions. ☐

B. I understand that the interview will be voice recorded and transcribed by a trusted external service. I understand that all information will be stored, analysed, and later destroyed at the University of Leeds according to current data protection laws. ☐

C. I agree to allow information or results arising from this study to be used for further medical research on the understanding that my identify will remain anonymous. ☐

D. I understand that I may freely withdraw from this optional study without affecting my participation in the main study, and without my medical care or legal rights being affected. I understand that it will be possible to withdraw from the study up to 7 days after my interview, but after this time withdrawal may not be possible. ☐

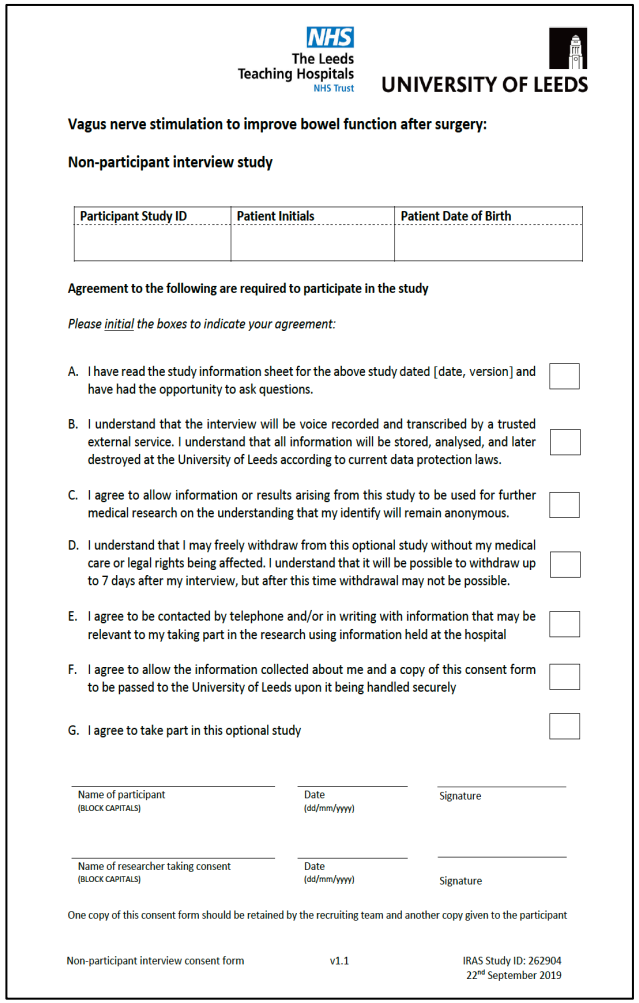
E. I agree to take part in this optional study ☐

Name of participant (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature

Name of researcher taking consent (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature

One copy of this consent form should be retained by the recruiting team and another copy given to the participant

A-4.2.5. Qualitative study participant consent form (trial non-participants)



NHS
The Leeds Teaching Hospitals
NHS Trust

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Vagus nerve stimulation to improve bowel function after surgery:

Non-participant interview study

Participant Study ID	Patient Initials	Patient Date of Birth

Agreement to the following are required to participate in the study

Please initial the boxes to indicate your agreement:

A. I have read the study information sheet for the above study dated [date, version] and have had the opportunity to ask questions. ☐

B. I understand that the interview will be voice recorded and transcribed by a trusted external service. I understand that all information will be stored, analysed, and later destroyed at the University of Leeds according to current data protection laws. ☐

C. I agree to allow information or results arising from this study to be used for further medical research on the understanding that my identify will remain anonymous. ☐

D. I understand that I may freely withdraw from this optional study without my medical care or legal rights being affected. I understand that it will be possible to withdraw up to 7 days after my interview, but after this time withdrawal may not be possible. ☐

E. I agree to be contacted by telephone and/or in writing with information that may be relevant to my taking part in the research using information held at the hospital ☐

F. I agree to allow the information collected about me and a copy of this consent form to be passed to the University of Leeds upon it being handled securely ☐

G. I agree to take part in this optional study ☐

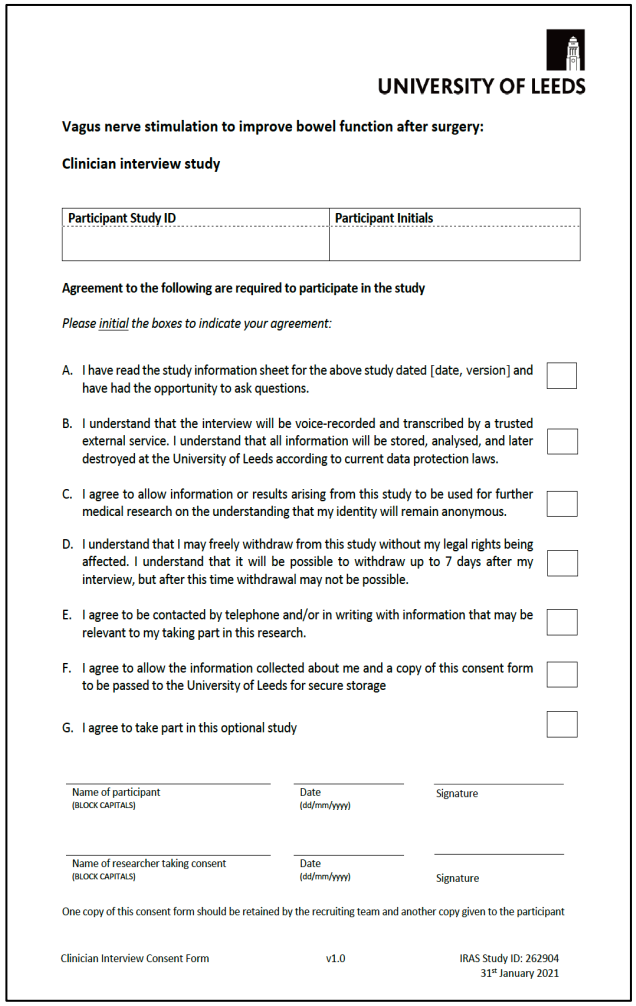
Name of participant (BLOCK CAPITALS) _____ Date (dd/mm/yyyy) _____ Signature _____

Name of researcher taking consent (BLOCK CAPITALS) _____ Date (dd/mm/yyyy) _____ Signature _____

One copy of this consent form should be retained by the recruiting team and another copy given to the participant

Non-participant interview consent form v1.1 IRAS Study ID: 262904
22nd September 2019

A-4.2.6. Qualitative study participant consent form (health professionals)



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Vagus nerve stimulation to improve bowel function after surgery:

Clinician interview study

Participant Study ID	Participant Initials

Agreement to the following are required to participate in the study

Please initial the boxes to indicate your agreement:

A. I have read the study information sheet for the above study dated [date, version] and have had the opportunity to ask questions. ☐

B. I understand that the interview will be voice-recorded and transcribed by a trusted external service. I understand that all information will be stored, analysed, and later destroyed at the University of Leeds according to current data protection laws. ☐

C. I agree to allow information or results arising from this study to be used for further medical research on the understanding that my identity will remain anonymous. ☐

D. I understand that I may freely withdraw from this study without my legal rights being affected. I understand that it will be possible to withdraw up to 7 days after my interview, but after this time withdrawal may not be possible. ☐

E. I agree to be contacted by telephone and/or in writing with information that may be relevant to my taking part in this research. ☐

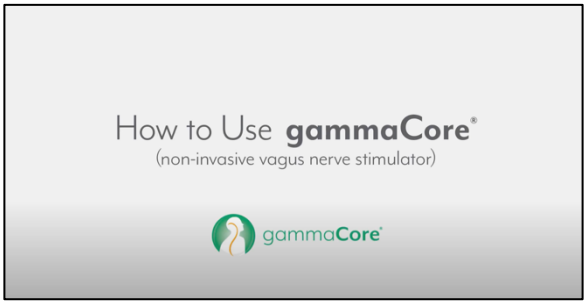
F. I agree to allow the information collected about me and a copy of this consent form to be passed to the University of Leeds for secure storage ☐

G. I agree to take part in this optional study ☐

Name of participant (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature
Name of researcher taking consent (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature

One copy of this consent form should be retained by the recruiting team and another copy given to the participant

A-4.3. gammaCore explanatory video



Selected screenshots from explanatory video shown to health professional participants who were not familiar with the study or the study intervention

A-4.4 – Final coding framework for patient-participants

Patient codes
Technical aptitude
Device accessibility
Pulse and positioning
Mitigation strategies
Learning curve
Perseverance
Familiarity
Life integration
Role of healthcare professionals
Role of family and friends
Role of research team
Ward environment and care
Emotional burden
Physical burden
Understanding of ileus/recovery
Understanding of study processes
Understanding of the device and mechanisms
Device training
Confidence
Independence
Participation in care
Belief in the intervention
Device experience and expectations
Motivation and investment
Administrative Burden
Balancing risks

A-4.5 – Final coding framework for health professional-participants

Health professional codes
Knowledge of science and mechanisms
Perspectives and experiences of ileus
Normalisation of ileus
Impact of ileus on recovery
Belief in treatments
Strength of evidence
Institutional bureaucracy
Supportive management
Priority research agenda
Participant recruitment challenges
Research team
Study set up
Patient empowerment
Recovery after surgery
Trust and confidence in patients
Implementation of new technology
Attitudes toward change
Cost of treatment
Device safety
Stigma of complications
Device stewardship
Familiarity
Communication
Responsibility of treatment
Device accessibility
Education

Chapter 5 Appendix (A-5)

A-5.1. Amendments to research ethics approval

Amendment 1 21st Nov 2020 Substantial amendment Approval: 11th Jan 2021	1) In 2020, coronavirus disease 2019 (COVID-19) was declared as a global pandemic by the World Health Organisation. Social distancing regulations enforced by national legislatures precluded the planned face-to-face consensus meeting due to take place in Auckland, New Zealand in November 2020. Following extensive consultation within the Steering Committee, a decision was made to convert the consensus meeting to a virtual event delivered via an online teleconference service. Care was taken to ensure inclusive and fair participation throughout the event by means of a dedicated event facilitator (SC) and independent chairperson (RF). The online consensus event was subsequently planned for 6th March 2021.

A-5.2. Steering committee and contributions

The Steering Committee membership is provided below, along with each individual's contribution according to the Contributor Roles Taxonomy (CRediT framework):

Mr Stephen J Chapman Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK	Conceptualisation; Methodology; Formal analysis; Investigation; Resources; Data Curation; Project administration
Mr Matthew J Lee Department on Oncology & Metabolism, Medical School, University of Sheffield, UK	Conceptualisation; Methodology; Resources
Ms Sue Blackwell Patient Representative, Liverpool	Patient and public involvement advocacy; Resources
Professor Robert Arnott Patient Representative, Green Templeton College, Oxford, UK	Patient and public involvement advocacy; Resources
Dr Richard PG ten Broek Department of Surgery, Radboud University Medical Centre, Nijmegan, The Netherlands	Validation; Resources
Professor Conor P Delaney Department of Colorectal Surgery, Cleveland Clinic, Cleveland, USA	Validation; Resources
Dr Nagendra Dudi-Venkata Faculty of Health & Medical Science, School of Medicine, University of Adelaide, Adelaide, Australia	Validation; Resources
Ms Rebecca Fish Division of Cancer Sciences, University of Manchester, Manchester, UK	Validation; Resources
Professor Daniel Hind Clinical Trials Research Unit, University of Sheffield, Sheffield, UK	Methodology, Validation; Resources
Professor David Jayne Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK	Validation; Resources
Ms Katie Mellor Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK	Validation; Resources
Prof Anurag Mishra Department of Surgery, Maulana Azad Medical College, New Delhi, India	Validation; Resources

Professor Greg O'Grady Faculty of Medicine & Health Sciences, University of Auckland, Auckland, New Zealand	Validation; Resources
Professor Tarik Sammour Colorectal Unit, Department of Surgery, Royal Adelaide Hospital, Adelaide, Australia	Validation; Resources
Dr Gabrielle Thorpe Faculty of Medicine & Health Sciences, University of East Anglia, Norwich, UK	Validation; Resources
Dr Cameron I Wells Faculty of Medicine & Health Sciences, University of Auckland, Auckland, New Zealand	Validation; Resources
Professor Albert M Wolthuis Department of Abdominal Surgery, University Hospital Leuven, Leuven, Belgium	Validation; Resources
Ms Nicola Fearnhead Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK	Conceptualisation; Validation; Resources

A-5.3. Study recruitment materials

A-5.3.1. Stakeholder consultation participant information sheet

Participant information: Development of a core outcome set for gastrointestinal recovery

Research team:

Matthew Lee, Academic Clinical Lecturer in Surgery, University of Sheffield
Steven Chapman, NIHR Doctoral Research Fellow, University of Leeds
Sue Blackwell, Lay representative
Miss Nicola Fearnhead, Consultant Colorectal Surgeon, Cambridge University Hospitals

Contact: Matthew Lee: m.j.lee@sheffield.ac.uk

1. Invitation paragraph

You are being invited to take part in a research project. Before you decide whether or not to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

2. What is the project's purpose?

Gastrointestinal recovery is something that is often measured in research studies. It describes the recovery of bowel function after surgery or after an episode of small bowel obstruction (often called a blockage). At the moment, researchers measure this in many different ways, which makes it difficult to compare studies or to test new treatments. We hope to develop a "core outcome set", which aims to standardise how researchers measure this in the future so that comparisons between studies becomes easier, and improve the value of research.

We are looking at these two conditions at the same time as we think there are some common areas between them, and it is efficient to consider them together.

The first step in developing this set of measures is look at published studies to see what outcomes have been reported, and to create a long list of potential items. We have already completed this.

The second step is to show this list to people including members of the public, people with experience of these conditions, and healthcare professionals. This helps us to see if we have missed anything important that should be routinely measured.

The third step is to undertake serial votes on the long list.

3. Why have I been chosen?

You are seeing this information because you have clicked on a link advertising the project in a tweet, or in an email from a charity or society who want to help promote this project. You might be a member of the public who has experienced a blocked bowel or ileus after surgery, or perhaps one of your family members has. You may be a health-care professional working with people who have these problems, or a researcher with an interest in the field.

4. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be be asked to sign a consent form, and you can still withdraw at any time without any negative consequences. You do not have to give a reason. If you wish to withdraw from the research, please contact Matthew Lee (m.j.lee@sheffield.ac.uk).

*Please note that if there is a point at which it will not be possible for a participant's data to be withdrawn from the research (e.g. once data have been anonymised and included within a large dataset), then it should be made clear that, whilst they can withdraw from any on-going or future data collection, their data cannot be removed from the study beyond this point. Ideally a date or time-frame should be provided for this.

5. What will happen to me if I take part? What do I have to do?

If you take part, we will ask you to call a free-phone telephone number or to use a web-chat system such as skype along with around 10 other participants. We will ask participants to spend five to ten minutes thinking about what outcome measures are missing from each of the two lists (ileus and bowel obstruction), and to make your own list of what items you think are missing. We will then ask participants in turn to give one of the outcomes from their list. This will continue around the group until no further outcomes are proposed. The group will then review the list generated and agree that there are no further items to add. We anticipate this will take from 30 minutes up to one hour. The discussion will not be recorded – we will only make a note of the outcomes identified by participants.

6. What are the possible disadvantages and risks of taking part?

Some people might feel uncomfortable raising some topics related to their recovery such as ability to go to the toilet. If you feel uncomfortable raising this, you will be able to raise a comment anonymously to the person running the telephone call. No one involved in the phone call will know your full name except for the person in charge of the phone call. This means that you shouldn't be recognisable from your comments in the phone call. Aside from social discomfort related to this, we do not think there are any major disadvantages to participation.

7. What are the possible benefits of taking part?

Whilst there are no immediate benefits for those people participating in the project, it is hoped that this work will help us design better research in the future to help improve outcomes in these conditions.

8. Will my taking part in this project be kept confidential?

All the information that we collect about you during the course of the research will be kept strictly confidential and will only be accessible to members of the research team. You will not be able to be identified in any reports or publications.

9. What is the legal basis for processing my personal data?

In order to participate, we will need to know your name, email address (for contact related to the study), and to know what your role is in relation to the research (e.g. member of public, health-care professional, non-clinical researcher, other stakeholder).

According to data protection legislation, we are required to inform you that the legal basis we are applying in order to process your personal data is that 'processing is necessary for the performance of a task carried out in the public interest' (Article 6(1)(e)). Further information can be found in the University's Privacy Notice https://www.sheffield.ac.uk/govern/data-protection/privacy/general.

10. What will happen to the data collected, and the results of the research project?

One researcher (based at the University of Sheffield) will have access to your email address which is stored on our secure REDCap database at the University of Sheffield. This researcher will co-ordinate the nominal group meeting using this email address from their own University email address.

We will capture data from the nominal group meeting into a word document, and the items suggested will be added to our long-list, which will go into a set of serial voting. If you wish to participate in this, please contact the research team.

We plan to share the findings of the study with the public and research community through publication in scientific journals and presentations at research meetings. We will retain your data until six months after publication of the final report, so that we can share this with you.

11. Who is organising and funding the research?

This study is not funded. It is jointly organised by researchers from the University of Sheffield, University of Leeds, and Cambridge University Hospitals.

12. Who is the Data Controller?

The University of Sheffield will act as the Data Controller for this study. This means that the University is responsible for looking after your information and using it properly.

13. Who has ethically reviewed the project?

This project has been ethically approved via the University of Sheffield's Ethics Review Procedure, as administered by the Medical School, reference 029907

14. What if something goes wrong and I wish to complain about the research?

We do not anticipate any problems arising from the study. However, if you have any concerns, please contact Matthew Lee (m.j.lee@sheffield.ac.uk) in the first instance.

If you feel your concerns has not been handled to their satisfaction, this can be passed to the Head of Department (details available on request), who will then escalate the complaint through the appropriate channels. If the complaint relates to how your personal data has been handled, information about how to raise a complaint can be found in the University's Privacy Notice: https://www.sheffield.ac.uk/govern/data-protection/privacy/general.

15. Contact for further information

Should you require further information, please contact Matthew Lee (m.j.lee@sheffield.ac.uk / @wannabehawkeye) or Stephen Chapman (S.Chapman@leeds.ac.uk)

A-5.3.2. Delphi prioritisation process participant information sheet

Participant information: Development of a core outcome set for gastrointestinal recovery

Research team:

Matthew Lee, Academic Clinical Lecturer in Surgery, University of Sheffield
Steven Chapman, NIHR Doctoral Research Fellow, University of Leeds
Sue Blackwell, Lay representative
Miss Nicola Fearnhead, Consultant Colorectal Surgeon, Cambridge University Hospitals

Contact: Matthew Lee: m.j.lee@sheffield.ac.uk

1. Invitation paragraph

You are being invited to take part in a research project. Before you decide whether or not to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

2. What is the project's purpose?

Gastrointestinal recovery is something that is often measured in research studies. It describes the recovery of bowel function after surgery or after an episode of small bowel obstruction (often called a blockage). At the moment, researchers measure this in many different ways, which makes it difficult to compare studies or to test new treatments. We hope to develop a "core outcome set", which aims to standardise how researchers measure this in the future so that comparisons between studies becomes easier, and improve the value of research.

We are looking at these two conditions at the same time as we think there are some common areas between them, and it is efficient to consider them together.

The first step in developing this set of measures is look at published studies to see what outcomes have been reported, and to create a long list of potential items. We have already completed this.

The second step is to show this list to people including members of the public, people with experience of these conditions, and healthcare professionals. This helps us to see if we have missed anything important that should be routinely measured.

The third step is to undertake serial votes on the long list. This helps us to reduce the items from a long list, down to around 10-15 outcomes that really matter to researchers and patients, and can be easily reported across future studies.

3. Why have I been chosen?

You are seeing this information because you have clicked on a link advertising the project in a tweet, or in an email from a charity or society who want to help promote this project. You might be a member of the public who has experienced a blocked bowel or ileus after surgery,

or perhaps one of your family members has. You may be a health-care professional working with people who have these problems, or a researcher with an interest in the field.

4. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be be asked to sign a consent form, and you can still withdraw at any time without any negative consequences. You do not have to give a reason. If you wish to withdraw from the research, please contact Matthew Lee (m.j.lee@sheffield.ac.uk). If you choose to withdraw, we will not be able to remove your data from any anonymised analysis that has completed. When you agree to take part we will ask you if you would like to rate outcomes related to ileus (bowel recovery after surgery) or bowel obstruction (blocked intestines), or both sets.

5. What will happen to me if I take part? What do I have to do?

If you take part, we will ask you to complete three survey rounds. You will receive an email when the window to complete each survey opens, and up to two reminders during the study to ensure the survey is completed.

The first survey will ask you to tell us if you are a member of the public, a health-care professional, a non-clinical researcher, or another stakeholder. This is to help us during the analysis. In each survey round, you will be asked to rate a list of outcomes related to the condition. Items will be rated from 1 (not important to measure) to 9 (essential to measure). Because of the methods we are using, we need you to rate every item on both lists. This will be a total of around 80 items for each of the two surveys (ileus and bowel obstruction) in the first round and this will take 15 minutes each to complete. We will ask you to repeat this in round two and round three, but we remove items after each round, so the time taken for each round should be shorter.

6. What are the possible disadvantages and risks of taking part?

We do not anticipate any disadvantages from taking part in this set of web-based surveys.

7. What are the possible benefits of taking part?

Whilst there are no immediate benefits for those people participating in the project, it is hoped that this work will help us design better research in the future to help improve outcomes in these conditions.

8. Will my taking part in this project be kept confidential?

All the information that we collect about you during the course of the research will be kept strictly confidential and will only be accessible to members of the research team. You will not be able to be identified in any reports or publications.

9. What is the legal basis for processing my personal data?

In order to participate, we will need to know your name, email address (for contact related to the study), and to know what your role is in relation to the research (e.g. member of public, health-care professional, non-clinical researcher, other stakeholder).

According to data protection legislation, we are required to inform you that the legal basis we are applying in order to process your personal data is that 'processing is necessary for the performance of a task carried out in the public interest' (Article 6(1)(e)). Further information can be found in the University's Privacy Notice https://www.sheffield.ac.uk/govern/data-protection/privacy/general.

10. What will happen to the data collected, and the results of the research project?

One researcher (based at the University of Sheffield) will have access to your email address which is stored on our secure REDCap database at the University of Sheffield. This researcher will co-ordinate emails about the survey using this email address from their own University email address.

Data from each survey round will be anonymised before download, and analysed to identify which outcomes should be kept, and which should be removed.

We plan to share the findings of the study with the public and research community through publication in scientific journals and presentations at research meetings. We will retain your data until six months after publication of the final report, so that we can share this with you.

11. Who is organising and funding the research?

This study is not funded. It is jointly organised by researchers from the University of Sheffield, University of Leeds, and Cambridge University Hospitals.

12. Who is the Data Controller?

The University of Sheffield will act as the Data Controller for this study. This means that the University is responsible for looking after your information and using it properly.

13. Who has ethically reviewed the project?

This project has been ethically approved via the University of Sheffield's Ethics Review Procedure, as administered by the Medical School, reference 029907

14. What if something goes wrong and I wish to complain about the research?

We do not anticipate any problems arising from the study. However, if you have any concerns, please contact Matthew Lee (m.j.lee@sheffield.ac.uk) in the first instance.

If you feel your concerns has not been handled to their satisfaction, this can be passed to the Head of Department (details available on request), who will then escalate the complaint through the appropriate channels. If the complaint relates to how your personal data has been handled, information about how to raise a complaint can be found in the University's Privacy Notice: https://www.sheffield.ac.uk/govern/data-protection/privacy/general.

15. Contact for further information

Should you require further information, please contact Matthew Lee (m.j.lee@sheffield.ac.uk / @wannabehawkeye) or Stephen Chapman (S.Chapman@leeds.ac.uk)

A-5.3.3. Consensus meeting participant information sheet

Participant information: Development of a core outcome set for gastrointestinal recovery

Research team:

Matthew Lee, Academic Clinical Lecturer in Surgery, University of Sheffield
Steven Chapman, NIHR Doctoral Research Fellow, University of Leeds
Sue Blackwell, Lay representative
Miss Nicola Fearnhead, Consultant Colorectal Surgeon, Cambridge University Hospitals

Contact: Matthew Lee: m.j.lee@sheffield.ac.uk

1. Invitation paragraph

You are being invited to take part in a research project. Before you decide whether or not to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

2. What is the project's purpose?

Gastrointestinal recovery is something that is often measured in research studies. It describes the recovery of bowel function after surgery or after an episode of small bowel obstruction (often called a blockage). At the moment, researchers measure this in many different ways, which makes it difficult to compare studies or to test new treatments. We hope to develop a "core outcome set", which aims to standardise how researchers measure this in the future so that comparisons between studies becomes easier, and improve the value of research.

We are looking at these two conditions at the same time as we think there are some common areas between them, and it is efficient to consider them together.

The first step in developing this set of measures is look at published studies to see what outcomes have been reported, and to create a long list of potential items. We have already completed this.

The second step is to show this list to people including members of the public, people with experience of these conditions, and healthcare professionals. This helps us to see if we have missed anything important that should be routinely measured.

The third step is to undertake serial votes on the long list. This helps us to reduce the items from a long list, down to around 10-15 outcomes that really matter to researchers and patients, and can be easily reported across future studies.

The fourth part of the study is a consensus meeting between stakeholders to agree on the final core outcome sets.

3. Why have I been chosen?

You are seeing this information because you have clicked on a link advertising the project in a tweet, or in an email from a charity/society who want to help promote this project. You might be a member of the public who has experienced a blocked bowel or ileus after surgery, or perhaps one of your family members has. You may be a healthcare professional working with people who have these problems, or a researcher with an interest in the field. You may have contacted the research team to participate after participating in a previous round of this study.

4. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form, and you can still withdraw at any time without any negative consequences. You do not have to give a reason. If you wish to withdraw from the research, please contact Matthew Lee (m.j.lee@sheffield.ac.uk).

5. What will happen to me if I take part? What do I have to do?

You will be invited to attend an online video call. This will involve up to 30 people including members of the public, healthcare professionals, researchers and other stakeholders.

In this meeting you will be presented with the outcomes that were voted on in stage three. You may be asked as a group to vote on removal of additional items from the set to ensure they are practically sized. We will encourage discussion or comment on outcomes, and these will be recorded in writing. We anticipate this process will take 1.5-3 hours.

6. What are the possible disadvantages and risks of taking part?

We will ask you to tell us whether you agree with the importance of items chosen for inclusion in the final list. You do not have to share your personal experience unless you wish to. There are no other disadvantages identified.

7. What are the possible benefits of taking part?

Whilst there are no immediate benefits for those people participating in the project, it is hoped that this work will help us design better research in the future to help improve outcomes in these conditions.

8. Will my taking part in this project be kept confidential?

All the information that we collect about you during the course of the research will be kept strictly confidential and will only be accessible to members of the research team. You will not be able to be identified in any reports or publications.

9. What is the legal basis for processing my personal data?

In order to participate, we will need to know your name, email address (for contact related to the study), and to know what your role is in relation to the research (e.g. member of public, health-care professional, non-clinical researcher, other stakeholder).

According to data protection legislation, we are required to inform you that the legal basis we are applying in order to process your personal data is that 'processing is necessary for the performance of a task carried out in the public interest' (Article 6(1)(e)). Further information can be found in the University's Privacy Notice https://www.sheffield.ac.uk/govern/data-protection/privacy/general.

10. What will happen to the data collected, and the results of the research project?

One researcher (based at the University of Sheffield) will have access to your email address which is stored on our secure REDCap database at the University of Sheffield. This researcher will co-ordinate emails about the consensus meeting using this email address from their own University email address.

Data on voting and free text comments will be aggregated and anonymised. We may link a quote to the type of participant (e.g. member of the public, healthcare professional) but we will not identify them.

We plan to share the findings of the study with the public and research community through publication in scientific journals and presentations at research meetings. We will retain your data until six months after publication of the final report, so that we can share this with you.

11. Who is organising and funding the research?

This study is not funded. It is jointly organised by researchers from the University of Sheffield, University of Leeds, and Cambridge University Hospitals.

12. Who is the Data Controller?

The University of Sheffield will act as the Data Controller for this study. This means that the University is responsible for looking after your information and using it properly.

13. Who has ethically reviewed the project?

This project has been ethically approved via the University of Sheffield's Ethics Review Procedure, as administered by the Medical School, reference 029907

14. What if something goes wrong and I wish to complain about the research?

We do not anticipate any problems arising from the study. However, if you have any concerns, please contact Matthew Lee (m.j.lee@sheffield.ac.uk) in the first instance.

A-5.3.4. Stakeholder consultation consent form

The University Of Sheffield. | Sheffield Teaching Hospitals NHS Foundation Trust | UNIVERSITY OF LEEDS | Cambridge University Hospitals NHS Foundation Trust

Consent Form

Study Title: Development of core outcome set in gastrointestinal recovery (nominal group)

We are asking if you would like to take part in a research project to help us choose the most important outcomes when undertaking research into how the gastrointestinal tract recovers after surgery or other problems.

Before you consent to participating in the study we ask that you read the participant information sheet and mark each box below with your initials if you agree. If you have any questions or queries before signing the consent form please speak to the principal investigator Matthew Lee (m.j.lee@sheffield.ac.uk).

	Please initial each box to show agreement
1. I confirm that I have read the information sheet and fully understand what is expected of me within this study	
2. I confirm that I have had the opportunity to ask any questions and to have them answered.	
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
4. I understand that once I have completed this exercise, my suggestions or votes cannot be removed	
5. I understand that my email address is required to participate in the study, and this will only be used by the research team to conduct tasks related to the study including invitation to the study, to be informed about the final meeting, and the results of the study.	
6. I understand that none of my personal data will be shared in the reports of this study.	
7. I consent to the study team retaining my email address until six months after the study report has been published	
8. I consent to take part in this study.	

Your name:_____
Your email address:_____
Date of form completion:_____

A-5.3.5. Delphi prioritisation process consent form

The University Of Sheffield. | Sheffield Teaching Hospitals NHS Foundation Trust | UNIVERSITY OF LEEDS | Cambridge University Hospitals NHS Foundation Trust

Consent Form

Study Title: Development of core outcome set in gastrointestinal recovery (Delphi)

We are asking if you would like to take part in a research project to help us choose the most important outcomes when undertaking research into how the gastrointestinal tract recovers after surgery or other problems.

Before you consent to participating in the study, we ask that you read the participant information sheet and mark each box below with your initials if you agree. If you have any questions or queries before signing the consent form please speak to the principal investigator Matthew Lee (m.j.lee@sheffield.ac.uk).

	Please initial each box to show agreement
1. I confirm that I have read the information sheet and fully understand what is expected of me within this study	
2. I confirm that I have had the opportunity to ask any questions and to have them answered.	
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
4. I understand that once I have completed ratings in a round, this cannot be removed, although I am free to withdraw from future rounds.	
5. I understand that my email address is required to participate in the study, and this will only be used by the research team to conduct tasks related to the study including invitation to the study, to be informed about the final meeting, and the results of the study.	
6. I understand that none of my personal data will be shared in the reports of this study.	
7. I consent to the study team retaining my email address until six months after the study report has been published	
8. I would like to rate outcomes related to ileus (bowel recovery after surgery)	
9. I would like to rate outcomes related to small bowel obstruction (blocked intestines.	
10. I consent to take part in this study.	

Your name:_____

Your email address:_____ Date of form completion _____

Delphi Consent v2.0 22/09/2019

A-5.3.6. Consensus meeting participant information sheet

The University Of Sheffield. | Sheffield Teaching Hospitals NHS Foundation Trust | UNIVERSITY OF LEEDS | Cambridge University Hospitals NHS Foundation Trust

Consent Form

Study Title: Development of core outcome set in gastrointestinal recovery (Consensus)

We are asking if you would like to take part in a research project to help us choose the most important outcomes when undertaking research into how the gastrointestinal tract recovers after surgery or other problems.

Before you consent to participating in the study, we ask that you read the participant information sheet and mark each box below with your initials if you agree. If you have any questions or queries before signing the consent form please speak to the principal investigator Matthew Lee (m.j.lee@sheffield.ac.uk).

	Please initial each box to show agreement
1. I confirm that I have read the information sheet and fully understand what is expected of me within this study	
2. I confirm that I have had the opportunity to ask any questions and to have them answered.	
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
4. I understand that once I have participated in the meeting, my responses cannot be removed from reports	
5. I understand that my email address is required to participate in the study, and this will only be used by the research team to conduct tasks related to the study including invitation to the study, to be informed about the final meeting, and the results of the study.	
6. I understand that none of my personal data will be shared in the reports of this study.	
7. I consent to the study team retaining my email address until six months after the study report has been published	
8. I consent to take part in this study.	

Your name:_____
Your email address:_____
Date of form completion:_____

Consensus Consent v2.0 22/09/2019

A-5.4. Plain English summaries for longlisted outcomes

Outcome description	Plain English summary
Time to first fluid intake	How long it takes after the operation to have a drink
Time to tolerate fluid intake	How long it takes after the operation to have a drink and not feel sick
Time to intake of > 1000 ml fluid per day	How long it takes after the operation to be able to drink more than 1 litre in a day
Time to first soft food	How long it takes after the operation to eat soft food
Time to tolerate low-residue diet	How long it takes after the operation to eat low fibre food and not feel sick
Time to first solid intake	How long it takes after the operation to eat solid food
Time to tolerate solid intake	How long it takes after the operation to eat solid food and not feel sick
Time to tolerate normal diet	How long it takes after the operation to eat a normal diet and not feel sick
Amount of food intake per meal	How much you are able to eat at mealtimes
Incidence of nausea	If you feel sick after the operation
Duration of nausea	How long you feel sick for after the operation
Incidence of vomiting	If you are being sick after the operation
Duration of vomiting	How long you are being sick for after the operation
Incidence of abdominal pain	If you have stomach pain after the operation
Severity of abdominal pain	Severity of stomach pain after the operation
Incidence of abdominal swelling/distension	If your stomach is swollen after the operation
Severity of abdominal swelling/distension	Severity of stomach swelling after the operation
Need for laxative medication	Whether you need laxative medication to help you poo
Need for antiemetic medication	Whether you need medication to stop you feeling/being sick
Need for parenteral nutrition	If you need liquid food via a drip/feeding line after the operation
Duration of parenteral nutrition	How long you need to be given liquid food via a drip/feeding line
Time to first passage of flatus	How long it takes after your operation to pass wind
Time to second passage of flatus	How long it takes after your operation to pass wind for the second time

Cumulative frequency of flatus	How often you pass wind after the operation
Time to first passage of stool	How long it takes after your operation to have a poo
Frequency of stool	How often after your operation you need to go for a poo (whilst still in hospital)
Consistency of stool	How hard or soft your poo is after the operation
Time to return of appetite	How long it takes after the operation to feel like you want to eat
Extent of hunger	How hungry you feel after the operation
Incidence of satiety	If you feel full after eating
Extent of satiety	How full you feel after eating
Incidence of belching	If you are belching after the operation
Duration of belching	How long after the operation that you are belching
Incidence of hiccups	If you have hiccups after the operation
Gastrointestinal quality of life	How your bowel function is impacting on your quality of life (whilst in hospital)
Time to first stoma output	If you have a stoma, how long after your operation it takes for it to work
Incidence of postoperative ileus	If your bowel "goes to sleep" after your operation
Incidence of prolonged postoperative ileus	If your bowel "goes to sleep" for longer than expected after your operation
Duration of postoperative ileus	How long your bowel is "asleep" after your operation
A measure of gastrointestinal recovery used a validated tool	How long your bowel takes to recover its function
Need for nasogastric placement	If you need a tube inserted up your nose to help your bowel recover
Duration of nasogastric tube placement	How long you need a tube inserted up your nose to help your bowel to recover
Volume of nasogastric tube aspirate	If you have a tube inserted up your nose, how much fluid is coming out of it
Incidence of nasogastric tube aspirate > 500 ml per day	If you have a tube up your nose, is it draining more than 500mls of fluid a day
Vomiting after nasogastric tube removal	If you are sick after having the tube up your nose removed
Time to first postoperative abdominal peristalsis	How long it takes after your operation for your bowel to physically move/churn
Time to detect bowel sounds	How long it takes after your operation to hear noises from your bowel
Frequency of bowel sounds	How often your bowel rumbles/makes noises
Incidence of readmission due to postoperative ileus	If you have to return to hospital due to your bowel still not working properly
Readiness for discharge based on gastrointestinal function	If you are ready to go home based on how well your bowel is working

Incidence of morbidity due to postoperative ileus	If you become ill after your operation as a result of your bowels not working
Nutritional status	How well-nourished your body is
Gastrointestinal motility	How much your bowel physically moves/churns
Gastric emptying	How quickly food/fluids empty into the bowel from the stomach
Quantification of bowel gas	How much gas is in your bowel
Gastrointestinal transit	How quickly food/fluids move from the start of the gut to the end
Anxiety	How nervous you feel after the operation
Vomiting with nasogastric tube in situ	If you are being sick whilst the tube up your nose is in place
Postoperative inflammatory response	How inflamed your bowel and other tissues are after the operation
Radiological intestinal dilatation	How swollen your intestines look on a scan
Overall fluid balance	How hydrated (or dehydrated) you are after the operation
Mobility	How much you can move around after the operation
Complications: Urinary	Problems with the bladder after the operation
Complications: Respiratory	Problems with the lungs after the operation
Complications: Pneumonia	A chest infection after the operation
Complications: Organ injury or failure	Organ failure after the operation
Complications: Thrombosis or embolism	Blood clots in the legs or lungs after the operation
Complications: Renal	Problems with the kidneys after the operation
Complications: Sepsis	Severe infection (septicaemia) after the operation
Complications: Cardiac	Problems with the heart after the operation
Complications: Abdominal infection	Infection inside the belly after the operation
Complications: Peritonitis	Inflammation inside the belly after the operation
Complications: Enterotomy	A hole in the bowel made accidentally during the operation
Complications: Anastomotic leak	A leak in the join between two pieces of bowel
Complications: Wound infection	An infection of the wound after the operation

A-5.5. Delphi prioritisation process participant feedback exemplar

Gastrointestinal Recovery Core Outcome Set

Delphi Survey Round 2 Results

Section 1: Progress so Far

After Round 2 of the Delphi survey, the following outcomes gained enough support to be carried to the next stage of the study. They will be discussed in detail during a consensus meeting later in the year.

Need for parenteral nutrition
Severity of abdominal pain
Complications: Enterotomy
Incidence of readmission due to postoperative ileus
A measure of gastrointestinal recovery using a validated tool
Time to first stoma output
Need for nasogastric tube placement
Incidence of postoperative ileus
Duration of postoperative ileus
Incidence of prolonged postoperative ileus
Incidence of morbidity due to postoperative ileus
Complications: Anastomotic leak
Readiness for discharge based on gastrointestinal function
Nutritional status
Volume of nasogastric tube aspirate
Duration of vomiting
Complications: Abdominal infection
Incidence of nausea
Complications: Sepsis
Need for intensive care unit admission
Complications: Peritonitis
Time without adequate nutritional intake

Section 2: Your Personal Report

The following outcomes have not yet received enough support to be carried to the next stage. They will be scored again in the third (final) round of the Delphi survey, which will inform the final decision.

Your score for the previous round, along with average scores for other stakeholders, are shown in the table. Please take a look at this table before completing the final survey.

Scores are expressed out of 9 (1=Not important, 9=Important)	Your Score	Patient Average	Nurse & Dietitian Average	Doctor Average
Frequency of bowel sounds	6	6	5.5	3
Complications: Renal	6	8	6	6
Time to tolerate fluid intake	6	7	7	7
Gastric emptying	6	6	7	5
Mobility	7	7	7	7
Incidence of abdominal pain	6	8	6.5	6
Incidence of vomiting	5	7	7	7
Radiological intestinal dilatation	6	7	7	5.5
Anxiety	5	6	6	5
Need for laxative medication	5	6	7	5
Incidence of nasogastric tube aspirate > 500 ml per day	6	7	7	7
Quantification of bowel gas	6	6	5	3
Time to first postoperative abdominal peristalsis	6	7	6.5	5
Incidence of satiety	6	5	6	5
Complications: Urinary	8	7	5	5
Complications: Pneumonia	7	8	6.5	7
Vomiting after nasogastric tube removal	5	7	7	7
Time to first solid intake	6	6	7	7
Time to return of appetite	4	6	7	6
Overall fluid balance	8	7	7	7
Postoperative inflammatory response	5	8	6	6
Duration of parenteral nutrition	7	7	7.5	8
Time to first passage of flatus	7	7	7	7
Extent of satiety	5	6	6	5
Duration of belching	5	5	6.5	5
Amount of food intake per meal	5	5	6	5
Time to second passage of flatus	6	6	7	5
Cumulative frequency of flatus	3	6	6	5
Complications: Thrombosis or embolism	8	8	6	6
Complications: Organ injury or failure	8	9	7	8
Time to detect bowel sounds	6	6	6	4
Time to tolerate normal diet	5	7	7	7
Need for antiemetic medication	6	7	6.5	6

Complications: Cardiac	7	8	6	6
Duration of nasogastric tube placement	6	8	7.5	7
Consistency of stool	5	6	6	4
Extent of hunger	6	5	7	5
Time to first soft food	6	7	7	6
Frequency of stool	6	7	7	5
Vomiting with nasogastric tube in situ	6	8	8	7
Incidence of abdominal swelling/distension	7	6	7	6
Duration of nausea	5	7	7	6
Complications: Respiratory	6	8	6.5	7
Complications: Wound infection	8	8	6	6
Time to first passage of stool	6	8	7	7
Incidence of hiccups	5	5	7	6
Severity of abdominal swelling/distension	8	7	7	6
Gastrointestinal-related quality of life	8	7	7	7
Time to tolerate solid intake	6	7	7	7
Time to tolerate low-residue diet	6	7	7	6
Incidence of belching	5	5	6.5	5
Gastrointestinal motility	6	7	6.5	5
Time to intake of > 1000 ml fluids per day	5	7	6	6
Gastrointestinal transit	7	7	7	6
Time to first fluid intake	5	7	7	7
Length of hospital stay	7	7	7	7
Mental well-being	6	7	7.5	6
Weight loss	6	6	6.5	6
Need for readmission (for any reason)	8	8	8	7
Incidence of hypokalaemia	6	6	7	6
Cost of admission	6	5	6	7

A-5.6. Consensus meeting agenda

Gastrointestinal Recovery Core Outcome Set

GI COS: Post-operative ileus Agenda

Consensus Event: 6th March, 9am-12pm (London GMT)

Time *All times are GMT*	**Description**
08:45-09:00	Registration opens – meet the investigators
09:00-09:10	Introduction and house rules
09:10-09:15	Summary of the GI COS study
09:15-09:45	Session 1: Outcome Discussion
09:45-10:30	Session 2: Outcome Voting
10:30-10:45	Break
10:45-11:55	Session 3: Presentation Voting
11:55-12:00	Final remarks and finish

A-5.7. Outcome suggestions during Round 1 of the Delphi prioritisation process

Verbatim proposal	Include	Reason not included	Refined outcome for presentation
“Length of stay”	Yes	-	Length of hospital stay
“ICU/HDU stay”	Yes	-	Need for intensive care unit admission
“Mental welfare”	Yes	-	Mental well-being
“Problems in gaining weight again”	Yes	-	Weight loss
“Readmission following complications”	Yes	-	Need for readmission
“Potassium level”	Yes	-	Incidence of hypokalaemia
“Number of days without adequate nutritional intake”	Yes	-	Time without adequate nutritional intake
“Healthcare costs”	Yes	-	Cost of admission
“General mobility”	No	NU - (Mobility)	-
“Any issues with wound fluid drainage”	No	NU - (Complications: wound infection)	-
“Blood pressure (often low due to low fluid intake)”	No	NU - (Fluid balance)	-
“Malnutrition”	No	NU - (Nutritional status)	-
“Additional complications”	No	NU - (Incidence of morbidity due to ileus)	-
“PTSD related to surgery”	No	NU - (Mental well-being)	-
“Time taken able to eat range of foods”	No	NU - (Time to tolerate normal diet)	
“Time taken for pain to ease”	No	NU - (Severity of abdominal pain)	-
“Post-operative length of stay”	No	NU - (Length of hospital stay)	-
“How long after the operation it takes to become mobile”	No	NU - (Mobility)	-
“How long after the operation it takes for pain to be controlled”	No	NU - (Severity of abdominal pain)	-
“BMI and MUST scores prior to surgery”	No	NU - (Nutritional status)	-
“Frequency of liquid stools after bowel starts working again”	No	NU - (Consistency of stool)	-
“Incidence of bile acid malabsorption”	No	NU - (Nutritional status)	-
“How to deal with trauma of surgery”	No	NU - (Mental well-being)	-
“Control of pain post-operative”	No	NU - (Severity of abdominal pain)	-
“Number of days it takes for patient’s appetite to return”	No	NU - (Time to return of appetite)	-
“Time to meet x % of estimated nutritional requirements orally”	No	NU - (Time without adequate nutritional intake)	-

NU: Not considered sufficiently unique by the Steering Committee – text in parentheses indicate similar existing outcome

Published Material

The following peer-reviewed manuscripts have been generated from this work to date:

1. **SJ Chapman**, MJ Lee, S Blackwell, R Arnott, RPG ten Broek, CP Delaney, NN Dudi-Venkata, R Fish, D Hind, DG Jayne, K Mellor, A Mishra, G O'Grady, T Sammour, G Thorpe, CI Wells, AM Wolthuis, NS Fearnhead On behalf of the Tripartite Gastrointestinal Recovery Postoperative Ileus Group. Core outcome set for clinical studies of postoperative ileus after intestinal surgery. *Br J Surg* 2022; 109:493-496,

2. **SJ Chapman**. M Naylor. CJ Czoski Murray. D Tolan. DD Stocken. DG Jayne. Non-invasive, vagus nerve stimulation to reduce ileus after colorectal surgery: Protocol for a feasibility trial with nested mechanistic studies. *BMJ Open* 2021;11:e046313