FULL TITLE
A randomised trial of gum chewing vs. no gum to reduce post-operative ileus in patients undergoing large bowel resection

SHORT TITLE
A randomised trial of gum chewing to reduce post-operative ileus

SPONSOR
University Hospitals Bristol NHS Foundation Trust
Research & Development Department
Level 3, UH Bristol Education Centre
Upper Maudlin Street
Bristol, BS2 8AR
Tel: 0117 3420233

CHIEF INVESTIGATOR
Dr. Charlotte Atkinson
Lecturer in Nutrition
Department of Oral and Dental Science
Bristol Dental School
Lower Maudlin Street
Bristol BS1 2LY
Tel: 0117 3423264
Emergency contact number: 07806 635 619

CO-INVESTIGATORS
(in alphabetical order)

Dr. Will Hollingworth
Senior Lecturer in Health Economics
Department of Social Medicine
University of Bristol
Canynge Hall
Whiteladies Road
Bristol BS8 2PR
Tel: 0117 9287355

Dr. Sam Leary
Lecturer in Statistics
Department of Oral and Dental Science
Bristol Dental School
Lower Maudlin Street
Bristol BS1 2LY
Tel: 0117 3423264

Dr. Stephen Lewis
Consultant Gastroenterologist
Department of Gastroenterology
Plymouth Hospitals NHS Trust
PL6 8DH
Tel: 01752 517649

Mr. Rob Longman
Consultant Surgeon
Colorectal Unit
United Hospitals Bristol NHS Foundation Trust
Tel: 0117 9284528

Professor Andy Ness
Professor of Epidemiology
Department of Oral and Dental Science
Bristol Dental School
Lower Maudlin Street
Bristol BS1 2LY
Tel: 0117 3422181

Professor Steve Thomas
Consultant Surgeon and Senior Lecturer
Department of Maxillofacial Surgery
University of Bristol
0117 3424500

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1. Background

The hypothesis to be tested is that chewing sugar free gum from the first post-operative morning following intestinal resection will reduce the length of ileus and its associated morbidities.

Post-operative ileus is a universal complication of abdominal surgery, with unfavourable consequences for both patients and healthcare systems. Ileus results in abdominal distension, pain, nausea, vomiting, and an inability to pass stools or tolerate a solid diet (1). It can substantially delay patient recovery following abdominal surgery, which can lead to an increase in length of hospital stay and an associated increase in healthcare costs (1, 2). The extent of ileus following abdominal surgery is influenced by a number of factors including the degree of surgical trauma and bowel manipulation (3). The effect of surgical trauma on ileus is mediated through a stress response that results in a state of high sympathetic activity; a known extrinsic inhibitor of intestinal motility (4). In addition, inflammatory mediators such as nitric oxide, vasoactive intestinal peptide, substance P, and calcitonin gene-related peptide are released as part of the stress response, and these also appear to contribute to post-operative ileus (3, 5, 6).

The influence of peri-operative interventions on the duration of ileus has been extensively studied (7-9). Certain anaesthetic drugs and opiates tend to inhibit bowel motility, with one study demonstrating a dose-response relationship between amount of morphine and time to return of bowel function (10, 11). Conversely, local anaesthetic-containing epidurals reduce the duration of ileus compared to systemic opiate therapy (12). There is some evidence that other therapies such as early postoperative mobilisation, early feeding, sham feeding, use of nasogastric tubes, or prokinetics can reduce postoperative ileus (13-17), but few definitive studies have been conducted.

In a systematic review and meta-analysis, we showed that early enteral feeding after gastrointestinal surgery was associated with improved clinical outcomes (18), but the risk of vomiting was increased among patients fed early. Chewing gum is a type of sham feeding that promotes intestinal motility, via cephalic-vagal stimulation. In normal volunteers, chewing gum is as effective as food in stimulating cephalic-phase gastric secretion, and has therefore been used as a modified form of sham feeding to investigate physiological responses such as gastric secretion (19, 20). A handful of small randomised controlled trials have investigated the effects of chewing sugar-free gum after abdominal surgery, with mixed results. In a recent systematic review of five prospective randomised controlled trials (21), patients who began chewing gum on the first postoperative day had earlier return of bowel function than those receiving standard postoperative management only; patients who chewed gum passed flatus 20.8 hours earlier (range 7.2-34.7 hours), had a bowel movement 33.3 hours earlier (range 16.0-64.8 hours), and had a hospital stay that was 2.4 days shorter (range 1.0-2.5 days) (21). Patients chewed gum three times a day until the first passage of flatus or bowel movement and, overall, gum chewing was well tolerated and complication rates were low. However, the trials were small. The largest consisted of 22 patients assigned to chewing gum and 21 to no gum (22), and the total number of randomised patients in all trials was 158 (21). Furthermore, the studies have been conducted in several countries with markedly different healthcare systems which could have affected the findings. Few studies have assessed patient reported outcomes, although one noted that most patients reported that chewing gum helped to keep their mouth moist and gave them a sense of well-being (23). An adequately powered, methodologically rigorous trial of gum chewing is required to confirm the findings to date, and to assess whether reported benefits result in differences in other clinically important outcomes such as vomiting and infection. We will also assess costs and post-hospital outcomes which, to our knowledge, have not previously been studied in detail.

If, as we hypothesise, chewing gum reduces ileus and its associated morbidities, as well as reducing length of hospital stay, its integration within an 'Enhanced Recovery Programme' has the potential to substantially improve patient health and well-being and to reduce costs of care. Since sugar-free

chewing gum is cheap and readily available, and is a simple intervention that can be administered from the first post-operative morning onwards, it will be relatively easy to implement within the NHS. We have 84% power to detect a difference in length of hospital stay of 1.5 days. Such a reduction would enable patients to return to their home environment sooner and lead to considerable cost savings to the NHS.

References

1. Senagore, A. J. Pathogenesis and clinical and economic consequences of postoperative ileus. Am J Health Syst Pharm, *64:* S3-7, 2007.
2. Baig, M. K., and Wexner, S. D. Postoperative ileus: a review. Dis Colon Rectum, *47:* 516-26, 2004.
3. Turler, A., Moore, B. A., Pezzone, M. A., Overhaus, M., Kalff, J. C., and Bauer, A. J. Colonic postoperative inflammatory ileus in the rat. Ann Surg, *236:* 56-66, 2002.
4. Sagrada, A., Fargeas, M. J., and Bueno, L. Involvement of alpha-1 and alpha-2 adrenoceptors in the postlaparotomy intestinal motor disturbances in the rat. Gut, *28:* 955-9, 1987.
5. Zittel, T. T., Lloyd, K. C., Rothenhofer, I., Wong, H., Walsh, J. H., and Raybould, H. E. Calcitonin gene-related peptide and spinal afferents partly mediate postoperative colonic ileus in the rat. Surgery, *123:* 518-27, 1998.
6. Espat, N. J., Cheng, G., Kelley, M. C., Vogel, S. B., Sninsky, C. A., and Hocking, M. P. Vasoactive intestinal peptide and substance P receptor antagonists improve postoperative ileus. J Surg Res, *58:* 719-23, 1995.
7. Scott, A. M., Starling, J. R., Ruscher, A. E., DeLessio, S. T., and Harms, B. A. Thoracic versus lumbar epidural anesthesia's effect on pain control and ileus resolution after restorative proctocolectomy. Surgery, *120:* 688-95; discussion 695-7, 1996.
8. Ng, W. Q., and Neill, J. Evidence for early oral feeding of patients after elective open colorectal surgery: a literature review. J Clin Nurs, *15:* 696-709, 2006.
9. Wind, J., Polle, S. W., Fung Kon Jin, P. H., Dejong, C. H., von Meyenfeldt, M. F., Ubbink, D. T., Gouma, D. J., and Bemelman, W. A. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg, *93:* 800-9, 2006.
10. Ogilvy, A. J., and Smith, G. The gastrointestinal tract after anaesthesia. Eur J Anaesthesiol Suppl, *10:* 35-42, 1995.
11. Cali, R. L., Meade, P. G., Swanson, M. S., and Freeman, C. Effect of Morphine and incision length on bowel function after colectomy. Dis Colon Rectum, *43:* 163-8, 2000.
12. Jorgensen, H., Wetterslev, J., Moiniche, S., and Dahl, J. B. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev*:* CD001893, 2000.
13. Bungard, T. J., and Kale-Pradhan, P. B. Prokinetic agents for the treatment of postoperative ileus in adults: a review of the literature. Pharmacotherapy, *19:* 416-23, 1999.
14. Hartsell, P. A., Frazee, R. C., Harrison, J. B., and Smith, R. W. Early postoperative feeding after elective colorectal surgery. Arch Surg, *132:* 518-20; discussion 520-1, 1997.
15. Roberts, D. J., Banh, H. L., and Hall, R. I. Use of novel prokinetic agents to facilitate return of gastrointestinal motility in adult critically ill patients. Curr Opin Crit Care, *12:* 295-302, 2006.
16. Steed, H. L., Capstick, V., Flood, C., Schepansky, A., Schulz, J., and Mayes, D. C. A randomized controlled trial of early versus "traditional" postoperative oral intake after major abdominal gynecologic surgery. Am J Obstet Gynecol, *186:* 861-5, 2002.
17. Nelson, R., Edwards, S., and Tse, B. Prophylactic nasogastric decompression after abdominal surgery. Cochrane Database Syst Rev*:* CD004929, 2007.
18. Lewis, S. J., Egger, M., Sylvester, P. A., and Thomas, S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. Bmj, *323:* 773-6, 2001.
19. Helman, C. A. Chewing gum is as effective as food in stimulating cephalic phase gastric secretion. Am J Gastroenterol, *83:* 640-2, 1988.

20. Wojdemann, M., Traberg, P., Stadil, F., Sternby, B., Larsen, S., Hilsted, L., and Olsen, O. Effect of sham feeding and acute suppression of acid secretion on human gastric lipase secretion. Am J Gastroenterol, *93:* 244-8, 1998.
21. Chan, M. K., and Law, W. L. Use of Chewing Gum in Reducing Postoperative Ileus After Elective Colorectal Resection: A Systematic Review. Dis Colon Rectum, 2007.
22. Matros, E., Rocha, F., Zinner, M., Wang, J., Ashley, S., Breen, E., Soybel, D., Shoji, B., Burgess, A., Bleday, R., Kuntz, R., and Whang, E. Does gum chewing ameliorate postoperative ileus? Results of a prospective, randomized, placebo-controlled trial. J Am Coll Surg, *202:* 773-8, 2006.
23. Quah, H. M., Samad, A., Neathey, A. J., Hay, D. J., and Maw, A. Does gum chewing reduce postoperative ileus following open colectomy for left-sided colon and rectal cancer? A prospective randomized controlled trial. Colorectal Dis, *8:* 64-70, 2006.

2. Aims and Objectives

The study is a non commercial trial, and the primary objective is to determine whether chewing sugar-free gum following surgery to the large bowel reduces the length of post operative ileus and consequently length of hospital stay. Secondary objectives are to determine the effects of post-operative chewing gum on a number of other specific outcomes including clinical factors (e.g., vomiting, infections, and anastomotic dehiscence), quality of life, and cost effectiveness. We will also assess factors such as time to first flatus and first bowel discharge, in addition to patient acceptability and compliance.

3. Study Design

We will conduct a randomised trial of gum chewing to reduce post-operative ileus. We have designed our study to provide adequate statistical power to look at the effects of chewing gum vs. no gum on outcomes such as length of hospital stay and time to first flatus and bowel discharge. The results of this study could ultimately impact on patient care; if successful, chewing gum may be a safe and effective method for reducing post-operative ileus.

Patients will be randomised to receive gum or no gum. Randomisation will minimise any potential differences (known or unknown) between groups by equally distributing participants with particular characteristics among both trial arms.

We will use commercially available sugar-free chewing gum. Patients assigned to gum will be asked to chew a piece of gum for at least 10 minutes four times a day, at times equivalent to the drug dispensing rounds (approximately 6-7 am, 12 noon, 6 pm, and 10 pm). They will be asked to begin the gum-chewing protocol on the first post-operative morning, and will discontinue chewing gum after 5 days or until time of discharge if sooner. The control group will not be asked to chew gum. We have not included a placebo treatment because any type of chewing action, or introduction of foodstuffs, may have similar effects to that of the intervention itself.

In order to reduce the potential for bias, we will attempt to blind the surgical team to treatment arm by providing all study patients with identical trial packets that either do or do not contain gum. In addition, all data analysis will be conducted without knowledge of treatment assignment.

Study participants will be in the study for a total of three months (12 weeks), but administration of the intervention and data collection will not occur continuously during this time frame. Those assigned to chew gum will be asked to chew gum for five days or until time of discharge if sooner. The majority of data collection will occur between enrolment and day 5 post-operation. Quality of

life will also be measured at 6 and 12 weeks post-operation, and information on post-discharge clinical events, complications, treatment received for complications, post-discharge use of NHS and personal social services, when the patient returned to work or 'usual activities', and how much time their carer took off work or 'usual activities' will be collected at 6 and 12 weeks post-operation. Please see **Tables 1-4** for a detailed description of data to be collected as part of this study.

All patients, irrespective of treatment group, will receive usual care throughout the study. Non-standard care includes the administration of chewing gum to those randomised to chew gum.

The study would be discontinued if patients were having adverse effects or adverse events as a consequence of chewing the gum, because of recruitment failure or if new findings were made available which made this study unethical or superfluous.

3.1 Primary and Secondary Endpoints

The primary endpoint is length of hospital stay, calculated from date of operation to date of discharge. Secondary endpoints include clinical factors (e.g., vomiting, infections, and anastomotic dehiscence), quality of life, cost effectiveness, time to first flatus and first bowel movement, and patient acceptability and compliance.

3.2 General information

In a recent meta-analysis of the effects of chewing gum on postoperative recovery following colectomy (Purkayastha et al. Arch Surg. 2008; 143(8):788-793), no adverse events were associated with the use of chewing gum in any of the included studies. As such, we do not anticipate any adverse events associated with chewing gum in this study. Nonetheless, potential risks to patients could include: aspirating the gum; swallowing the gum (which may result in bowel obstruction); problems with dentures/dental damage; and allergy to mint. We will attempt to minimise these risks by: asking patients to be seated in an upright position when chewing gum (to avoid accidental aspiration/swallowing); not giving chewing gum to patients who are drowsy; by monitoring issues related to denture wear/tooth damage and asking patients to chew gum without their dentures if necessary or to chew gum gently and without clenching their teeth; and by including screening questions on allergies and providing an alternative flavour of gum for those with known, or suspected, allergy to mint. We will ask potential study participants to try the gum, as some individuals may never have chewed gum before or not for many years. It is important that the participants are happy chewing gum before consenting to be in the study. **We will not ask patients to try the gum if they are meeting with the study nurse on the day of their surgery as it may interfere with their pre-surgery care.**
It is possible that some study participants may find questions about their bowel habits embarrassing. In order to avoid embarrassment, we will collect data from individuals and not in groups, and study questionnaires on bowel habits will be self-completed rather than interviewer-administered. Furthermore, prior to consenting to participate in the study, patients will be made fully aware that such questions will be asked of them. We will also emphasise that the information collected will not be shared with anyone else, and that their data will be analysed along with everyone else's from the study (i.e., as a group, not individually) and that no information will be published in a way that they can be identified. Study participants will not be expected to answer any questions they do not wish to answer. Although small studies have suggested benefits of chewing gum on a number of outcomes associated with post-operative ileus, no large, definitive studies have been conducted. The findings of this study will also be applicable to other surgeries in which ileus is common, including urological surgeries. Thus, with little risk to study participants, this study will generate data that may ultimately be beneficial to a wide range of individuals.

3.3 Use within the trial

The intervention (chewing gum) will be administered by ward staff and patients will be asked for information on acceptability (gum chewing group only) and compliance (gum chewing and control groups). The intervention is non-invasive, and does not involve radioactive substances. It is intended only to provide benefit for a short period of time, i.e., until ileus has resolved. We envisage no further benefits of continuing to chew gum once bowel habits have returned to a somewhat normal pattern. Nonetheless, if found to be beneficial in terms of resolving post-operative ileus, we will endeavour to make this information available to all who may benefit from it.

4. Subjects

4.1 Subject selection

The source of subjects will be elective surgery lists for large bowel resection at selected hospitals in the UK. This group is appropriate for assessing the effects of gum chewing on post-operative ileus because almost all patients that undergo large bowel resections suffer from post-operative ileus. We aim to recruit 400 patients over a 3 year period.

4.2 Inclusion Criteria

1. Patients scheduled to have elective colorectal (large bowel) resection due to colorectal neoplasia (invasive cancer or benign dysplasia), DD, or UC
2. Men and women aged 18 years or older.

4.3 Exclusion Criteria

1. Patients with Crohn's disease
2. Patients aged less than 18 years
3. Patients having large bowel resection in emergency situations
4. Women who are pregnant or lactating

If a potential study participant is involved in a research study or has been involved in past research studies, the study nurse will ask for details of the research study. The clinical leads at each centre will determine whether or not including them in the present study could compromise patient safety or undermine the scientific basis of the study.

4.4 Subject recruitment

We will target recruitment efforts towards men and women scheduled to undergo elective large bowel resection due to colorectal neoplasia, UC, or DD. At some sites the colorectal consultant surgeons will briefly introduce the study to the patient at their clinic visit, provide them with a study pack (which will include an introductory letter, the Patient Information Sheet, and some chewing gum), and ask them if they are happy for our research nurse to call them in a couple of days to talk about the study. If they are happy for this to happen, the research nurse will call the patient and ask if they would be interested in participating. If they are interested in participating, the research nurse will send them the consent form, the baseline questionnaires, and a stamped addressed envelope for returning the completed consent and questionnaires. The patients' weight and height will be measured when they are admitted to hospital for surgery. At other sites patients will be approached about taking part in the study by the study nurse via out-patient clinics when they are listed for surgery or through pre-clerking clinics prior to surgery. Patients will be provided with a detailed information sheet about the study and will be asked to trial the chewing gum to check they are happy to chew gum if they are randomised to the chewing gum group. If willing to participate, they

will be asked to provide written informed consent. Once a patient has been enrolled in the study, they will be asked to complete the baseline questionnaires and they will have their weight and height, measured. Where appropriate, we will enlist the use of an interpreter to explain the study and to go over any written materials that are in English. If, in the opinion of the clinical lead, a patient is considered unsuitable for participation in the study, e.g. if they are incapable of providing adequate responses/information for the study due to some forms of mental illness or are unsuitable for other reasons, they will not be included in the study. Patients will not be paid for participating in this study.

4.5 Randomisation

Individual patients will be randomly allocated to one of two groups (approximately even numbers of patients will be allocated to each group) to receive usual post-operative care plus chewing gum, or usual post-operative care only. Randomisation will be stratified by hospital site and pathology of disease (i.e. colorectal neoplasia, UC, or DD). Patients will be randomly assigned to either group using Microsoft Access; within the patient's Access record, the researcher will simply click the randomisation button to generate the randomisation code for that patient. This method ensures that randomisation can occur at any time of day and on any day of the week. Patients will be notified of their assigned group on the first post-operative morning by the nursing staff on the ward.

4.6 Blinding and other measures taken to avoid bias

The primary outcome measure for this trial is length of hospital stay. This will be calculated from date of operation to date of discharge. We will also record date of admission and date medically fit for discharge (if different from date of discharge). Discharge plans (i.e., when the patient is medically fit for discharge) will be made by members of the surgical team, and this information will be recorded in the patients' notes. As the decision to discharge the patient is made by the surgical team it is important that they are blind as to which patients are chewing gum and which are controls. Attempts will be made to blind the surgical/medical team (not nursing staff) to the treatment arm by providing all study patients with identical trial packets that either do or do not contain gum. The gum will be stored in the drug trolley and dispensed during the drug round. It will be recorded on the drug cardex that the patient is partaking in the trial. It is not possible to blind the ward nurses; however, they will be trained not to inform the surgical team about which treatment arm the patient has been allocated to.
The participants cannot be blinded but they will be requested not to disclose this information to their surgical team. The study nurses at each site will be responsible for extracting data on date fit for discharge from patients' notes. Actual date of discharge, which will be used for the assessment of our primary outcome, will be obtained from the computerised records kept by ward staff. In addition, all data analysis will be conducted without knowledge of treatment assignment.

4.7 Subject compliance

We will formally monitor compliance with the intervention during the study. Specifically, we will ask patients in the gum chewing arm to record when, and for how long, they chewed gum, to retain wrappers and the chewed pieces of gum, and to return any unused gum. A log book will be provided for recording all gum-chewing activities. Patients will be asked to follow the gum chewing protocol for five days or until discharge; therefore, all data pertaining to compliance with the intervention will be collected during their hospital stay. We will ask patients in the control group at the time of discharge if they chewed gum during their inpatient stay and, if so, how often. On a monthly basis, the study coordinator will collate and review data on the gum chewing habits of both treatment groups. If it appears that there is a problem in terms of large numbers of control group patients chewing gum, we will convene an investigators meeting to discuss potential strategies for dealing with this. Potential strategies include having the ward staff remind control

patients on a daily basis not to chew gum, and emphasising the importance to the study results of them not chewing gum. However, we recognise that it will not be possible for us to prohibit any individual from chewing gum if he/she wishes to do so. Although the primary statistical analyses will be conducted on an intention-to-treat basis, we will explore whether gum chewing in the control group, if it occurred, might have influenced our results in secondary analyses.

4.8 Withdrawal of Subjects

Patients who suffer a serious adverse event which affects their ability to chew gum for example a post-operative stroke or post-operative loss of gag reflex, or patients who are intubated or ventilated will be withdrawn from the study. All data analyses will be conducted on an intention to treat basis. However, if a patient wishes to be withdrawn from the study, all identifiable data collected from that patient will be removed (i.e., destroyed). Data which is not identifiable to the research team will be retained. No additional data will be collected from the withdrawn patient. In order to achieve our recruitment target, the patient will be replaced with another who is scheduled to undergo large bowel resection for colorectal neoplasia, DD, or UC, and they will be randomly allocated to treatment group as described above.

5. Data

5.1 Data collection

A detailed list of all data to be collected is provided in **Tables 1-4**, and is also described below.

Pre-operative data: We will review patient's medical records to collect information on: pathology of disease; any previous abdominal surgery; pre-adjuvant chemotherapy/radiation regimens; use of bowel preparations; use of dietary preparations; use of prophylactic antibiotics; and preventive measures for thromboembolism. In addition, patients will have their weight and height, measured at enrolment by the study nurse.

Operative data: We will review patient's medical records to collect information on: type of operation; open or laparoscopic surgery; surgeon; duration of operation (time between first incision and placement of last suture); anaesthetic agents; average intraoperative temperature; intraoperative complications; blood loss; and amount of IV fluids.

Post-operative care: The study nurse will prospectively collect information on: analgesics regimen; use of anti-emetics; use of nasogastric tubes (including when removed, and when re-inserted if needed); physiotherapy protocol; mobilisation and ambulation plan; amount of IV fluids; and post-operative feeding protocol.
Outcome measures: We will record date of operation and date of discharge. We will also record date of admission and date fit for discharge (if different to date of discharge), and the time the anaesthetic was completed and the actual time of discharge, where possible, from logging out books and electronic data kept by ward staff. Clinical outcomes will be collected daily for five days or until discharge (if sooner) and include the following: clinical complications [including anastomotic leakage (clinical or radiological), intra-abdominal abscess without anastomotic leakage, post-operative haemorrhage, wound dehiscence, wound infection (using the ASEPSIS score where available), any other infection requiring treatment (e.g., pneumonia, urinary tract infection, proven infective diarrhoea), deep vein thrombosis/pulmonary embolism, and primary cardiac event. Complications will be defined using International Classification of Diseases criteria]; treatment for complications; time to first and second bowel discharge (BD) (or first and second emptying of semisolid faecal material from stoma bag); time to first flatus; time to first bowel sounds; re-

operation; intensive therapy unit and high dependency unit usage; and mortality. Data will be collected prospectively by the study nurse in combination with detailed chart review.

We will assess quality of life using the SF-36 and EuroQol (EQ)-5D questionnaires. Questionnaires will be administered pre-operatively (at the time of enrolment) and on day 4 post-operation (EQ-5D only), and at 6 and 12 weeks and post-operation. Data on pain and nausea will be collected daily for five days post-operation using visual analogue scales. Information on vomiting will be collected via chart review. The study nurse will assess intakes of supplement drinks (e.g., Build-up) via chart review and by asking patients how much they consumed. When patients begin consuming solid food, they will be asked to record how much (e.g., 1/4, 1/2) of the meal they ate. Tolerability of food will be defined as the consumption of at least 1/2 a meal at each of three mealtimes over 24 hours without vomiting.

For economic analyses, data on post-operative hospital care (including readmissions) will be recorded via medical record review, and resource use data collected will include: days in hospital by ward type; subsequent surgery and other procedures; imaging tests; laboratory tests; medications; chewing gum used; and dietary intakes. Unit costs of hospital care will be obtained from the finance departments of both hospitals for a micro-costing of hospital care.

Acceptability and compliance: Acceptability of chewing gum will be assessed via a brief interview after patients have completed at least one day of the gum chewing protocol, and patients will be encouraged to notify ward staff of any problems. Compliance will be assessed by asking patients to record when, and for how long, they chewed gum, to retain wrappers and the chewed pieces of gum, and to return any unused gum. We will ask patients in the control group at the time of discharge if they chewed gum during their inpatient stay and, if so, how often.

Follow-up: All discharged patients will be contacted by telephone at 6 and 12 weeks post-randomisation to obtain information on: clinical events (e.g., readmission/re-operation); complications (e.g., infections; see above); treatment prescribed for complications; quality of life (SF36 and EQ-5D); and post-discharge use of NHS and personal social services (PSS, e.g. home care). We will also record when the patient returned to work or 'usual activities' and the amount of time their carer took off work or usual activities to look after the patient. The cost of care post-discharge will be estimated using national unit costs.

5.2 Data handling and record keeping

The study nurses at each centre will be responsible for data collection from patients, medical charts, and medical records and the Chief Investigator will take overall responsibility for data quality. Databases (e.g., Access, Excel) for data entry will be developed prior to the start of the study and provided to the study nurses at both study sites. All data will be entered into the databases on site. Checks will be built into the data entry system to detect, for example, implausible numbers. Data will also be checked for potential outliers, and the data verified where possible.
In order to independently verify data extracted from patients' notes, source data verification will be carried out at each site by appropriately trained staff delegated by the sponsor .
Any personal data that is stored electronically will be password protected, and will only be shared with the healthcare team or other members of the research team if it is deemed absolutely necessary. Passwords will not be written down or shared with other users under any circumstances. De-identified electronic data (i.e., with study ID only) will be transferred weekly, via a secure procedure, to the study coordinator based in Bristol.
All hard copies of study documents (e.g., completed questionnaires) will be stored in locked filing cabinets at each study site, and will be transferred to Bristol every couple of months, where they will also be stored in a locked filing cabinet. Only the study nurses and study coordinator will hold the key to their respective filing cabinets.

All persons who are granted access to any personal data will need to show evidence of having received training in good clinical practice (ICH-GCP).
All source documents paper and electronic will be retained for a period of 5 years following the end of the study. If trial related information is documented in medical records, those records will be identified by a 'Do not destroy before dd/mm/yyyy' label where the date is 5 years after the last patient's last contact.
Data will be collected and retained in accordance with the Data Protection Act 1998.
When destroyed, all copies of the data will be destroyed in a secure way (e.g., by shredding). Records of destruction will be kept, as these may be required for audit or other purposes at a later date.

5.3 Access to Source Data

In order to fulfil monitoring and audit procedures, relevant sections of participants' medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust. Study participants are notified of this on the consent form.

6. Statistics

6.1 Statistical analysis

General data analysis plan:
All randomised patients will be analysed on an intention-to-treat basis. Preoperative characteristics of each group will be tabulated using means and standard deviations for normally distributed data, medians and interquartile ranges for non-normally distributed data, and percentages and counts for categorical data. In order to assign an estimate of difference between groups with 95% confidence interval, survival analysis will be conducted in which discharges appear as events and deaths appear as censored observations. This will allow the calculation of a hazard ratio. Secondary outcomes such as clinical complications, time to first flatus and BM, quality of life, tolerability of food, pain, nausea, and vomiting will be assessed using further survival analysis, linear or logistic regression as appropriate. Multiple imputation will be used to estimate missing responses. Data analyses will be conducted by Dr. Sam Leary (co-applicant, University of Bristol) when all data collection and cleaning of datasets has been completed.

Economic data analysis plan:
Incremental care costs (or savings) of patients receiving chewing gum vs. usual care will be calculated. In the primary analysis, costs will include all NHS, personal social services, patient, and carer costs up to 3 months post-randomisation. In accordance with updated NICE guidelines on health technology appraisal (1), we will use EQ-5D responses to calculate any difference in quality adjusted life years (QALYs) between groups over the 3 month period. The primary economic outcome is the incremental cost per QALY ratio of the intervention, with 95% confidence intervals calculated by non-parametric bootstrapping. Results will also be presented using the 'net monetary benefit statistic' using willingness to pay thresholds of £20,000 and £30,000 per QALY in accordance with NICE guidelines. For key parameters (e.g. local unit costs of hospital care) we will perform multiway sensitivity analysis to assess the generalisability of our economic results to other hospitals where the cost of inpatient care may be different. Multiple imputation will be used to estimate missing EQ-5D responses and resource use data. Economic analyses will be conducted by Dr. Will Hollingworth (co-applicant, University of Bristol) when all data collection and cleaning of datasets has been completed.
(1) National Institute for Health and Clinical Excellence Guide to the Methods of Technology Appraisal. 2007.

As we anticipate no harm we do not propose any interim analyses.

6.2 Sample size calculation

The study will be conducted at selected sites in the UK. Similar proportions of cancer and non-cancer patients are likely to be recruited at each centre in the study. We aim to recruit 400 patients across the sites.
Data from prior studies were used for power calculations (Chan & Law, 2007). One trial reported data from a UK population (Quah et al. 2006), and was used in calculating power for length of hospital stay. However, standard deviations in the UK study tended to be higher than other studies (Chan & Law, 2007), which may have led to a conservative estimate of power in our proposed study. Power to detect differences between groups for length of hospital stay and time to first flatus and BM, and to detect differences in complication rates, are shown below. We have 84% power to detect a difference in length of hospital stay of 1.5 days, and ≥93% for the other outcomes. A reduction of 1.5 days in length of stay would enable patients to return to their home environment sooner and lead to considerable cost savings to the NHS.

Power to detect a difference between groups (n=200/group) using a t-test and 5% two-sided significance

OUTCOME	STANDARD DEVIATION	DIFFERENCE	POWER
Length of hospital stay	5 days†	1.5 days	84%
Time to first flatus	18.5 hours‡	24 hours	>99%
Time to first BM*	34.4 hours‡	24 hours	>99%

[*BM=bowel movement; †From Quah et al. 2006; ‡Mean of studies in Chan & Law 2007]

Power to detect a difference between groups (n=200/group) using a $\chi 2$ test and 5% two-sided significance

OUTCOME	GUM	NO GUM	POWER
% with complications	16.7%*	31.3%*	93%

[*From Chan & Law 2007]

All randomised subjects will be used in the statistical analyses, i.e., according to an intention to treat analysis. Multiple imputation will be used to estimate missing responses.
Any modifications to the statistical plans will be reported in papers.

References

Chan, M. K., and Law, W. L. Use of Chewing Gum in Reducing Postoperative Ileus After Elective Colorectal Resection: A Systematic Review. Dis Colon Rectum, 2007.

Quah, H. M., Samad, A., Neathey, A. J., Hay, D. J., and Maw, A. Does gum chewing reduce postoperative ileus following open colectomy for left-sided colon and rectal cancer? A prospective randomized controlled trial. Colorectal Dis, *8:* 64-70, 2006.

7. Safety

7.1 Safety Assessments

Adverse events will be recorded in accordance with University Hospitals Bristol NHS Foundation Trust (UH Bristol) & Plymouth Hospitals NHS Trust Research Related Adverse Event Reporting Policy. These are two separate policies but both trusts have corresponding methods for reporting and recording adverse events.

In this study, an adverse event would be considered serious if it: a) results in death; b) is life-threatening; c) requires prolongation of existing hospitalisation (excluding prolongation of admission for social or administrative reasons); or d) results in persistent or significant disability or

incapacity. In large bowel surgery post operative complications are not unexpected and are not infrequent, often causing an extension of the patients hospital admission. The research team will only notify fatal and unexpected non-fatal SAEs to the trial sponsor.

The following adverse events are 'expected':

Anastomotic leakage (clinical or radiological)
Atelectasis
Cardiac arrhythmias
Deep vein thrombosis
Infective diarrhoea
Intestinal obstruction
Intra-abdominal abscess
Intra-operative haemorrhage
Intra-operative iatrogenic injury of any intra-abdominal organ
Peri-operative or post-operative myocardial infarction
Pneumothorax
Post-operative haemorrhage
Pulmonary embolism
Respiratory tract infection
Sepsis
Stoma related complications
Stroke
Transient ischaemic attack
Urinary tract infection
Wound dehiscence
Wound infection

All adverse events will be recorded in detail on a case record form. The investigator will make an assessment of intensity, causality, expectedness, and seriousness. At the conclusion of the study, all adverse events recorded during the study will be subject to statistical analysis, and the analysis and subsequent conclusions will be included in the final study report. Abnormalities in laboratory test results or other investigations will only be recorded if they are considered to be clinically significant.

Within 24 hours of a member of the research team becoming aware of a serious adverse event, the sponsor (UH Bristol) will be notified. The investigator (or delegated person) will make an initial report, orally or in writing. Oral reports will be followed up in writing within 24 hours of the initial report. The UH Bristol Research Related SAE/SUSAR Initial Report form will be used, and will include as much information as is available at the time. At the same time as notifying the sponsor, the investigator will also notify the Chief Investigator.

The subject will be actively followed up, and the investigator (or delegated person) will provide information missing from the initial report within five working days of the initial report.

The investigator (or delegated person) will provide follow-up information each time new information is available, using the UH Bristol Research Related SAE/SUSAR Follow-up Report form until the SAE has resolved or a decision for no further follow-up has been taken.

The Chief Investigator will provide the main REC with copies of all reports. In addition, a progress report will be submitted to the main REC one year following the granting of a favourable ethical opinion and thereafter annually. These reports will include information on the safety of participants.

At the end of the study, the Chief Investigator will submit an end of study report to UH Bristol R&D department and the research ethics committee that granted approval.

7.2 Stopping/discontinuation rules and breaking of randomisation code

The study will be considered complete when the last enrolled patient has been followed-up for all study outcomes. The trial would be prematurely discontinued if patients were having
1. Adverse events due to illness
2. Adverse events as a consequence of chewing the gum
3. If new findings were made available that made this study unethical or superfluous. This decision would be made by the Steering group.

As we anticipate no harm we do not propose any interim analyses.

The randomisation code may need to be broken if a patient has an adverse allergic reaction to the chewing gum. The ward staff and patients themselves know which arm of the study they belong to and will be able to inform the necessary personnel.

7.3 Monitoring

The study will be monitored and audited in accordance with UH Bristol policy. All trial related documents will be made available on request for monitoring and audit by UH Bristol & the relevant Research Ethics Committee.

All investigators who have contact with patients as part of this trial will have received training in ICH-GCP.

A steering group will be set up consisting of CA, ST, SL, RL & JEJ, this committee will meet biannually. This committee will assess patient recruitment, protocol violations, project progression.

8. Ethics

8.1 Ethical considerations

There are no extraneous ethical considerations to this study, other than those already listed in the inclusion/exclusion criteria and any matters raised from the ethics application will be addressed.

8.2 Ethics and R&D approval

The study will be performed subject to Research Ethics Committee (REC) approval, including any provisions of Site Specific Assessment (SSA), and local Research and Development (R&D) approval.

8.3 Research Governance

This study will be conducted in accordance with the Research Governance Framework for Health and Social Care and Good Clinical Practice.

9. Finance

9.1 Finance

The study is funded by the National Institute for Health Research. The UH Bristol, as sponsor, will be responsible for financial management of the study.

Patients will not receive payment for participating in this study, and there will be no out of pocket expenses incurred through participation in this study.

9.2 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

10. Reporting and dissemination

We will disseminate our research findings at national conferences and via original research articles published in high-end peer-reviewed journals. Depending on the results of the trial, we will attempt to disseminate the findings of our research to all who could benefit from them. If successful in reducing ileus and its associated morbidities, there will be a need to promote the use of post-operative chewing gum at all levels from the patient through to the physician and surgeon, in order to ensure the implementation of this intervention across the NHS. We will therefore disseminate our findings in a number of ways. Initially, we will conduct seminars with service providers within the UK centres to present the results of our findings and to provide recommendations for the incorporation of chewing gum within usual care practices. We will also arrange meetings with patient user groups, at which we will present the results of our work in lay terms. We will then produce, in collaboration with patient user groups, a leaflet to be distributed to patients that will explain the benefits of including chewing gum as part of their post-operative care. These materials will be sent to all PCTs, along with peer-reviewed papers generated from this study. If requested, we will visit other hospitals to talk with physicians or patients about the results of our work. We recently submitted a systematic review on gum chewing and ileus to the Annals of Surgery and we plan to update that review as part of this project. A final report will be submitted to the Department of Health, and we also will disseminate the findings via the Research Findings Electronic Register.

Appendices: Tables 1 – 4

Table 1. Summary of data collection at recruitment

Data	**Source of data / method of data collection**	**When collected**	**Data collected by whom**	**How often collected**	**Approximate length of time (for participant) to complete procedure**	**Why data are collected (e.g., baseline, main outcome, etc.)**	**Standardised tool or other used for data collection**	**Form of data (e.g. binary, continuous)**
Eligibility	In-person meeting	At booking appointment / when admitted	Study nurse/ Investigator	Once	30 minutes	To determine eligibility		Binary (eligible / ineligible)
Informed consent	In-person meeting	At booking appointment / when admitted	Study nurse/ Investigator	Once	10 minutes	n/a	Consent form developed for this study	n/a
Demographics 'Tell us about yourself'	Patient questionnaire	At booking appointment / when admitted	Patient-completed questionnaire	Once	10 minutes	Baseline data and adjustment variables	Questionnaire developed for this study	Various
Quality of life SF 36 EQ5D	Patient questionnaire	At booking appointment / when admitted	Patient-completed questionnaire	Once	2 minutes for the EQ-5D and 20 minutes for the SF36	Secondary outcome	Standard SF36 and EQ-5D	Various
Weight	Measurement made in clinic	At booking appointment / when admitted	Study nurse/ Investigator	Once	1 minute	Adjustment variable	Calibrated scales	Continuous
Height	Measurement made in clinic	At booking appointment / when admitted	Study nurse/ Investigator	Once	1 minute	Adjustment variable	Stadiometer	Continuous
Willingness to chew gum / tried gum	In-person meeting	At booking appointment / when admitted	Study nurse/ Investigator	Once	< 1 minute	To check for allergy to mint and to see if patient has tried gum	Questions developed for this study	Binary (yes/no)
Pathology of disease	Medical record review	At time of listing for large bowel resection (data needed for randomisation)	Study nurse/ Investigator	Once	n/a	Stratification variable	Data collection form developed for this study	Categorical

Table 2. Summary of data collection during hospital stay; patient-completed questionnaires (with or without accompanying chart review / other data collection method) or measurements made on patient

Data	Source of data / method of data collection	When collected	Data collected by whom	How often collected	Approximate length of time (for participant) to complete procedure	Why data are collected (e.g., baseline, main outcome, etc.)	Standardised tool or other used for data collection	Form of data (e.g. binary, continuous)
Post-surgery feeding protocol	Patient questionnaire, chart review	Patient asked to complete a questionnaire at 8 pm each day; review of chart approx. every other day	Patient and Study nurse/Investigator	Daily for five days	5 minutes	Adjustment variable	Questionnaire and data collection form developed for this study	Various
First and second bowel movement (or emptying of semisolid faecal material from stoma bag)	Patient questionnaire and chart review	Patient asked to complete a questionnaire at 8 pm each day; review of chart approx. every other day	Patient and Study nurse/Investigator	Daily for five days	1 minute	Secondary outcome	Questionnaire and data collection form developed for this study	Date
Flatus	Patient questionnaire and chart review	Patient asked to complete a questionnaire at 8 pm each day; review of chart approx. every other day	Patient and Study nurse/Investigator	Daily for five days	1 minute	Secondary outcome	Questionnaire and data collection form developed for this study	Date
Bowel sounds	Nurse listens for bowel sounds/chart review	Daily	Study nurse/Investigator	Daily for five days	1 minute	Secondary outcome	Standard protocol for listening for bowel sounds	Date
Intervention group use of chewing gum	Log book completed during hospital stay	At each chewing episode	Patient-completed log book	Four times a day (intervention group only)for five days	4 minutes	Compliance / secondary outcome (economic analysis)	Log book developed for this study	Various
Control group use of chewing gum	Brief interview by study nurse	At time of discharge	Study nurse/Investigator	Once (control group only)	2 minutes	Compliance	Interview developed for this study	Binary (yes/no) and continuous (how often)
Acceptability of chewing gum	Brief interview by study nurse	After patients have completed at least one day of the gum chewing protocol	Study nurse/Investigator	Once	2 minutes	Acceptability	Questionnaire developed for this study	Various

Quality of life	Patient questionnaire	Day 4 post-op	Patient-completed questionnaire	Once	2 minutes for the EQ-5D and 20 minutes for the SF36	Secondary outcome	EQ-5D	Various
Pain, nausea, hunger etc.	Visual analogue scale (VAS) completed by patient	Patient asked to complete a questionnaire at 8 pm each day	Patient-completed VAS	Daily for five days	5 minutes	Secondary outcome	Standard VAS	Scale
Vomiting	Patient questionnaire and chart review	Patient asked to complete a questionnaire at 8 pm each day; review of chart approx. every other day	Patient-completed questionnaire and study nurse/investigator	Daily for five days	1 minute	Secondary outcome	Data collection form and questionnaire developed for this study	Binary (yes/no) and continuous (number of times)
Dietary intake 'what did you eat & drink today'	Patient questionnaire & Chart review by study nurse	Patient asked to complete a questionnaire at 8 pm each day	Patient-completed questionnaire	Daily for five days	2 minutes	Secondary outcome	Questionnaire developed for this study	Binary (yes/no) and continuous (amount consumed)

Table 3. Summary of data collection during hospital stay; medical record / chart review (no patient contact needed)

Data	Source of data / method of data collection	When collected	Data collected by whom	How often collected	Approximate length of time (for participant) to complete procedure	Why data are collected (e.g., baseline, main outcome, etc.)	Standardised tool or other used for data collection	Form of data (e.g. binary, continuous)
Previous abdominal surgery; pre-adjuvant chemotherapy / radiation regimens; bowel preparations prior to surgery; dietary preparations prior to surgery; prophylactic antibiotics prior to surgery; preventive measures for thromboembolism prior to surgery	Medical record review	Approx. 1-2 days post-op	Study nurse/Investigator	Once	n/a	Adjustment variables	Data collection form developed for this study	Various
Date of admission; date of operation; open or laparoscopic surgery and operative data	Medical record review	Approx. 1-2 days post-op	Study nurse/Investigator	Once	n/a	Baseline data, and data for main outcome, secondary outcomes, and adjustment variables	Data collection form developed for this study	Various
Post-op analgesics regime and use of anti-emetics; use of nasogastric tubes (including when removed, and when re-inserted if needed); IV fluids (amount received)	Chart review	Review of chart approx. every other day post-op	Study nurse/Investigator	Daily for five days	n/a	Adjustment variable	Data collection form developed for this study	Various
Date fit for discharge; date of discharge; time of discharge	Chart review / ward log book / electronic information	At or post-discharge	Study nurse/Investigator	Once	n/a	Main outcome	Data collection form developed for this study	Date / time
Post-surgery physiotherapy and mobilisation and ambulation plan	Chart review	Review of chart approx. every other day	Study nurse/ Investigator	Daily for five days	n/a	Adjustment variable	Data collection form developed for this study	Various
Clinical complications* and treatment for complications during hospital stay	Chart review (and medical record review)	Review of chart approx. every other day post-op	Study nurse/Investigator	Daily for five days	n/a	Secondary outcome	Data collection form developed for this study	Various
Re-operation; intensive therapy unit usage; high dependency unit usage; mortality	Chart review (and medical record review)	Review of chart approx. every other day post-op	Study nurse/Investigator	Once at end of hospital stay	n/a	Secondary outcome	Data collection form developed for this study	Various

* Data on clinical complications to be collected includes the following: anastomotic leakage (clinical or radiological), intra-abdominal abscess without anastomotic leakage, post-operative haemorrhage, wound dehiscence, wound infection (using the ASEPSIS score where available), any other infection requiring treatment (e.g., pneumonia, urinary tract infection, proven infective diarrhoea), deep vein thrombosis/pulmonary embolism, and primary cardiac event. Complications will be defined using International Classification of Diseases criteria.

Table 4. Summary of data collection post discharge; follow-up telephone calls with patient and medical record review

Data	Source of data / method of data collection	When collected	Data collected by whom	How often collected	Approximate length of time (for participant) to complete procedure	Why data are collected (e.g., baseline, main outcome, etc.)	Standardised tool or other used for data collection	Form of data (e.g. binary, continuous)
Quality of life	Telephone administered questionnaire	6 weeks and 3 months post-op	Questionnaire administered via telephone by study nurse/investigator(unless still in hospital)	Each questionnaire administered at 6 weeks and 3 months post-op (i.e., twice each)	2 minutes for the EQ-5D and 20 minutes for the SF36	Secondary outcome	Standard SF36 and EQ-5D	Various
Post-discharge clinical complications* and treatment received for complications	Telephone administered questionnaire and medical record review	6 weeks and 3 months post-op	questionnaire administered via telephone by study nurse/investigator	Twice	n/a	Secondary outcome	Data collection form and questionnaire developed for this study	Various
Days in hospital by ward type	Medical record review / electronic information	3 months post-op	Study nurse/Investigator	Once	n/a	Secondary outcome	Data collection form developed for this study	Continuous
Subsequent surgery and other procedures	Medical record review	3 months post-op	Study nurse/Investigator	Once	n/a	Secondary outcome	Data collection form developed for this study	Various
Imaging tests; laboratory tests; medications	Medical record review	3 months post-op	Study nurse	Once	n/a	Secondary outcome	Data collection form developed for this study	Various
Unit costs of hospital care	Finance dept, Bristol & Derriford	3 months post-op	Study nurse or health economist	Once	n/a	Secondary outcome	Data collection form developed for this study	Various
Post-discharge use of NHS and personal social services	Telephone administered questionnaire	3 months post-op	Study nurse/Investigator	Once	5 minutes	Secondary outcome	Questionnaire developed for this study	Various
When patient returned to work or ‘usual activities’	Telephone administered questionnaire	3 months post-op	Study nurse/Investigator	Once	2 minutes	Secondary outcome	Questionnaire developed for this study	Various
How much time the patients carer took off work or ‘usual activities’	Telephone administered questionnaire	3 months post-op	Study nurse/Investigator	Once	2 minutes	Secondary outcome	Questionnaire developed for this study	Various

* Data on clinical complications to be collected includes the following: anastomotic leakage (clinical or radiological), intra-abdominal abscess without anastomotic leakage, post-operative haemorrhage, wound dehiscence, wound infection (using the ASEPSIS score where available), any other infection requiring treatment (e.g., pneumonia, urinary tract infection, proven infective diarrhoea), deep vein thrombosis/pulmonary embolism, and primary cardiac event. Complications will be defined using International Classification of Diseases criteria.