TRIAL PROTOCOL

Optimisation before Crohn's surgery using Exclusive Enteral Nutrition

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: 3.0

Version Date: 07-DEC-2023

PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
SA-01	20-DEC-2023	3.0	Substantial	• Removed reference to rectal steroids from the steroid secondary outcome. • Creatinine testing has been removed and replaced with eGFR. • "Post-operative care level 1.5-2 bed" has been removed from section 10.3 as it is not an SAE/AE, it is a consequence of a complication. • Rewording of the clinical outcomes • Addition of the ISRCTN number • Removed reference to collection of Hospital Number as it will not be collected. • Amended instruction for completion of the consent form.

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NOTE:

The following are not funded by the NIHR HTA:

- The COAST sub study is funded by Crohn's and Colitis UK.
- The Microbiome sub study is funded by Helmsley Charitable Trust.

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	OCEaN Trial
Protocol version number:	Version: __ __
Protocol version date:	__ __ / __ __ __ / __ __ __ __
CI name:	Dr Rachel Cooney
Signature and date:	_____ __ __ / __ __ __ / __ __ __ __

Sponsor statement

By signing the IRAS form for this trial, the University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance statement

This protocol describes the OCEaN trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the OCEaN trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031), Human Tissue Act 2004 and subsequent amendments thereof.

Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial name:	OCEaN Trial
Protocol version number:	Version: __ __
Protocol version date:	__ __ / __ __ __ / __ __ __ __
PI name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

Reference Numbers	
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ISRCTN reference number	ISRCTN73953171
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ABBREVIATIONS

Abbreviation	Term
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
ANOVA	Analysis of Variance
API	Associate Principal Investigator
ASA	American Society of Anaesthesiologist
ASV	Amplicon Sequence Variant
BCTU	Birmingham Clinical Trials Unit
BMI	Body Mass Index
BNF	British National Formulary
CACE	Complier Average Causal Effect
CCI	Comprehensive Complication Index
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDC	Clavien-Dindo classification
CI	Chief Investigator
CLIQ	Crohn's Life Impact Questionnaire
CRF	Case Report Form
CRP	C-reactive protein
CT	Computerised Tomography
DAPA	Diet, Anthropometry and Physical Activity
DCF	Data Clarification Form
DGH	District General Hospitals
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSA	Data Sharing Agreement
ECCO	European Crohn's and Colitis Organisation

eCRF	Electronic Case Report Form
EEN	Exclusive Enteral Nutrition
eGFR	Estimated Glomerular Filtration Rate
EPIC	European Prospective Investigation into Cancer and Nutrition
EQ-5D-5L	EuroQoL-5D-5 Level
ESPC	European Society of Coloproctology
FR-QoL	Food -related quality of life
GCP	Good Clinical Practice
GIP	Gluten Immunogenic Peptide
GP	General Practitioner
HBI	Harvey-Bradshaw Index
HEAP	Health Economics Analysis Plan
HRA	Health Research Authority
HTA	Health Technology Assessment
IBD	Inflammatory Bowel Disease
IBDU	Inflammatory bowel disease unclassified
ICER	Incremental cost effectiveness ratios
ICF	Informed Consent Form
ISF	Investigator Site File
LCRN	Local Comprehensive Research Network
MCID	Minimum Clinically Important Difference
MDT	Multidisciplinary Team
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMDS	Non-Metric Multidimensional Scaling
ONS	Oral Nutritional Supplements

OOB	Out-Of-Box error rate
OR	Odds Ratio
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PROM	Patient Reported Outcome Measure
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QoR-15	Surgical Quality of Recovery-15
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGT	University of Birmingham Research Governance Team
ROC	Receiver Operating Characteristic
SACN	Scientific Advisory Committee on Nutrition
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCFA	Short Chain Fatty Acids
SD	Standard Deviation
SoECAT	Schedule of Events Cost Attribution Template
TMF	Trial Master File
TMG	Trial Management Group
TPN	Total Parenteral Nutrition
TSC	Trial Steering Committee
UK	United Kingdom
UoB	University of Birmingham
UoG	University of Glasgow

TRIAL SUMMARY

Title

Optimisation before **C**rohn's surgery using **E**xclusive entera**l** **N**utrition (OCEaN)

Objectives

The primary aim of this trial is to determine whether pre-operative Exclusive Enteral Nutrition (EEN) is more clinically and cost effective compared with usual diet in patients undergoing surgery for Crohn's disease (CD).

Trial design

Multi-Centre, Two arm, Parallel group, Open label, Pragmatic Randomised Controlled Trial, with a mixed methods internal pilot (assessing both quantitative and qualitative data) and full economic evaluation.

Participant population and sample size

Adult patients aged 16 years or older undergoing planned surgery for small bowel and / or colonic CD (primary or repeat surgery). 618 participants (309 in each arm) are required.

Setting

40 UK-wide NHS hospitals including tertiary centres and District General Hospitals.

Eligibility criteria

Inclusion criteria

- Any patient undergoing planned surgery for small bowel and / or colonic CD (primary or repeat surgery)
- Age ≥16 years
- Willingness to go on EEN for the duration of the intervention period (minimum of 6 weeks)
- Capacity to give consent

Exclusion criteria

- Surgery for peri-anal CD, ulcerative colitis, or inflammatory bowel disease unclassified (IBDU)
- Patients who require parenteral nutrition in the 6 weeks prior to surgery
- Inability to comply with the trial schedule and follow up

Intervention and Comparator

6 weeks of EEN prior to surgery vs usual diet as per local standard care.

Outcome measures

Dual primary outcomes at 6 weeks post-surgery:

- Crohn's Life Impact Questionnaire (CLIQ; a CD-specific patient reported outcome tool assessing quality of life)
- Post-surgery complications using the Comprehensive Complication Index (CCI)

Secondary Outcomes:

Patient-reported outcomes

- Quality of life over time using the CLIQ which will be collected fortnightly until 12 weeks post-surgery and then monthly to 24 weeks post-surgery
- Post-surgery recovery using the Surgical Quality of Recovery-15 (QoR-15) on day 3 post-surgery (or pre-discharge if discharged before day 3)

Clinical outcomes (all related to index surgery only)

- Length of post-operative hospital stay (in nights following operation)
- Length of bowel resected (in centimetres measured along anti-mesenteric border) at the time of surgery
- Number of anastomoses formed at surgery
- Stoma formation either at index operation or within 30 days of surgery due to re-operation
- Anastomotic leak within 30 days of surgery
- Hospital re-admission within 30 days of discharge
- Re-operation within 30 days of surgery
- Enterocutaneous fistulae within 90 days of surgery
- Clinical recurrence of CD at 24 and 52 weeks post-surgery, as assessed by Crohn's disease activity index
- Endoscopic disease recurrence on colonoscopy performed between 24 and 52 weeks post-surgery
- Able to wean off steroids prior to surgery
- Safety assessed through adverse event and serious adverse event reporting

We will also record and report descriptively, without making formal comparisons:

- Number of participants whose planned surgery did not proceed due to clinical improvement
- Number of participants who required expedited surgery

Health economic analysis

An incremental cost-utility analysis will determine the cost per quality adjusted life year (QALY) gained over the 52 weeks post-surgery (using the EQ-5D-5L questionnaire).

Qualitative Research

Interviews will be undertaken with participants in both trial groups, and also with staff involved in the trial. This research aims to provide in-depth qualitative data concerning the acceptability and experience of EEN as a pre-surgical intervention.

TRIAL SCHEMA

Population

Adult patients having elective surgery for small bowel and/or colonic Crohn's Disease (CD) – primary or repeat surgery allowed - identified as potentially eligible for trial during acute hospital admission, MDT discussion or outpatient clinic.

Eligibility

Eligibility criteria:

- Any patient undergoing planned surgery for small bowel and/or colonic CD (primary or repeat surgery)
- Age ≥16 years
- Willingness to go on EEN for the duration of the intervention period (minimum of 6 weeks)
- Capacity to give consent

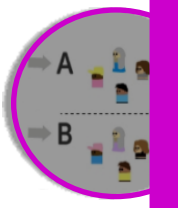
Consent

Initial trial discussion and Participant Information Sheet given to patient. Patient consented into the trial.

Randomisation

Baseline parameters measured and recorded

RANDOMISATION
(1:1; N=618)



Treatment Allocation

INTERVENTION ARM n = 309 pts
EEN for 6 weeks pre-op

CONTROL ARM n = 309 pts
Usual diet pre-op

SURGERY

SURGERY

Follow-up

Follow-up at 6, 24 and 52 weeks post-surgery at surgical, IBD or research clinic. Surveillance colonoscopy between 24 and 52 weeks post-operatively.

Internal pilot with embedded qualitative evaluation during first 9 months.
In-depth qualitative data concerning the acceptability of EEN as a pre-surgical intervention as well as in-depth understanding of the comparative experience of pre- and post-operative periods for participants in both arms.

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1. BACKGROUND AND RATIONALE

1.1 Background

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract, with increasing incidence worldwide. (1, 2) In the United Kingdom (UK), it is predicted that the prevalence of inflammatory bowel disease (IBD) will be 1% by 2030. (3, 4, 5) Medication such as oral immunosuppressants and biologics are the mainstay of treatment for CD. (6) However, surgery continues to have a role in disease management.

The main indications for surgery are stricturing disease, penetrating complications and medication-refractory inflammatory disease. (7, 8) There is some suggestion that the current more aggressive treat to target approach has reduced surgical rates. (7, 9-11) However, despite this, 23-47% of patients still require surgery at some stage in their disease course, (12-14) with approximately 22% of these patients requiring repeated surgery. (15, 16)

Surgery may be the preferred first line treatment as per the LIR!C study, which showed that primary ileocecal resection in patients with isolated ileocecal disease had similar quality of life scores one year after surgery compared to those randomised to medical treatment. (17) The European Crohn's and Colitis Organisation (ECCO) and European Society of Coloproctology (ESCP) consensus guidelines suggest that surgery should be considered at an early stage in those with penetrating or fistulising disease, and in those with localised ileocecal disease and obstructive symptoms but no significant active inflammation. (18)

Exclusive Enteral Nutrition (EEN) is the term used when a patient replaces their habitual diet with an exclusive liquid diet for a defined period of time. EEN is widely used in paediatric CD as first line therapy for the induction of remission without the use of steroids. Six to 8 weeks of EEN is the recommended duration, with induction of remission of CD occurring in 60-80% of children and adolescents. (14, 19) To date, there have been no randomised controlled trials (RCT) assessing the ability of EEN to induce remission in adults compared to usual unrestricted diet, and a Cochrane review (2018) showed that EEN was effective, but inferior to steroids; perhaps due to lack of compliance with EEN. (20)

1.1.1 Review of existing evidence

i) Benefits to Patients

Previous studies have shown the following potential benefits of pre-operative EEN in patients with CD:

Reduced steroid use

Steroids are the first line therapy for adults presenting acutely with active CD. (6)

Emergency surgery in CD should ideally be avoided, due to the increased risk of intra-abdominal complications, high stoma rate and poor outcomes. (21, 22) Drainage of collections and nutritional

optimisation is recommended prior to surgery. (18) Steroids are sometimes used to control symptoms and in the treatment of refractory disease, whilst awaiting elective surgery. However, steroid use is a risk factor for intra-abdominal septic complications (Odds Ratio (OR): 1.99; 95% Confidence Interval: 1.54-2.57). (23) Steroids also delay wound healing and increase the risk of superficial and deep surgical site infection, pneumonia, myocardial infarction, renal insufficiency and prolonged intubation. (24-26) Steroid use also increases the risk of readmission within 30 days by 58%, risk of reoperation by 21%, hospital stay longer than 30 days by 19% and risk of mortality by 32%. (27)

Two single centre prospective studies showed that the use of EEN pre-operatively allowed up to 62.5% of steroid dependent CD patients to be successfully weaned off steroids pre-operatively. (28, 29) Another single centre prospective study assessing the impact of EEN on perioperative outcomes in CD patients following immunosuppressive therapy noted that EEN therapy prolongs the immunosuppressant free (which included steroids) interval, reduces the risk of urgent surgery and reoperation, and most importantly, decreased complications after surgery. (30, 31)

Reduced operative complications

There are no RCTs assessing operative complications, with evidence limited to retrospective cohort studies and case-control studies. (28, 32, 33) Heerasing et al. demonstrated that those started on EEN had a shorter operating time and were nine times less likely to develop an abscess or anastomotic leak compared with matched controls. (32) Li et al. showed that patients who were immunosuppressant free prior to the operation and given EEN had a lower rate of stoma formation, reduced incidence of post-operative complications and a reduced need for an urgent operation. (31) Pre-operative management of fistula/abscesses is recommended to reduce post-operative complications and data suggests that EEN may play a role in this, alongside radiological or surgical drainage. Retrospective studies in adults have shown that EEN can be effective at inducing remission and help resolve fistula/abdominal abscess formation. (34-37) Heerasing et al. demonstrated that those started on EEN had a lower C-reactive protein (CRP) at time of surgery and 25% of patients avoided surgery altogether compared with matched controls. (32) In 2022, a large retrospective study from a single tertiary referral site in the UK also showed lower operative complications at day 30 in patients receiving enteral nutrition for a median of 55 days pre-operatively compared to non-optimised patients (37/204 [18.1%] vs 36/96 [37.5%]; $p < 0.001$). (38)

Reduced need for stoma formation

Several studies have suggested that pre-operative EEN reduces the requirement for stoma formation at the time of operation. (31, 32, 35, 39) Stomas are usually created during CD surgery if the patient is at high risk of an anastomotic leak, because of multiple anastomoses, or because of significant ongoing infection at the time of operation. CD patients may have several risk factors for anastomotic leak – steroid use, malnutrition and smoking status. It is likely that the tendency for reduced stoma formation in the literature is because 6 weeks of pre-operative optimisation with EEN gives enough time for the patient to be weaned off steroids and improve nutritional status. (40, 41) Anecdotal evidence suggests that the possibility of decreasing the risk of stoma formation is a significant motive for patients to accept and comply with 6 weeks of EEN.

ii) Benefits to the NHS and health care economics

As CD predominantly affects young adults, the inherent costs both to the health system and to the patient can be substantial. Pre-operative optimisation, which can be undertaken at home in the 6 weeks leading up to surgery, may reduce the rate of post-operative complications, shorten length of hospital stay and accelerate recovery and thus facilitate a quicker return to work. (32) All of these will have substantial economic benefits to both the patient and the healthcare system. Furthermore, reducing temporary covering stoma rates will significantly reduce the cost, as patients may have a shorter length of hospital stay, decrease resource utilisation (stoma nurses/devices etc.) and will not require further surgery to reverse the stoma. It also avoids possible readmissions with stoma complications and the costs of pre-reversal investigations such as flexible sigmoidoscopy or gastrografin enema to assess the downstream colon. (42, 43)

iii) Evidence for the pre-operative use of EEN from systematic reviews

A systematic review published in 2017 included 14 original studies and 15 reviews assessing pre or perioperative nutritional support in CD. (24) The review included studies of EEN, but also studies of nutritional supplementation and total parenteral nutrition (TPN). The authors concluded that malnutrition was consistently demonstrated to be a major risk factor for post-operative complications, and that both enteral and parenteral routes were effective in reducing post-operative morbidity.

Another systematic review and meta-analysis (2018) aimed to explore whether pre-operative EEN or TPN reduced post-operative complications in CD. (39) Five studies met the inclusion criteria (total of 1111 patients); two studies were on EEN and three were on TPN. Overall, the rate of post-operative complications was 20% in those who had received either EEN or TPN vs. 61.3% in those who did not (OR: 0.26; 95% Confidence Interval: 0.07-0.88; $p<0.001$). The rate of post-operative complications in those who received only EEN was 21% vs. 73% in those who did not (OR: 0.09; 95% Confidence Interval: 0.06-0.13; $p<0.001$).

A systematic review (2019) of four studies assessing the relationship of pre-operative EEN on post-operative complications in adults with CD included all EEN formulas, routes of administration and regimens, both exclusive and supplemental, both as a complement to parenteral nutrition or a conventional diet. (37) In all studies, EEN was well tolerated. In the two largest studies, EEN was an independent factor against both infectious and non-infectious complications, anastomotic leaks and abscesses. (32, 31) In the largest study, it also appeared to increase pre-operative immunosuppressant-free intervals, protect against anastomotic leaks, surgical wound infections, ileus, stomas and re-operations. (31)

In 2021, we undertook a systematic review to update the current evidence base for the use of EEN in the pre-operative optimisation of adult patients undergoing elective surgery for CD. Seven studies were included in the review. Of these, five were retrospective reviews of prospectively kept databases and two were retrospective case-control studies (Table 1). Overall, although there was a trend in some of the studies towards improved pre-operative nutritional outcomes and inflammatory biomarkers, and improved post-operative outcomes, the quality of the studies was either medium or poor, largely retrospective in design and not powered to demonstrate significance. No studies looked at patient reported outcomes or quality of life.

Table 1: Impact of EEN on post-operative outcomes

Paper	Number in each arm EEN: Non-EEN	All complications	Stoma creation	Anastomotic leak	Infectious complications	Length of Stay (days)	Readmission	Recurrence
Ge 2015 (35)	45 EEN: 75 Non-EEN	17.8%: 36% (p=0.033)	20%: 32% (p=0.154)	2.2%: 6.7% (p=not stated)	SSI: 8.9%: 24% (p=0.038) Incisional SSI: 6.7%: 14.7% (p=0.186) Organ/ Space SSI: 2.2%: 9.3% (p=0.103)	9.4: 10.3 (p=0.444)	Not stated	Endoscopic recurrence significantly less at 6 months in the EEN group (p=0.044) At 12 months: Endoscopic recurrence 26.2%: 37.5% (p=0.059) Clinical recurrence 8.9%: 12% (p=0.82)
Heerasing 2017 (32)	38 EEN: 76 Non-EEN	8%: 32% (p<0.001)	3%: 8% (Not significant)	Anastomotic leak, abscess or collection 3%: 20% (p=0.019)		Not stated	3%: 14% within 28 days (p=0.11)	Not significant
Lil 2014 (30)	55 EEN: 68 Non-EEN	Not stated	Not stated	1.8%: 11.8% (p=0.079)	Intra-abdominal abscesses and anastomotic leak: 3.6%: 17.6% (p=0.02)	Not stated	Not stated	Not stated
Li 2015 (31)	219 immunosuppressive free interval and EEN (Group 4) 128 immunosuppressive free interval only (Group 3) 332 Not exposed to immunosuppressive agents 8 weeks pre-op (Group 1)	Significantly increased compared to Group 3 (p=0.03) and Group 1 (p=0.003)	Group 4: Group 3 17.8%: 34.4% (p<0.05) Group 4: Group 1 17:8%: 22% (p<0.001)	Group 4: Group 3 4.1%: 10.2% (p<0.05) Group 4: Group 1 4.1%: 3% (Not significant)	Total infectious complications: Group 4: Group 3 18.7%: 28.9% (p<0.01) Not significant in Group 4: Group 1	Not stated	No significant difference between groups	Not stated
Wang 2016 (44)	42 EEN: 39 Non-EEN	Not clearly stated Non-infectious complications: 26%: 51% (p=0.02)	Not stated	7%: 15% (p=not stated)	Infectious complications: 21%: 44% (p=0.03)	Not stated	Not stated	Endoscopic recurrence significantly less at 6 months in the EEN group (p= 0.03) Not significant at 12 months
Beaupal 2017 (28)	Feasibility study. EEN for complicated CD (N=35)	22.9%: 23.8% (p=1.0)	Ileostomy: 11.4%: 0% (p=0.286) Ileocolostomy: 31.4: 23.8% (p=0.761)	2.85%: 0% (Not significant)	Infectious complications: 14.3%: 23.8% (p=0.476)	7.46: 8.16 (p=0.222)	Not stated	Not stated
Yamamoto 2019 (45)	24 EEN: 24 Control	21%: 29% (p=0.51)	Not stated	N=1: N=3 (p=Not stated)	4%: 25% (p=0.04)	Not stated	Not stated	Not stated

1.2 Trial rationale

1.2.1 Justification for participant population

CD is a chronic disease with a significant burden amongst young patients. Despite the increasing array of treatments available to patients with CD, many patients still require surgery for stricturing or penetrating disease. There are low quality, largely retrospective studies suggesting that EEN may improve patient outcomes in the peri-operative period, in particular decreasing complication rates and rates of stoma formation. The National Institute for Health and Care Excellence (NICE), as well as surgical, nutrition, and gastroenterological societies in the UK and internationally, have highlighted the need for a prospective RCT to determine whether pre-operative EEN is beneficial in surgical outcomes for CD. (6, 22, 18, 46) The James Lind alliance also highlighted the importance of research into the role of diet and EEN in CD. (47) Surgery remains an important part of the management of CD, and if a relatively cheap intervention such as 6 weeks of EEN could reduce complications, and thus reduce resource utilisation and improve patient quality of life, this needs to be investigated. Our systematic review has highlighted that there is evidence from retrospective studies that EEN may be effective, and hence a large prospective RCT is now required to inform future care. During the development of this trial, a Patient and Public Involvement (PPI) group (consisting of 12 members) indicated that the use of EEN in the pre-operative period is something that patients are keen to see researched, in order to optimise post-operative outcomes and improve quality of life.

1.2.2 Justification for design

RCTs are the gold standard for the assessment of interventions in a clinical setting. We therefore plan to undertake a multicentre, two arm, parallel group, open label, pragmatic RCT to determine whether EEN is superior to usual diet. The trial includes a mixed methods internal pilot to assess recruitment, adherence to EEN and delays in surgery, and a full economic evaluation to assess cost-effectiveness.

1.2.3 Justification for choice of intervention(s)

Currently, optimisation of patients before surgery for CD involves drainage of any sepsis, weaning of steroids to the lowest possible dose and correction of any nutritional deficiencies. However, there is no agreed protocol for how to achieve steroid reduction and address malnutrition. EEN is an attractive intervention that may assist in both of these aims.

There is evidence that EEN may have a role in the surgical pathway for CD, and this now needs assessing against standard care.

Duration of intervention

Options considered for the duration of EEN within this trial were 4 weeks, 6 weeks or longer. (14) 6 weeks of EEN was chosen as European paediatric guidelines suggest 6 weeks is the shortest optimal duration for the induction of remission in paediatric populations. Studies on biochemical markers of disease activity, particularly gut inflammatory biomarkers, also support this time frame, with a

higher proportion of patients presenting with normal values after 6 weeks. (48, 49) We also discussed this at our patient panel meetings, and patients felt in their experience that 6 weeks was acceptable, with any longer being difficult. They also did not want a shorter duration in case the shorter intervention was ineffective. Our experience from clinical practice suggests that most patients who stop EEN due to poor tolerance will do so within the first few days. The aim is for OCEaN to provide a definitive assessment of EEN in the pre-operative context; as such we need to avoid any suggestion that EEN may not have been given for a long enough period to achieve its maximal potential benefit.

Type of EEN

We considered mandating the use of a particular type of liquid feed for this trial - for example Modulen IBD. However, data from our group shows that there is no benefit of one particular feed over another. (50) Therefore, in this pragmatic trial, we will allow each centre to use a feed of their choice to allow local dietitians to use the feed with which they are most familiar. If a patient does not like the taste of a particular feed, each site will choose their second- and third-line options in line with patient preference/centre experience and availability. This will significantly enhance the external validity of the trial, as well as facilitate deliverability across the National Health Service (NHS) if a positive benefit is seen for the intervention.

Provision of dietitian support

Dietitian input is crucial in instituting EEN and supporting patients and is recommended by national bodies. (6, 51) EEN does not need additional specialist dietitian training; hospital dietitians are trained in prescribing this therapy, but they may require some support. Therefore, senior research dietitians/nutritionists in the research team at the University of Glasgow (UoG), who are experienced in conducting similar multicentre studies, will be available to support local dietitians. (50, 52) Once a patient has been randomised, the Trial office will provide the local dietician with the Glasgow teams contact details. The Glasgow team will be available to support the local dietitians; answer any queries raised and provide advice with any aspects of the research protocol, if needed. In order to reduce the burden on local dietitians, we will provide an on-line patient support tool. Peer support will also be available through this website.

1.2.4 Justification of choice of primary outcome(s)

Dual primary outcomes at 6 weeks post-surgery have been selected, which assess the:

- Impact of Crohn's using the Crohn's Life Impact Questionnaire (CLIQ; a CD-specific patient reported outcome assessing quality of life (QoL))
- Post-surgery complications using the Comprehensive Complication Index (CCI)

The decision to have dual primary outcomes was informed by discussions with our patient panel, expert clinical input within the research team, and review of available measures and the literature. There was consensus amongst our patient panel that both recovery from surgery (which is significantly influenced by post-operative complications) and post-surgical disease-specific health-related QoL were key concerns for people with CD.

A systematic review found only 5 out of 44 patient reported outcome measures (PROMs) examined showed relevance, comprehensiveness and comprehensibility, and CLIQ was one of these five. (53) In addition, a panel of 27 experts looked at key performance indicators for surgery in CD (TP co-applicant). The CLIQ was the only PROM chosen as a key outcome measure for small bowel and ileocecal surgery. (54)

The second primary outcome chosen, after our patient panel discussion, is a measure of surgical complication rates. The CCI is based on the conventional Clavien-Dindo classification (CDC) which has been widely used in surgical research. (55, 56) The CCI is the mathematical summation of complications graded using the conventional CDC and takes into account the number and severity of each complication to obtain a value from 0 (no complications) to 100 (death). As all post-operative complications are included, it is more sensitive than other surgical morbidity endpoints. (57)

The time point at which the dual primary outcomes should be assessed was discussed extensively by the co-applicant group and with our patient panel. 6 weeks post-surgery was agreed, as patients often have their routine post-operative follow-up at this time, and they will have sufficiently recovered from surgery such that any difference between groups may be related to EEN rather than the surgery itself. Patients were also keen to measure the rate of recovery and we will capture this through repeated remote measurements of CLIQ at multiple time points.

2. AIMS AND OBJECTIVES

To determine if pre-operative EEN is more clinically and cost-effective compared with usual diet in patients undergoing surgery for CD.

2.1 Internal pilot objectives

The trial includes a 9-month internal pilot phase, which will inform any decision on the continuation of the trial to complete recruitment as planned. The aims of the internal pilot phase are to assess:

- Acceptance rate of eligible patients
- Number and rate of patients recruited
- Number of site openings
- Adherence to EEN diet
- Number of participants who experience delays in surgery
- Acceptability and participant experience of EEN assessed via qualitative research

Section 8.1 details the criteria that will determine continuation of the trial beyond the pilot.

2.2 Main trial objectives

2.2.1 Clinical aims and objectives

Primary Objective:

The primary clinical objectives are to determine whether pre-operative EEN in patients undergoing surgery for CD improves patient reported QoL and reduces post-operative complications at 6 weeks post-surgery.

Secondary Objectives (all related to index surgery):

Secondary objectives are to determine whether pre-operative EEN in patients undergoing surgery for CD:

- Improves QoL up to 24 weeks post-surgery
- Improves post-surgery recovery
- Reduces length of hospital stay
- Reduces length of bowel resected at surgery
- Reduces number of anastomoses formed at surgery
- Reduces need for stoma formation at surgery
- Reduces risk of anastomotic leak within 30 days of surgery
- Reduces hospital re-admission within 30 days of discharge
- Reduces need for re-operation within 30 days of surgery
- Reduces risk of enterocutaneous fistulae within 90 days of surgery
- Reduces risk of recurrence (clinical and endoscopic) in CD at 24 and 52 weeks after surgery
- Reduces steroid use at the time of surgery
- Is safe

The number of participants whose planned surgery did not proceed due to clinical improvement, and the number of participants who required expedited or emergency surgery will also be assessed.

2.2.2. Economic aims and objectives

The health economic evaluation will assess the cost-effectiveness of pre-operative EEN compared to standard care over a 12-month period for patients due to undergo elective surgery for CD. A prospectively planned economic evaluation will be conducted from an NHS and personal social services perspective, following an agreed Health Economics Analysis Plan (HEAP), and the methods will adhere to the recommendations of the NICE Reference Case. (58)

2.2.3 Qualitative aims and objectives

The internal pilot will include qualitative research to assess the acceptability and experience of EEN as a pre-surgical intervention.

2.2.4 Sub-Studies aims and objectives

Crohn's Optimisation And Surgical Timing (COAST)

This is an optional sub-study that is funded separately by Crohn's and Colitis UK. The aims of this sub-study are:

(i) To determine whether early or late surgery for terminal ileal CD results in improved QoL and is more cost-effective.

(ii) To assess whether surgery improves dietary intake, diet quality, dietary diversity and food related QoL, and whether pre surgical EEN impacts outcome QoL.

The participant will be given additional information about the sub study before providing consent.

3. TRIAL DESIGN AND SETTING

3.1 Trial design

The OCEaN trial is a multicentre, two arm, parallel group, open label, pragmatic RCT, with a mixed methods internal pilot (assessing both quantitative and qualitative data) and a full economic evaluation. Patients undergoing surgery for CD will be randomised to either 6 weeks of pre-operative EEN or usual diet (standard care).

3.2 Trial setting

40 UK-wide NHS hospitals including tertiary centres and District General Hospitals (DGHs).

Any hospital is eligible to take part. It is envisaged that each site will recruit a minimum of 6 patients/year. Each hospital needs to have a gastroenterology and surgical lead with support from their Trust IBD multidisciplinary team (MDT). This is an interface trial between gastroenterology and surgery. At each site, a consultant gastroenterologist and a consultant colorectal surgeon will work closely alongside each other to deliver the trial. The Principal Investigator (PI) at a given site can be either the consultant gastroenterologist, consultant colorectal surgeon or senior dietitian. We strongly encourage sites to participate in the National Institute for Health and Care Research (NIHR) Associate Principal Investigator (API) scheme.

Prior to opening, all sites must undergo trial-specific training, both on the logistical and operational aspects of the trial. trial-specific training can be provided to members of the research team by the PI or nominated delegates, such as the associate PI/lead trainee and/or lead research nurse. This will be captured on the OCEaN Site Signature and Delegation Log and OCEaN Training Log.

3.3 Sub-studies

There is one optional sub-study in the OCEaN trial.

The Crohn's Optimisation And Surgical Timing (COAST) sub-study will compare dietary habits pre-operatively, 6 weeks post-operatively and 52 weeks post-operatively, and focus on early and late surgery. The focus will be on food related QoL and variety of food consumed as assessed by the Food Frequency Questionnaire (European Prospective Investigation into Cancer and Nutrition (EPIC)) and the food-related quality of life (FR-QoL) questionnaire.

3.4 Assessment of risk

Participants in both arms of this trial will be undergoing elective surgery as part of their standard medical care. The trial intervention is purely nutritional, with the main risk relating to poor tolerance of the EEN. This could mean that some patients in the EEN arm may not meet their nutritional requirements. However, this risk will be mitigated by having close dietitian follow up and by not mandating a particular type of EEN to be used within the trial. Hospitals have more than one type of EEN available. Participants will be allowed to choose from the EEN available at each site until they can find one that they can tolerate. They can also use a variety of EEN supplements to minimise taste fatigue.

All clinical trials can be considered to involve an element of risk, and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures, this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation: No higher than the risk of standard medical care.

4. ELIGIBILITY

Adult patients aged 16 years and over, undergoing planned surgery for small bowel and/or colonic CD (primary or repeat surgery).

4.1 Inclusion criteria

- Any patient undergoing planned surgery for small bowel and/or colonic CD (primary or repeat surgery)
- Age ≥16 years
- Willingness to go on EEN for the duration of the intervention period (minimum of 6 weeks)
- Capacity to give informed consent

4.2 Exclusion criteria

- Surgery for peri-anal CD, ulcerative colitis, or inflammatory bowel disease unclassified (IBDU)
- Patients who require parenteral nutrition in the 6 weeks prior to surgery
- Inability to comply with the trial schedule and follow up

4.3 Co-enrolment

Co-enrolment into other trials will be considered by the Trial Management Group (TMG) on a case-by-case basis. Trials where co-enrolment is allowed will be listed in a co-enrolment log housed at the OCEaN Trial Office, and can be accessed upon request by the site staff. Should centres wish to co-enrol patients to OCEaN and another trial, and the trial is not listed in the co-enrolment log, this **must** be discussed and agreed with the TMG **prior** to enrolment into OCEaN, or if the patient is already participating in OCEaN, enrolment into the other trial.

5. CONSENT

It is the responsibility of the PI to obtain informed consent for each participant prior to performing any trial related procedures. This task can be delegated by the PI to other members of the local research team (e.g. consultants, registrars, research nurses), if local practice allows and this responsibility has been documented on the OCEaN Site Signature and Delegation Log. All those delegated to take consent must have undertaken Good Clinical Practice (GCP) training.

5.1 Consent procedure

The consent process can be undertaken remotely or face-to-face.

In both cases, a Participant Information Sheet (PIS; either in paper or electronic format) will be provided to facilitate the consent process (available from the OCEaN Trial Office). The PI or delegate will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial. They will also explain that participation is voluntary and that the potential participant is free to decide to take part and may withdraw from the trial at any time without affecting their care. The potential participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. The potential participant will also be given the opportunity to ask questions before the latest version of the Informed Consent Form (ICF) is completed. Paper copies of the PIS will be available from the Trial Office and will be printed or photocopied onto the headed paper of the local NHS Trust.

5.2 Consent documentation

Face to face consent

If the potential participant expresses an interest in participating in the trial, and has been confirmed as eligible to participate, they will be asked to electronically sign and date the latest version of the ICF which will be made available to all participating sites online. The PI or delegate will then also electronically sign and date the ICF via the trial system.

A copy of the signed ICF will be emailed to the participant or a hard copy provided, as per the participant's preference.

Remote consent – Method 1 (electronically)

Where the consultation is undertaken remotely, the potential participant will be asked to provide their e-mail address and the person taking consent will enter the e-mail onto the trial database for a unique electronic link to be sent to the participant for them to access the ICF and ask them to complete it electronically. Once the potential participant has completed the ICF, the person taking consent will electronically countersign the ICF.

Remote consent – Method 2 (verbally)

In cases where the potential participant does not have an e-mail address or access to the internet, they will be asked to provide consent verbally, after the person taking consent has read out each of the statements on the ICF to the potential participant in the presence of a witness. The witness will verify that informed consent has been taken; the witness does not need to be named on the Signature Site and Delegation Log. As the potential participant agrees with each statement, the person taking consent ticks the associated box of the electronic consent form. The ICF will then be electronically signed by both the person taking consent and the witness.

Both face to face and remote consent

For both face to face and remote consent, agreement (or not; to optional parts) to each section of the ICF will be inputted onto the trial database. The potential participant must give explicit consent for the regulatory authorities, members of the research team and/or representatives of the sponsor to be given direct access to the participant's medical records.

In addition, the participant understands and acknowledges that, a copy of the signed ICF will be transferred to the Trial Office for review.

Consent for the participant's preferred method of contact, i.e., e-mail address, mobile number, and/or postal address will be obtained in order to send participants either online links to complete the electronic questionnaires or hard paper copies depending on what is preferred by the participant.

Once the participant is entered into the trial, the participant's signed ICF will be stored in the site-specific section of the trial database. The participant's trial number will be linked to the consent form stored in the trial database. The participant's trial number will be entered on the copy of the ICF that is maintained in the Investigator Site File (ISF), and a copy will be filed in the participant's medical notes. Sites can download and print the completed ICF from the trial database.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to the participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be

made in the medical notes as to what time the consent was obtained and what time the procedures started.

5.3 Ongoing consent

At each visit, the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial, the participant will have the opportunity to ask questions about the trial.

Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participant's decision to continue, the participant will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

5.4 Additional consent

We will also add additional statements to the ICF for the participant to acknowledge that they understand that the Trial Office might in the future, for other related research, collect participant data available in NHS routine clinical datasets, including primary care data (e.g., Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS Digital and other central UK NHS bodies. The participant will acknowledge that they understand that the Trial Office might send their name, address, date of birth and NHS number to the relevant national registry, and then for the national registry to link this to their data and send the information back to the Trial Office. The acknowledgement by the participant will also allow access to other new central UK NHS databases that will appear in the future. This will allow us (subject to receipt of additional funding via another grant application) to assess longer-term impact and health service usage data without needing further contact with the trial participants.

5.5 Consent and recruitment- qualitative research

During the internal pilot phase, once the patient has been consented into the main trial the PI or delegate will give the participant a PIS regarding participating in the qualitative research. The PIS will outline the purpose of the qualitative study, and what taking part in the research will involve for them (e.g., interviews). They will be asked if they may be interested in participating in the qualitative study. If they express an interest in taking part, the qualitative research fellow will contact the participant to discuss the qualitative research in more detail, answer any questions and arrange a suitable time, date, and method (telephone, online, face-to-face) for the first interview. Participant contact details will be accessed via the Trial database, once the participant has given permission to be contacted by the qualitative research fellow.

Prior to commencement of the interview, verbal consent will be obtained by the qualitative researcher. The researcher will read each of the statements detailed on the ICF for the qualitative

study asking participants to confirm that they understand and provide consent. This consent process will be audio-recorded and the completed paper ICF for the qualitative study will be securely stored in locked filing cabinets in locked offices, which can only be accessed by qualitative researchers. There will be separate audio recording files for consent and the interview, both will be stored securely on UoB servers for 10 years.

Site staff involved in delivering the OCEaN trial will be emailed an invitation to participate in this qualitative research by the qualitative researcher, with a clinician focused PIS included in the email invitation. The consent process for site staff will mirror that described above.

5.6 Optional consent for COAST sub-study

Participation into COAST will be discussed with the patients, who are having surgery for terminal ileal CD, at time of consent for OCEaN, and participants will be given the opportunity to consent for the sub-study.

5.7 COVID 19 and trial process resilience

Participant contact throughout the informed consent process and beyond, has been designed to coincide with routine care via either face-to-face and/or remote assessments. Appointments will take place in person at the clinic, or by telephone or video call as per local practice where patient and/or public health circumstances dictate and according to local and national guidance on COVID-19.

6. IDENTIFICATION, SCREENING, ENROLMENT, RANDOMISATION and BLINDING

6.1 Identification

This trial sits at the interface between surgery and gastroenterology; engagement from both specialities at each site will be required for delivery of the trial. Local Research teams will involve surgeons, gastroenterologists, trainees, nurse specialists and dietitians. Embedding surgical and gastroenterological trainees within the site teams will maximise the ability to screen eligible patients. OCEaN is participating in the API scheme.

Patients undergoing planned surgery for small bowel and/or chronic CD will be identified and screened for eligibility from one of the following:

- **Colorectal, gastroenterology or IBD nurse specialist or Dietitian led clinics**

At routine outpatient clinics, potential participants will be identified and approached by a member of the local research team acting in their capacity as a member of the participant's direct care team.

- **IBD MDTs**

Potential participants seen by other surgeons and/or gastroenterologists at the Investigator site may be identified at these meetings, who can then be identified to the local research team.

- **Inpatients**

Patients that have been admitted for Crohn's flare-up or relapse will be identified and approached by a member of the local research team acting in their capacity as a member of the participant's direct care team.

- **IBD databases, review of IBD patient medical records and local IBD helpline records**

Existing patient records that are available to the local research team will be screened for potentially eligible participants using the inclusion/exclusion criteria.

Potential participants will then be contacted by the direct care team (via an invitation letter) to introduce the trial, ascertain interest and invite them to meet with a member of the local research team.

- **Surgical waiting lists**

Surgical waiting lists will be screened for potentially eligible participants that are undergoing planned surgery for small bowel and/or chronic CD using the inclusion/exclusion criteria.

Potential participants will then be contacted by the direct care team (via an invitation letter) to introduce the trial, ascertain interest and invite them to meet with a member of the local research team.

- **Social media via Twitter or Facebook and patient groups.**

Potential participants will be asked to contact the OCEaN Trial Office for further information. The Trial Office will direct the potential participant to the nearest site open for the trial or inform the potential participant how they can be referred to an open site.

The trial team will work with Crohn's disease related charities to advertise and raise awareness of the trial to their members, with the aim to cover as much of the target population as possible.

6.2 Screening and enrolment

Once identified, potentially eligible patients will be provided with a PIS and invited to attend an appointment at an outpatient or research clinic, either in person or remotely, where a member of the clinical team (surgeon or gastroenterologist) or a member of the research team (with the appropriate delegated duty) will discuss the trial with the potential participant and assess their willingness to take part in the OCEaN Trial. The potential participant will have the opportunity to ask questions and discuss the trial.

If the potential participant meets all the eligibility criteria and confirms that they are willing to take part in the OCEaN trial, they will be asked to formally consent to participate in the trial as described in the Consent section (see section 5). Eligibility must be confirmed by a suitably qualified medical practitioner who is delegated this task on the OCEaN Site Signature and Delegation Log.

Details of all patients approached about the trial will be recorded on the OCEaN Participant Screening/Enrolment Log. This will be stored electronically on the Trial database. Since screening will occur prior to the participants providing consent, they will be identified by their sex, year of birth and date of screening only on the screening log.

6.3 Randomisation process

Randomisation will be provided by BCTU using a secure online system (available at *<insert web address>*), thereby ensuring allocation concealment. Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the trial as detailed on the OCEaN Site Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access either system using another person's login details. The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

In the rare instance of the online system being unavailable, a telephone toll-free randomisation service ((0044) 0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays, government guided closures and University of Birmingham (UoB) closed days.

Please note: to randomise a patient when the online system is down sites should call the free phone number above. For all other general enquires about the OCEaN Trial the OCEaN Trial Office should be contacted directly via email or telephone using the contact details outlined on page 5 of the protocol.

6.4 Randomisation procedure

After eligibility has been confirmed and informed consent has been received, the participant can be randomised into the trial using the ***online*** system. A worksheet replicating the electronic Randomisation Form may be used to collate the necessary information prior to randomisation. All questions and data items on the online Randomisation Form must be answered prior to a potential participant being randomised into the trial and a Trial Number being issued.

Following randomisation, a confirmatory e-mail will be sent to the local PI, responsible clinician, randomising clinician, local research nurse, and local dietitian. The confirmatory email will also be sent to the OCEaN Trial mailbox.

The local research team should add the participant to the OCEaN Participant Recruitment and Identification Log which links participants with their Trial Number. The PI must maintain this document securely and it must not be submitted to the Trial Office. The OCEaN Participant Recruitment and Identification Log should be held in strict confidence.

6.5 Randomisation method

Participants will be randomised at the level of the individual in a 1:1 ratio to either pre-operative EEN or standard care via a central secure web-based randomisation system available 24 hours/day at the BCTU. A minimisation algorithm will be used within the randomisation system to ensure balance in the intervention allocations over the following variables:

- age (<50 or ≥50)
- previous CD surgery (Yes or No)
- Body Mass Index (BMI) (<20, 20-29.9 or ≥30kg/m^2)
- Current therapeutic oral steroid use (Yes or No)
- American Society of Anaesthesiologist grade (ASA 2 or ≥3)
- recruiting centre

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.6 Blinding

This trial is unblinded. It would not be possible to blind the participants in the intervention arm, as they need to take a diet that is made up exclusively of liquid feeds. Participants on EEN are also likely to speak of their experience to their clinician as they may need support with this diet, so the clinical team will also be aware of the randomisation group for each participant.

6.7 Informing the participant's GP and other parties

If the participant has agreed, the participant's General Practitioner (GP) will be notified that they are taking part in the OCEaN trial, using the trial specific GP Letter.

The trial specific GP Letter will be sent to the participant's GP directly from the site that randomised the patient into the trial.

7. TRIAL INTERVENTION

7.1 Trial intervention(s) and dosing schedule

Participants will be randomised to receive:

- A minimum of 6 weeks of EEN prior to surgery

  Participants will be invited to continue on EEN until they undergo surgery, even if surgery is delayed.
- Usual diet prior to surgery (standard of care)

7.2 Intervention: Pre-operative EEN

The intervention is a minimum of 6 weeks of EEN pre-operatively.

Following randomisation into the trial, participants will be reviewed by the local dietitian, and their feed will be prescribed. The type of EEN formula prescribed to each participant will be decided by dietitian preference and/or local availability. If participants cannot tolerate the first feed prescribed, an alternate EEN formula can be used, or participants can use a variety of EEN feeds to reduce taste fatigue. Feeds may be concentrated to reduce volume of feeds consumed. If tolerance remains poor, nasogastric feeding can be offered.

The start date of EEN will be agreed between the dietitian and the participant. EEN should ideally be started 6-8 weeks prior to the planned surgery date. The EEN prescription will provide participants with the daily energy requirements for their sex, accounting for an extra 10-20% for those who are undernourished (with a BMI <18.5 kg/m^2) and need to gain weight for nutritional rehabilitation. Energy requirements will be based on the Scientific Advisory Committee on Nutrition (SACN) Dietary Reference Values for Energy or as per local practice. (59)

An on-line support tool (FutureLearn Ltd), developed with our patient panel and Crohn's and Colitis UK, will provide information, peer support and assistance to participants randomised to EEN, which will also help facilitate adherence to an EEN diet. The UoG team will interact directly with the local dietitians at each hospital if any questions are raised or if advice is needed. Participants will otherwise be supported by their local dietitians according to local practice.

The OCEaN trial team have developed some EEN diet patient support sheets to help support patient on the liquid diet, as well as standardise the delivery of the EEN across the sites as much as possible.

EEN is often started by the hospital dietitian and then continued by either the hospital or provision is transferred to the community dietitians and/or the GP. This pathway is likely to vary between sites, and so will be directed by local practice and local resources.

Participants will continue on an EEN diet until they undergo surgery, even if surgery is delayed. However, our patient panel have advised that continuation of EEN beyond 12 weeks may be unrealistic, and so at this point, a discussion will be had with the participant, and they will be given the opportunity to continue on EEN or not.

7.3 Comparator: Standard care

Participants randomised to the standard of care arm will continue with their usual diet as per local practice until surgery. This may include interaction with a local dietitian who may provide the participant with oral nutritional supplements (ONS) as per standard local care. Use of ONS is recommended (at a maximum of 25% of energy requirements or 600kcals (whichever is lower)) for pre-operative optimisation of malnourished patients or those at risk of malnutrition (i.e., with unintentional weight loss). Previous research has shown that provision of ONS at 25% of energy requirements is unlikely to influence disease outcomes. (18, 60, 61) Participants in the standard of care arm may also follow a low residue diet, low Fodmap (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet or high protein, high carbohydrate diet as per local practice and patient requirements.

7.4 Interaction or contraindications

As EEN is a form of nutrition, there are no interactions or contraindications.

7.4.1 Permitted medication(s)/intervention(s) (including rescue medication)

Participants will continue on any other medication they may be receiving, including their IBD medication.

7.4.2 Concomitant medication(s)/intervention(s)

No changes to any concomitant medications are required.

7.4.3 Prohibited medication(s)/intervention(s)

No medications are prohibited.

7.4.4 Clinical deterioration during the trial

Should a participant develop symptoms of a flare of disease needing additional or incremental treatment (e.g., steroids or antibiotics) during the trial, they will be managed appropriately by their local team.

If a participant is admitted with progressive or recurrent symptoms prior to their date of elective surgery, such that they require expedited surgery, the participant will have surgery as needed, and then continue in the trial as per the trial protocol (e.g., complete follow-up assessments as planned).

If a participant has expedited surgery, due to progressive or recurrent symptoms as described above, and therefore has less than the 6 weeks of EEN, this is not considered to be a deviation from the protocol. Details of the expedited surgery and the duration of EEN will be captured on the trial specific CRFs.

7.5 Intervention modification or discontinuation

If a participant does not tolerate or does not like a certain type of EEN feed, different types of or a variety of EEN feeds can be offered to allow the participant to find one that they like and to reduce taste fatigue. The types of EEN feeds offered will be according to local prescribing practices and local availability. In addition, if tolerance to EEN remains a problem, nasogastric feeding can be offered.

7.6 Intervention supply and storage

7.6.1 Intervention supplies

EEN will initially be supplied by the hospital, additional prescriptions can be supplied by either the hospital or GP as per local practice.

7.6.2 Packaging and labelling

Not applicable.

7.6.3 Storage

EEN feed can be stored at home. Some EEN formulations (e.g. Modulen) require that the feed is kept in the fridge or freezer once it has been made up. Others do not need refrigeration (e.g., Fortisip, Ensure). Therefore, storage should be as per standard practice for the product used, and the participant will be advised of the storage requirements by their local dietitian.

7.6.4 Accountability

Local dietitians will oversee the start of EEN, and both inform the local research team and the trial office of the date that EEN will be/was started. They will choose an appropriate EEN depending on participant preference, and also facilitate changes to alternative liquid feeds if the participant does not tolerate a particular EEN. Accountability will be via the UoG team of dietitians who will telephone the participants at weeks 1-2 and weeks 5-6 after EEN initiation to assess dietary intake and compliance with EEN.

7.7 Adherence

We will estimate adherence to EEN (expressed as % of daily energy intake from EEN) and dietary intake, using 24-hour multiple pass recalls; firstly 7-14 days after EEN initiation, and then again 35-42 days after EEN initiation.

Since EEN is the least diverse dietary regime, and the aim is to estimate EEN adherence rather than actual nutrient intake, we propose that two days of diet recording will be adequate to achieve our objectives and will also minimise participation burden. A central dietitian/nutritionist from the UoG research team will contact participants in the EEN arm by phone or video call (as per the participant's preference) 7-14 days after EEN initiation, and then again at 35-42 days after EEN initiation. We will not inform the participant on which day they will be contacted by the central dietitian, in order to avoid the participant changing their dietary habits.

We will follow the instructions from the NIHR Diet, Anthropometry and Physical Activity (DAPA) measurement toolkit. Dietary records will be analysed using the dietary analysis software Nutritics. Intake of EEN will be expressed as a % of energy prescribed and as a % of actual total energy intake reported as received (EEN adherence). Average intake of macronutrients (e.g., carbohydrates, fibre, protein etc.) will be estimated and expressed as absolute intake in grams and as % of energy intake, and also as a % of the UK dietary reference values. Adherence to the prescribed volumes of EEN and adherence to the dietary restrictions of EEN will also be assessed using Likert scales that the participants will complete during the interview with the Glasgow researcher.

Participants' adherence to EEN will be rated by the central dietitian in Glasgow as low, average, good if <50%, 50-79% and ≥80% respectively, of the participant's total energy (%) intake comes from EEN. This measure of adherence forms part of the stop/go criteria in the internal pilot phase.

The presence/absence of gluten in faeces will be recorded separately, and the absence of gluten in the stool will be used to identify participants with 100% adherence to an EEN diet as the liquid feeds are gluten free, and this will be cross-checked against responses from the dietary assessment. The Glasgow dietitian will be unaware of the gluten results, and therefore unbiased of participants' response to EEN and study primary outcomes. They will also be independent to the local clinical team of the participants, which is expected to reduce bias from diet misreporting. Energy misreporting (e.g., under-reporting) will be assessed as a ratio of energy intake/basal metabolic rate (i.e., minimal requirements to sustain life). A ratio <1.2 will indicate energy under-reporting as we have described previously in the literature. (62)

8. OUTCOME MEASURES

8.1 Internal pilot outcomes

The success of the internal pilot phase will be based upon:

- Acceptance rates of eligible patients
- Number and rate of patients recruited
- Number of site openings

- Adherence to EEN diet
- Number of participants who experience delays in surgery
- Acceptability and participant experience of EEN assessed via qualitative research

In the internal pilot, we are aiming to recruit 100 participants (20% of the total sample size of the trial) from 20 sites. At the end of the internal pilot phase, the TMG and Trial Steering Committee (TSC) will review the pilot data against a set of pre-specified criteria (Table 2) and a traffic light system. In-depth data collected in the qualitative study on the acceptability and experience of EEN will also contribute to the discussions.

Table 2: Internal Pilot Progression criteria

Progression criteria for Pilot	Red *(stop)*	Amber *(modify)*	Green *(go)*
Acceptance rate (% eligible who agree to take part in the trial)	<44%	45-59%	≥60%
Trial recruitment (% of target for internal pilot; n=100)	<50% (i.e. <50 pts)	50-99% (i.e. 50-99 pts)	≥100% (i.e. ≥100 pts)
Recruitment rate/ site/ month*	<0.43/site/month	0.43-0.85/site/month	0.86/site/month
Number of sites opened	<10	10-15	15-20
% Participants adherent to enteral nutrition)**	<50%	50-79%	≥80%
% Participants with delay in surgery beyond 6 weeks	≥80%	41-79%	≤40%

***** Based on an average recruitment rate of 0.86 participants per site/month which takes into account staggered opening of sites during the pilot.

**A participant is defined as having good adherence to EEN if ≥80% of the participant's total energy intake comes from EEN.

The following actions will be taken:

- If all criteria are **GREEN (Go)**: progress to main trial; following the pilot phase we would still review trial processes to assess whether any changes could/need to be implemented to improve the trial.
- If any of the criteria are **AMBER (Modify):** review the trial processes to identify implementable changes. This may include recruiting additional centres and/or retraining centres in trial pathways and procedures. We would discuss with the TSC and funder about the need for a second internal pilot phase to verify resolution of issues, then if progress is satisfactory continue to the main trial.

- If any of the criteria are **RED (Stop)**: abandon the trial if the TSC and Funder feel this the appropriate course of action.

8.2 Main trial outcomes

8.2.1 Primary outcome(s)

Dual primary outcomes at 6 weeks post-surgery:

- Crohn's Life Impact Questionnaire (CLIQ; a CD-specific patient reported outcome assessing QoL)
- Post-surgery complications using the Comprehensive Complication Index (CCI)

If we demonstrate benefit for EEN on either of the primary outcomes this establishes effectiveness.

Crohn's Life Impact Questionnaire

CLIQ is a validated PROM developed using qualitative methodology. (63, 64) The measure was developed directly from interviews with patients with CD and was assessed with patients at every stage. It is purposely designed so that it is easy to complete by patients and is quick and easy to score by researchers/clinical staff. It consists of 27 'True/False' questions covering self-esteem, continence, and nutrition. This needs-based model of QoL score has the advantage over other IBD PROMs in that it was developed specifically in the UK by patients with CD. Our patient panel felt the questions in CLIQ were relevant to them, capturing both the physical and psychological elements of their symptoms, and they liked the binary nature of the responses. They felt that the CLIQ better reflected issues important to them and captured these better than other more general IBD questionnaires.

Comprehensive Complication Index

The CCI is based on the conventional CDC which has been widely used in surgical research. (55, 56) The CCI is the mathematical summation of complications graded using the conventional CDC and takes into account the number and severity of each complication to obtain a value from 0 (no complications) to 100 (death). As all post-operative complications are included it is more sensitive than other surgical morbidity endpoints. (57) There is an online tool available to calculate the CCI at CCI® Calculator (cci-calculator.com).

8.2.2. Secondary outcomes

8.2.2.1 Patient reported outcomes

- QoL over time using the CLIQ which will be collected post-surgery, fortnightly until 12 weeks post-surgery and then monthly up to 24 weeks post-surgery
- Post-surgery recovery using the Surgical Quality of Recovery-15 (QoR-15) on day 3 post-surgery (or pre-discharge if discharged before day 3). The QoR-15 is a short form version of the QoR-40 and consists of 15 items each with a numerical rating score of 0-10. The total

score therefore ranges from 0 to 150, with higher scores indicating better quality of recovery.

8.2.2.2 Clinical (all related to the index surgery)

- Length of post-operative hospital stay (measured in nights in hospital)
- Length of bowel resected (in centimetres measured along anti-mesenteric border) at time of surgery before being put in formalin
- Number of anastomoses formed at surgery as documented in the operation notes or from discussion with the operating surgeon
- Stoma formation either at index operation or within 30 days of surgery due to re-operation
- Anastomotic leak (either radiological concern or confirmed at reoperation) within 30 days of surgery
- Hospital re-admission within 30 days of date of discharge
- Re-operation within 30 days of surgery
- Enterocutaneous fistulae within 90 days of surgery. This is defined as any new fistula tract from any point in the gastrointestinal tract opening on to skin at any site from day of surgery to 90 days later. Enterocutaneous fistula diagnosis can be confirmed following clinical assessment. Radiological confirmation is not required.
- Clinical recurrence of CD at 24 and 52 weeks post-surgery as assessed by the Crohn's Disease Activity Index (CDAI) (65)
- Endoscopic disease recurrence assessed endoscopically on colonoscopy performed between 24 and 52 weeks post-surgery as part of standard of care. (66, 67) Modified Rutgeert's score should be used to grade the severity of recurrence. (67) If endoscopy is not performed but patient has cross sectional imaging (e.g. Magnetic resonance imaging (MRI), Computerised Tomography (CT) or ultrasound) as part of standard of care (routine assessments), the presence or absence of disease recurrence on imaging can be used as an alternative.
- Able to wean off steroids prior to surgery. Steroid usage and dosage (including prednisolone (oral), Budesonide (oral), Hydrocortisone (intravenous/oral) will be recorded at baseline and on day of surgery to determine change in use or dose. Inhaled or topical steroid use is not relevant to this trial.
- Safety assessed through adverse event and serious adverse event reporting

We will also record and report descriptively, without making formal comparisons:

- Number of participants whose planned surgery did not proceed due to clinical improvement. If planned surgery is cancelled by the local team because clinical improvement deems it no longer necessary, these participants will continue to follow the trial protocol (e.g., follow-up assessments etc).
- Number of participants who required expedited or emergency surgery. This refers to participants whose elective/planned CD surgery date is brought forward due to clinical deterioration.

8.2.2.3 Economic

- The EuroQoL-5D-5 Level (EQ-5D-5L) questionnaire and an incremental cost-utility analysis will determine the cost per quality-adjusted life year (QALY) gained over the 52 weeks post-surgery. The EQ-5D-5L will be collected pre-operatively, and then at 6 weeks post-operatively, and then also at 24 and 52 weeks post operatively.

8.2.2.4 Qualitative research

- Interviews will be undertaken with participants randomised to both trial groups, and also with staff involved in the trial. This research aims to provide in-depth qualitative data concerning the acceptability and experience of EEN as a pre-surgical intervention.

8.2.2.5 Exploratory outcome (microbiome)

- Change in the Harvey-Bradshaw Index (HBI) and CLIQ between baseline and pre-operatively to determine if EEN improves HBI and CLIQ. (68, 69)
- To determine if baseline microbiome compositional and metabolomic signatures, and changes after 6-weeks of EEN, can predict primary and secondary trial outcomes including post-surgical complications and likelihood of disease recurrence at follow-up. The samples are being collected as part of the main trial in order to measure faecal calprotectin. Further analysis will be performed and funded separately by UoG.

8.2.2.7 COAST Sub-study

COAST will analyse the subset of participants who are having surgery for terminal ileal CD to determine the impact of surgical timing on QoL and cost.

8.2.2.8 Microbiome analysis

As an exploratory trial outcome, we will study if baseline microbiome compositional and metabolomic signatures, and changes after 6-weeks of EEN, can predict primary and secondary trial outcomes including post-surgical complications and likelihood of disease recurrence at follow-up.

9. TRIAL PROCEDURES

The following should be performed at screening:

- Confirming eligibility

Once eligibility has been confirmed, the below should be performed:

- Taking valid informed consent
- Consent for the COAST sub-study (optional)

- Consent for the qualitative research (optional)
- Randomisation

The following information should be collected/completed at the baseline assessment (pre-randomisation):

- Participant contact details
- Participant demographics
- Smoking status
- Disease phenotype
- Crohn's medication review
- Medical history
- Surgical history
- Clinical history
- Results from recent routine blood tests (if available as part of local standard of care)
- Nutritional markers
- CLIQ
- EQ-5D-5L questionnaire
- CDAI
- Patient reported HBI
- Stool sample for faecal calprotectin analysis

Participants randomised to the intervention arm (EEN) will be referred to a dietitian. Participants randomised to the control arm will continue with their usual diet.

A stool collection kit will be dispensed by BCTU to all participants to measure faecal calprotectin and for those randomised to EEN, Gluten Immunogenic Peptide (GIP). For participants randomised to:

- EEN arm, the kit will be sent to the participant a week prior to their starting EEN.
- Usual diet arm, the kit will be sent within 0-10 days of being randomised

The following should be collected/completed following 5-6 weeks of EEN or usual diet:

- Stool sample for faecal calprotectin analysis
- Patient reported HBI

For participants allocated to EEN, the following should be collected/completed 1-2 weeks after start of EEN and then 5-6 weeks after start of EEN:

- Dietary Assessments

The following should be collected/completed at the pre-operative stage (on the day of surgery or within 7 days prior to surgery):

- Smoking status
- Crohn's medication review
- Results from recent routine blood tests (if available as part of local standard of care)
- CLIQ
- EQ-5D-5L questionnaire
- For those randomised to the intervention arm, information on the type and duration of EEN will be collected.

The following information should be collected during the participant's hospital stay for their index surgery:

- Surgery (length of bowel resected, number of bowel anastomosis, mode of surgery and any surgical complications)

The following should be completed on day 3 post-surgery (+/- 2 days; to allow for weekends) or date of discharge, depending on which comes first:

- QoR-15 questionnaire
- Discharge details

The following should be completed at 2 and 4 weeks from the date of the index surgery:

- CLIQ

The following should be completed at 6 weeks from the date of the index surgery:

- CCI
- CLIQ
- EQ-5D-5L questionnaire

The following should be completed at 8, 10, 12, 16 and 20 weeks from the date of the index surgery:

- CLIQ

The following should be completed/collected at 24 weeks from the date of the index surgery:

- CDAI (if patient is not seen in clinic as part of routine care for this to be assessed, the patient reported HBI to be completed as an alternative to the CDAI)
- Results from recent routine blood tests (if available as part of local standard of care)
- CLIQ
- EQ-5D-5L questionnaire
- Health resource use questionnaire

The following should be completed/collected at 52 weeks from the date of the index surgery:

- CDAI (if patient is not seen in clinic as part of routine care for this to be assessed, patient reported HBI to be completed as an alternative to CDAI)
- Colonoscopy (this should be carried out between 24 and 52 weeks post index surgery) if clinically appropriate. An MRI or ultrasound may also be conducted if a colonoscopy is not standard of care at the site.
- Results from recent routine blood tests (if available as part of local standard of care)
- CLIQ
- EQ-5D-5L questionnaire
- Health resource use questionnaire

9.1 Schedule of assessments

Table 3: Schedule of assessments

									Post-Surgery									
Visit	**Screening**	**Confirmed eligibility**	**Baseline**	**1-2 weeks of EEN**	**5-6 weeks of EEN/usual diet**	**Pre-operative**	**During hospital stay for index surgery**	**Day 3 post surgery (± 2 days) or date of discharge**	**2 weeks follow up (±3 days)**	**4 weeks follow up (±3 days)**	**6 weeks follow up (±7 days)**	**8 weeks follow up (±7 days)**	**10 weeks follow up (±7 days)**	**12 weeks follow up (±7 days)**	**16 weeks follow up (±7 days)**	**20 weeks follow up (±7 days)**	**24 weeks follow up (±4 weeks)**	**52 weeks follow up (±4 weeks)**
Eligibility check	x																	
Valid informed consent		x																
Randomisation		x																
Contact details[1]			x															
Height		x																
Weight		x	x		x	x											x	x
Crohn's medication review			x			x												
Smoking status			x			x												
Results from routine blood & stool tests[2]			x			x											x	x

									Post-Surgery									
Visit	**Screening**	**Confirmed eligibility**	**Baseline**	**1-2 weeks of EEN**	**5-6 weeks of EEN/usual diet**	**Pre-operative**	**During hospital stay for index surgery**	**Day 3 post surgery (± 2 days) or date of discharge**	**2 weeks follow up (±3 days)**	**4 weeks follow up (±3 days)**	**6 weeks follow up (±7 days)**	**8 weeks follow up (±7 days)**	**10 weeks follow up (±7 days)**	**12 weeks follow up (±7 days)**	**16 weeks follow up (±7 days)**	**20 weeks follow up (±7 days)**	**24 weeks follow up (±4 weeks)**	**52 weeks follow up (±4 weeks)**
Stool sample collection[3]			x[7]		x													
Patient demographics			x															
Disease phenotype			x															
Medical history			x															
Surgical history			x															
Clinical history			x															
Nutritional markers			x															
Surgery [4]							x											
Discharge details								x										
Patient reported HBI			x		x												[5](x)	[5](x)
CCI											x							

									Post-Surgery									
Visit	**Screening**	**Confirmed eligibility**	**Baseline**	**1-2 weeks of EEN**	**5-6 weeks of EEN/usual diet**	**Pre-operative**	**During hospital stay for index surgery**	**Day 3 post surgery (± 2 days) or date of discharge**	**2 weeks follow up (±3 days)**	**4 weeks follow up (±3 days)**	**6 weeks follow up (±7 days)**	**8 weeks follow up (±7 days)**	**10 weeks follow up (±7 days)**	**12 weeks follow up (±7 days)**	**16 weeks follow up (±7 days)**	**20 weeks follow up (±7 days)**	**24 weeks follow up (±4 weeks)**	**52 weeks follow up (±4 weeks)**
CLIQ			x			x			x	x	x	x	x	x	x	x	x	x
EQ-5D-5L			x			x					x						x	x
CDAI assessment			x														x	x
QoR-15								x										
Health resource use questionnaire																	x	x
Colonoscopy[6]																	x	
EEN arm patients only Dietary Assessments				x	x													
SAE review period				x														

NOTES

[1]**Contact details;** mobile number, email address, postal address

[2]**Routine blood tests;** haemoglobin, WCC, platelet count, CRP, eGFR, albumin (taken as part of standard care, if available)

[3]**Stool sample collection;** for faecal calprotectin analysis. Patients randomised to the intervention arm will have their stool sample tested for GIP.

[4]**Surgery;** length of bowel resected, number of bowel anastomosis, mode of surgery.

[5]**Patient reported HBI**; If CDAI not possible, HBI can be done instead.

[6]**Colonoscopy;** to be undertaken between 24 and 52 weeks post-surgery if clinically appropriate. Cross-sectional imaging (e.g. MRI, CT) or ultrasound can be used as an alternative when endoscopy is not suitable or cannot be performed.

[7]**Stool sample kits;** for patient randomised to the EEN arm stool kits will be sent a week prior to starting EEN. For those randomised to the usual diet arm the kit will be sent within 0-10 days of being randomised.

9.2 Trial treatment - intervention arm

Once a patient has been randomised to EEN, the Trial office will provide the local dietitians with the Glasgow teams contact details. The Glasgow team will interact directly with the local dietitian to support them and answer any queries raised and provide advice if required.

Participants randomised to the EEN arm will have a consultation with the local dietitian at the participating site. This consultation can be over the phone, via video or face to face as per the participant's preference. The local hospital dietitian will instruct the participant on the volume of feeds that they are required to consume in order to meet their individual nutritional requirements and will prescribe the EEN feed. The EEN prescription will provide participants with the daily energy requirements for their sex, accounting for an extra 10-20% for those who are undernourished (with a BMI <18.5 kg/m^2) and need to gain weight for nutritional rehabilitation. Energy requirements will be based on the SACN Dietary Reference Values for Energy or as per local practice. (59) The type of EEN used will be decided by local availability and/or dietitian preference. The participants will be told about the on-line support tool which provides further information on EEN and offers peer support.

Participants will be supported by local dietitians as per local standard practice. If participants cannot tolerate the first feed prescribed, an alternate liquid feed can be used, or feeds may be concentrated to reduce volume of feeds consumed. A combination of EEN feeds is allowed to reduce risk of taste fatigue and increase EEN tolerance. If tolerance remains problematic nasogastric feeding may be offered.

Participants will receive contact from the Glasgow dietitians at 7-14 days and again 35-42 days after initiation of EEN. At each contact, the dietitian will record the percentage of energy intake from EEN feeds participants report consuming, their reported tolerance (Scale 1-5 of poor – well) and any reported side effects of treatment. (70) Two 24-hour recalls of all diet will also be undertaken by Glasgow dietetics team at these contacts (weeks 1-2 and weeks 5-6).

9.3 Delayed surgery

If a participant's surgery is delayed, they will continue on their randomised treatment until surgery occurs. Thus, participants will continue on an EEN diet until they undergo surgery, even if surgery is delayed. However, our patient panel have advised that continuation of EEN beyond 12 weeks may be unrealistic, and so at this point a discussion will be had with the participant, and they will be given the opportunity to decide whether to continue on EEN or not.

9.4 Expedited surgery

If a participant is admitted with progressive or recurrent symptoms prior to the date of elective surgery, such that they require expedited surgery, the participant will have surgery as needed, and then continue in the trial as per the trial protocol (e.g., complete follow-up assessments as planned).

9.5 Pregnancy in the trial

As EEN is a different form of food, there are no known safety concerns for pregnant women or foetuses. Participants that become pregnant during the course of the trial will be assessed and their need for surgery will be at the discretion of the treating clinical team.

9.6 Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits. Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a *particular a*spect of the trial.

Participants found to be ineligible post randomisation should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation.

The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected and used in the trial analysis).

No trial related follow-up: The participant does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No further data collection: The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).

Sub-study withdrawal: The participant wishes to withdraw specifically, from the sub-study (COAST).

Qualitative research withdrawal: The participant wishes to withdraw specifically from the qualitative research part of the trial.

The details of changes of levels in participation within trial (date, reason and category of status change) should be clearly documented in the source documents.

10. ADVERSE EVENT REPORTING

10.1 Definitions

Table 4: Definitions for Adverse Events

Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	RE	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Consists of a congenital anomaly/ birth defect Or is otherwise considered medically significant by the Investigator**
Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

Table 5: Definitions of severity for Adverse Events

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities (including life threatening events and fatality).

10.2 Adverse event recording – general

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the principles of GCP as set out in the UK Policy framework for Health and Social Care Research and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed in the table of definitions in section 10.1, Table 4.

It is routine practice to record AEs in the participant's medical notes, and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

10.3 Adverse event reporting in OCEaN

The reporting period for AEs in OCEaN will be:

- For EEN-related AEs: From the start of EEN until the day of surgery for participants that are randomised to EEN.
- For surgery-related AEs: From the day of surgery until 30 days post-surgery for all participants

The overall defined reporting period will end 30 days post-surgery. After the participant has reached 30 days post-surgery, sites will not be actively following up participants for serious adverse events (SAEs).

Participants randomised to EEN

All participants who are randomised to EEN, should ideally have surgery 6 weeks after starting EEN. If surgery is delayed, the participant will continue on EEN until they reach 12 weeks, at this point a discussion will be had with the participants, and they will be given the opportunity to continue on EEN or not. (See Delayed Surgery, Section 9.3)

Safety of EEN is well established in paediatric and adult clinical practice. The severity and causality of all AEs should be recorded in the participants medical notes (source data), a strategy of targeted reporting of AEs will not affect the safety of participants. We will only collect specific AEs and side effects that have a high probability of being related to an EEN diet (as detailed below) and these will be recorded on trial specific Case Report Forms (CRFs):

- Severe weight loss requiring admission to hospital (greater than 10% of body mass)
- Loose stools/diarrhoea
- Abdominal cramps
- Nausea
- Hunger
- Bloating/wind
- Headaches/irritability

All participants

As part of the OCEaN trial, we will also be collecting surgical complications (as detailed below), these will be collected for the trial related Crohn's surgery (the index surgery), and will be recorded on trial specific CRFs:

- Wound infection
- Anastomotic leak
- Bleeding +/- requirement of blood products
- Venothrombo-embolism
- Hospital acquired infection e.g. pneumonia, catheter related urinary tract infection

10.4 Serious Adverse Advents (SAE) reporting in OCEaN

For all SAEs, the PI or delegate must do one of the following:

1. **Record safety reporting-exempt SAEs** in the medical notes but **not report** them to the trials office on an SAE form as per Section 10.4.1 Serious Adverse Events not requiring reporting to the Trial Office.

2. **Report SAEs to the trial office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 10.4.2 Serious Adverse Events requiring non-expedited reporting to the trial office.

3. **Report SAEs to the trial office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above 2 categories must be reported as per Section 10.5 SAE Reporting process.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the

hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

10.4.1 Serious Adverse Events not requiring reporting to the Trial Office

At whatever time they occur during an individual's participation, the following are not considered to be critical to evaluations of the safety of the trial:

- Pre-planned hospitalisation
- SAEs related to a pre-existing condition

All events which meet the definition of serious must be recorded in the participant medical notes, including the causality and severity, throughout the participant's time in the trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

10.4.2 Serious Adverse Events requiring non-expedited reporting to the trial office

Where the safety profile is well established, the causal relationship between the intervention (or the participant's underlying condition or surgery), and the SAE, may be known. That is, such events are protocol-defined as "expected" (see Section 10.5.2 Assessment of expectedness of an SAE by the CI).

Such events should still be recorded by the local research team in the participant's medical notes and on the relevant CRFs, but do not require expedited reporting on an SAE form (immediately on the site becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined.

These include:

- Hospital admissions lasting less than 24 hours (to be reported on trial-specific follow-up CRF)
- Surgical complications (to be reported on the surgery CRF)
- SAEs that are related to symptoms or progression of CD

10.4.3 Serious Adverse Events requiring expedited reporting to the trial office

All SAEs **not** listed in Sections 10.4.1 and 10.4.2, and the following SAEs must be reported to the Trial Office on a trial specific SAE form within 24 hours of the site research team becoming aware of the event.

- Death

Any other SAEs that are related and unexpected would require expedited reporting to the trial office.

10.5 SAE Reporting process

On becoming aware that a participant has experienced an SAE which requires reporting on an SAE form, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the Trial Office.

To report an SAE to the Trial Office, the PI or delegate must complete, date and sign the SAE form via the OCEaN trial system using the information below in the timeline specified in sections 10.4.2 and 10.4.3. Any other relevant, appropriately anonymised, data should be submitted to the OCEaN Trial Office using the OCEaN Trial Mailbox (OCEaN@trials.bham.ac.uk).

To report an SAE, the PI or delegate should:

Complete, date and sign the SAE form via the OCEaN trial system

Email OCEaN@trials.bham.ac.uk to make the OCEAN Trial Office aware that an SAE has been submitted, along with any other relevant anonymised documentation.

Where an SAE Form has been completed by someone other than the PI (or medically qualified delegate) initially, the original SAE form must be countersigned by the PI (or medically qualified delegate) to confirm agreement with the causality and severity assessments.

On submission of an SAE form, a unique reference number will be assigned. The site and the OCEaN Trial office should ensure that the SAE reference number is quoted on all correspondence. The site should also e-mail the trial mailbox to inform the OCEaN Trial office that they have submitted an SAE.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE reference number within 1 working day of reporting, the site should contact the OCEaN Trial Office.

Copies of the completed SAE form should be printed on resolution of the SAE and filed in the ISF.

10.5.1 Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see Table 6**:** Categories of causality) of the event.

In defining the causality, the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per Table 6**:** Categories of causality, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the trial office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the trials office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Table 6: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE Form, the Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) or delegate who will independently* review the causality of the SAE. An SAE judged by the PI or CI or delegate to have a reasonable causal relationship ("Related" as per Table 6**:** Categories of causality) with the intervention will be regarded as a related SAE. The severity and causality assessment given by the PI will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI, an independent clinical causality review will be performed.

10.5.2 Assessment of expectedness of an SAE by the CI

The CI or delegate will also assess all related SAEs for expectedness with reference to the criteria in Table 7**:** Categories of expectedness.

Table 7: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

If the event is unexpected (i.e., it is not defined in the protocol as an expected event) it will be classified as a related and unexpected SAE.

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

10.5.3 Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted to the Trial Office and the original kept in the ISF.

10.6 Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The Trial Office will submit a progress report to the Research Ethics Committee (REC) and UoB Research Governance Team (RGT) annually starting 12 months after the date of the favourable opinion was given. An electronic copy should be emailed to the REC within 30 days of the end of the reporting period.

The Trial Office will report all events categorised as Unexpected and Related SAEs to the REC and UoB RGT within 15 days of being notified.

Details of all Unexpected and Related SAEs, and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

10.7 Urgent Safety Measures

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the reason why they have been taken.

10.8 Follow-up of pregnancy outcomes

There is no data to suggest any impact of EEN on pregnancy or pregnancy outcomes. However, any participants that become pregnant from date of randomisation until 30 days after the last day of exclusive elemental feeding will be followed up to outcome of the pregnancy. The outcome of these pregnancies will be recorded via the pregnancy notification form and in the event of congenital anomalies or birth defects these should be reported as an SAE.

11. DATA HANDLING AND RECORD KEEPING

11.1 Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

Typically, the data provided on all CRFs should routinely be recorded in the participant's medical notes, when this is not being conducted then data collected for the purpose of OCEaN can be recorded on the paper CRFs. Data should then be transcribed to the Trial database and the data on paper will be considered the source data and should subsequently be filed in the ISF.

Some data variables may be entered directly onto the CRF, these are clearly identified and detailed below in Table 8: Source data in OCEaN.

Table 8: Source data in OCEaN

Data	Source
Participant Reported Outcomes	The original record of questionnaire completion is the source data. Questionnaires can be completed by participants electronically or on paper. If completed electronically the electronic record will be the source data, held on BCTU servers as part of the electronically-enabled questionnaire completion. If completed on paper, the paper record will be the source data and will be entered onto the trial database.
Lab results	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice. Information will be transcribed onto CRFs.
Imaging	The source is the original imaging usually as an electronic file. Data may be supplied to the Trials Office as a password-protected, anonymised, copy of the electronic file, or as an interpretation of the imaging provided on a CRF. Where data is interpreted, the CRF onto which it is transcribed becomes the source. Copy of the CRF should be provided to the trial office.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
Health economics data	Data will be completed directly on to the CRF via interview with the participant and this will constitute the source data. Often obtained by interview directly with the participant for transcription onto the CRF. The CRF is source data.
Dietary data	Data will be completed directly onto the CRF following a call with the participant by the Glasgow team and this will constitute the source data.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source documents.

11.2 Case Report Form (CRF) completion

For the OCEaN trial, CRFs will be an electronic record completed at site, for each individual participant, only by those at site delegated the task of doing so.

The CRFs will include (but will NOT be limited to) the following Forms (see Table 9: Case report forms in OCEaN).

Table 9: Case report forms in OCEaN

Form Name	Schedule for submission
Screening Log	When a participant is being considered for approach to participate in the OCEaN Trial.
Informed Consent	Prior to randomisation
Randomisation Form	At the point of randomisation
Baseline Data Form	As soon as possible after consent
Patient Contact Form	As soon as possible after consent
Research dietitian/ nutritionist Follow-up (Day 7-14 and 35-42)	As soon as possible after assessment
EEN Assessment Form	Completed post EEN diet
Usual Diet Assessment Form	Completed post usual diet
Pre-operative Form	Completed on the day of surgery or up to 7 days prior
Index Surgery Form	Completed during hospital stay for index surgery
Quality of Recovery-15 Questionnaire	Day 3 post surgery (+/- 2 days) or date of discharge, whichever comes first.
Follow-up CRFs including participant reported outcome measures	As soon as possible after each follow-up assessment time point
Serious Adverse Event Form	If expedited: within 24 hours of site research team becoming aware of event If non-expedited: in accordance with section 10.
Pregnancy Notification Form	As soon as possible after becoming aware of participant's pregnancy
Pregnancy Outcome Form	As soon as possible after outcome of pregnancy and/or birth of the child
Trial Exit/Change of status CRF	At the point of becoming aware of withdrawal/change of status or death

In all cases, it remains the responsibility of the PI to ensure that the electronic CRF (eCRF) has been completed correctly and that the data is accurate. This will be evidenced by the electronic signature

of the PI, or delegate(s). The Site Signature & Delegation Log will identify all those personnel with responsibilities for data collection. The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the eCRF.

Data reported on each eCRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to the OCEaN trial specific working instructions on CRF completion.

The following guidance applies to data and partial data:

- Time format – all times should be in accordance with the 24hr clock
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office
- Repeat tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

The eCRFs will be considered “complete” once all data fields have been either completed unambiguously or it has been made explicit that the data is unobtainable.

11.3 Participant completed questionnaires

A list of all participant completed forms can be found in Table 10.

Table 10: A list of participant completed questionnaires

Name of questionnaires
EQ-5D-5L
Quality of Recovery-15 questionnaire
CLIQ questionnaire
Health Resource Usage questionnaire
EPIC FFQ (COAST Sub-study only)

FR-QOL (COAST Sub-study only)
Harvey Bradshaw Index questionnaire

Participant completed questionnaires can be completed online or on paper. Questionnaires should generally be completed by the participant alone, however physical assistance in completing the form can be given by the research staff or the participant's friends and relatives where appropriate. In such circumstances, questions are to be read to the participant verbatim and responses must not be led by the person assisting with the form completion. This requirement must be made clear when the participant's friends and relatives are providing the assistance. Participants should be encouraged to respond to all questions but can refuse to answer any, or all, of the questions should they wish to by selecting 'Prefer not to answer'.

11.4 Data management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan (DMP) and include the processes of data entry and data queries on trial data.

Data entry will be completed by the site staff via a bespoke BCTU Trial database. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis.

11.5 Self-evident corrections

No self-evident corrections will be permitted.

11.6 Data security

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

- **Physical security measures:** restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- **Logical measures for access control and privilege management:** including restricted accessibility, access controlled servers, separate controls of non-identifiable data.
- **Network security measures:** including site firewalls, antivirus software and separate secure network protected hosting.

- **System management:** the system will be developed by the Programming Team at the Trial Office and will be implemented and maintained by the Programming Team.
- **System design:** the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- **Operational processes:** the data will be processed and stored within BCTU.
- **System audit:** The system will benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessment
- **Data Protection Registration:** UoB's Data Protection Registration number is Z6195856.

Data that will be shared with University of Glasgow will be stored on the University of Glasgow secure servers which are backed by commercial digital storage which is audited on a twice-yearly basis for compliance with the ISO27001 Information Security Management standard.

All COAST anonymised data will be stored at King's College London on secure servers following the research data management policy and procedures.

11.7 Qualitative research data management and security

Interviews will be recorded using UoB approved Zoom/Teams accounts with the consent of participants and transcribed clean verbatim for analysis. Transcripts will be produced by a UoB approved professional transcription company. A confidentiality agreement is in place between the transcription service provider and UoB to ensure data is handled securely. Audio files of interviews and transcripts will be uploaded to an encrypted, secure cloud server. Only members of the qualitative research team and the assigned transcriber will have access to the transcripts stored on the cloud. Once the files have been received by a member of the qualitative research team or the transcriber, they will be deleted from the cloud server. Analysis will be conducted with reference to recordings, transcripts and field notes taken at the time of the interviews. Paper consent forms will be stored securely in locked filing cabinets in locked offices, which can only be accessed by qualitative researchers. The audio records of verbal consent and assent will be saved on an encrypted UoB IT server. The qualitative research data will be stored as per the guidelines in the Data Security section (section 11.6).

11.8 Archiving

All records created by following trial procedures and all documents listed in guidance relating to the conduct of the trial must be retained and archived for the specified period.

The TMF is normally composed of a sponsor file, held by the sponsor organisation, and an ISF, held by the site investigator. Documents are archived following regulatory requirements and local procedures.

Retained data should still be accurate, accessible and stored securely and confidentially.

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g., signed ICFs, ISFs, participants' hospital notes, copies of CRFs) at their site are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 10 years. Audio recordings for the qualitative research interviews will also be stored securely and confidentially at UoB for at least 10 years. BCTU has standard processes for both hard copy and computer database legacy archiving. No documents will be destroyed without prior approval from the OCEaN Trial Office.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Site set-up and initiation

All PIs will be asked to sign the necessary agreements including an OCEaN Site Signature and Delegation log between the PI and the Trial Office and supply a current CV and GCP certificate. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of site initiation, either a meeting or a tele/video conference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial. The PI or delegate is required to keep the ISF up to date throughout the trial.

12.2 Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

12.2.1 On-site monitoring

All sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the OCEaN trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff. Any issues noted will be followed up to resolution.

12.2.2 Central monitoring

The Trial Office will check received ICFs and eCRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the DMP. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

12.3 Audit and inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

12.4 Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial. Sites are therefore requested to notify the OCEaN Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the OCEaN Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

13. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the REC within 15 days of the end of trial. The Trial Office will provide the REC and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

14. STATISTICAL CONSIDERATIONS

14.1 Sample size

The trial has dual primary outcomes: the CLIQ and CCI. Sample sizes have been based on 90% power with a two-sided alpha of 0.025 to account for the trial having dual primary outcomes. This means

that if we demonstrate benefit for EEN on either of the primary outcomes this establishes effectiveness.

The CLIQ score ranges from 0 to 27, with higher scores indicating worse QoL. There is limited data on its use in practice, and no published data on the minimum clinically important difference (MCID). In the absence of an MCID, the sample size estimation for CLIQ has been based on an effect size. To detect an effect size of 0.3 (considered a moderate effect size) between groups in the CLIQ score with 90% power (two-sided at 2.5% level) requires 556 participants (278 per arm). In the 2015 development and evaluation paper by Wilburn et al. they reported a mean CLIQ score of 12 (standard deviation (SD)=6.8) and median score of 12 (IQR: 7 to 17) in 248 people with CD. (63 An effect size of 0.3 (with SD=6.8) would translate to a 2 point difference in the CLIQ (17% relative difference).

Data from the team who developed the CLIQ shows that there is a clear difference in CLIQ scores in patients who consider their disease to be mild vs moderate – see Table 11. (63 The data in Table 11 are not effect sizes, but it does indicate how changes in CLIQ scores have a real impact on patient perception of their disease and their overall wellbeing.

Table 11: CLIQ scores

Patients perception of their disease	*Mean CLIQ score (SD)*
Mild	8.6 (5.8)
Moderate	14 (6.3)
Quite Severe	17.8 (4.3)
Very Severe	21.7 (2.7)
Overall wellbeing	
Very Good	5.3 (4.2)
Good	8.5 (5.2)
Fair	14.5 (5.4)
Poor	20 (3.7)

The CCI score ranges from 0 (no burden from complications) to 100 (death). There is no published MCID for the CCI, but a difference of 10 points for the CCI reflects a 1-grade difference in the established CDC, which our group considered clinically meaningful. (71) Data on the CCI is variable across studies, with the mean ranging from 5.8 (SD=11.7; gastric cancer surgery) to 40.3 (SD=32.6; Hartmann's colonic resection), and SDs ranging from 11.7 (gastric cancer surgery) to 33.1 (colonic resection first surgery). (57, 71, 73) To provide a conservative estimate for the sample size, we have used the largest SD of 33.1 (which was following colonic resection). (72) To detect a 10-point difference in the CCI score (with SD=33.1; effect size 0.302) with 90% power (two-sided at 2.5% level) requires 548 participants (274 per arm).

The sample size for the CLIQ is slightly larger, thus the required sample size for the trial is 556 participants. Allowing for a 10% attrition rate, the sample size increases to 618 participants (309 per arm).

14.2 Analysis of outcomes

A separate Statistical Analysis Plan (SAP) will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below.

The primary comparison groups will be composed of those randomised to pre-operative EEN versus those randomised to usual diet (standard of care). The primary analyses will be based on a modified intention to treat population, which includes only those who have had their CD surgery, and these participants will be analysed in the intervention group to which they were randomised irrespective of adherence to randomised intervention or protocol deviations. For all outcomes, appropriate summary statistics and differences between groups e.g., mean differences, relative risks, absolute differences, will be presented, along with confidence intervals. Where possible intervention effects will be adjusted for the minimisation variables listed in Section 6, and baseline values (where appropriate and available).

14.2.1 Primary outcome(s)

The dual primary outcome measures will be analysed separately using a mixed effects linear regression model (centre included as a random effect) to estimate the adjusted mean difference between groups at 6 weeks post-surgery, along with the corresponding 97.5% confidence interval and two-sided p-value. To account for the dual primary outcomes, $p<0.025$ will be used to determine statistical significance. If we demonstrate benefit for EEN on either of the primary outcomes this establishes effectiveness of the intervention.

14.2.2 Secondary outcomes

Differences between groups for the secondary outcomes will be presented alongside 99% confidence intervals. Continuous secondary outcome measures (e.g., QoR-15, length of bowel resected) will be analysed as per the primary outcome using mixed effects linear regression models. The CLIQ is being collected at multiple time points up to 24 weeks post-surgery, and so will also be analysed using a mixed effected repeated measures analysis. Binary secondary outcomes (e.g., anastomotic leak, recurrence) will be analysed using mixed effects log-binomial regression models to estimate the adjusted relative risk. The adjusted absolute risk difference between groups will also be reported.

14.2.3 Planned subgroup analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see Section 6.5 – Randomisation method) and performed on the dual primary outcomes only. The effects of these subgroups will be examined by including an intervention group by subgroup

interaction parameter in the regression model, which will be presented alongside the effect estimate and 97.5% confidence interval within subgroups. The results of these pre-specified subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.2.4 Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all trial participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. Full details will be included in the SAP, but in brief, this will include multiple imputation methods.

Further sensitivity analysis will include complier average causal effect (CACE) and per-protocol analyses to assess the effect of adherence/non-adherence. These analyses will be limited to the dual primary outcomes.

14.3 Planned final analyses

The primary analysis for the trial will occur once all participants have completed the 52 week follow-up planned for the trial, and the corresponding outcome data has been entered onto the trial database and validated as being ready for analysis.

15. HEALTH ECONOMICS

A separate HEAP will be produced and will provide a more comprehensive description of the planned analyses. A brief outline of these analyses is given below.

15.1 Aims and objectives

The health economic evaluation will aim to assess the cost-effectiveness of pre-operative EEN compared to no EEN over a 12-month period for patients due to undergo major surgery for CD. A prospectively planned economic evaluation will be conducted from an NHS and personal social services perspective, following an agreed HEAP, and the methods will adhere to the recommendations of the NICE Reference Case.

15.2 Resource use and costs

Resource use information will consider healthcare contacts, medication and medical investigations/intervention, and this will be obtained mainly from patient-completed questionnaires. In order to value resource use data, unit costs from standard sources such as the British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) publication on costs and NHS reference costs will be obtained. Total healthcare costs will be calculated by multiplying the resource items by the respective unit cost and summing over all resource use items.

15.3 Health Outcomes

The EQ-5D-5L questionnaire will be used to obtain health related QoL data from patients and QALYs estimated for each trial participant, using the area under the curve method. Imbalances in baseline utility (EQ-5D-5L) scores between the two trial arms will be controlled for by using a regression approach. In line with NICE recommendations, responses to the EQ-5D-5L questionnaire will be mapped onto the 3-level version. Following best practice, missingness mechanisms in cost and outcomes will be explored, and multiple imputation methods will be used where appropriate.

15.4 Data analysis

A within-trial analysis will be conducted following best practices. Initially, a cost-consequences analysis will be conducted to describe important costs and outcomes. Subsequently, a cost-utility analysis with the QALY as the primary outcome will be conducted. Differences in mean costs and QALYs between pre-operative EEN and no EEN will be estimated and Incremental cost effectiveness ratios (ICERs) estimated by dividing the difference in mean cost between the trial arms by the difference in mean QALYs.

Non-parametric bootstrapping will be used to illustrate and quantify uncertainty. This will be achieved through a Monte Carlo method involving the simulation of 1000 replications of the ICERs from a joint distribution of incremental costs and incremental QALY. To determine the probability of pre-operative EEN being cost-effective, cost-effectiveness acceptability curves will be constructed to show the probability that pre-operative EEN is cost-effective, relative to no EEN, across a range of values that represent a decision makers' willingness-to-pay for an additional QALY.

The base-case analysis will be from an NHS perspective with a sensitivity analysis considering wider societal costs. Although not anticipated to be necessary, more extensive economic modelling using analytic decision methods may be considered in order to extend the time horizon and decision context if costs and QALY profiles are non-convergent. Such modelling will draw upon the best available information from the literature and stakeholder consultations to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. Longer-term costs and QALYs will be discounted to present values using the 3.5% discount rates recommended for health technology appraisal in the UK.

16. QUALITATIVE RESEARCH

We will conduct qualitative research within the pilot phase of the OCEaN trial, with both trial participants and staff to assess the feasibility and acceptability of the trial and the intervention(s) and to inform the main trial. With the participants' consent, we will interview (semi-structured interviews) a sample of participants in each arm of the trial and trial staff. The main aim of this qualitative research is to provide in-depth qualitative data concerning the acceptability and experience of EEN as a pre-surgical intervention. These data will also provide in-depth understanding of the comparative experience of the pre- and post-operative periods for patients that receive EEN,

and those who do not. We will interview patient participants at two time points. Initial interviews will take place between one and two weeks prior to the planned date of surgery. We will explore participant's experience of EEN, the trial recruitment process, and the immediate pre-operative period. Follow up interviews at approximately 12 weeks post-surgery will collect further data pertaining to participants' post-surgical experience and further views regarding the EEN intervention and the trial. Discussions with the patient panel highlighted the post-surgical recovery period and their experience of it as a key concern. We will also conduct interviews with staff at sites recruiting during the pilot phase to provide data pertaining to the clinical acceptability of EEN and to reflect on trial processes.

It is likely that the majority of interviews will take place remotely (e.g. telephone/video call), but we will explore the possibility face-to-face interviews where logistics (geography, COVID-19) allow. Data collection will proceed iteratively until the research team judge that the data and sample have sufficient depth and breath. Experience from previous studies indicates that a sample of approximately 25-30 trial participants is sufficient to achieve this. We will aim to recruit a similar number of site staff.

16.1 Ethics

Within the participant research interviews, there is the potential for participants to introduce and discuss potentially emotional or distressing elements of their experience. The qualitative researchers will be mindful of this and follow predefined steps for checking that participants are happy and able to continue with the interview, without causing undue distress to research participants whilst ensuring that interviews are not intrusive. The nonclinical status of the qualitative researchers will be clearly communicated to interview participants, so that expectations about clinical knowledge and information giving can be appropriately managed.

16.2 Data analysis

Interviews will be recorded with the consent of the trial and site staff participants and transcribed clean verbatim for analysis. Analysis will be conducted with reference to recordings, transcripts and field notes taken at the time of data collection. A thematic analysis of content will be informed by the framework analytic approach (74). Following initial familiarisations with the interview data, development of thematic frameworks and data coding will proceed in an iterative manner. Framework matrices will facilitate comparative analysis, for example between the qualitative data from EEN and comparator groups.

17. SUB-STUDY

17.1 COAST Sub-study

Crohn's Optimisation And Surgical Timing (COAST) will focus on outcomes related to early and late surgery and dietary aspects in terms of nutrient intake, dietary habits and food related quality of life.

17.1.1 Objectives

17.1.1.1 Early or late surgery

To determine whether early or late surgery for terminal ileal Crohn's disease results in improved QoL and is more cost-effective to determine the optimal time for surgery.

17.1.1.2 Objectives - Nutrition

To assess whether surgery improves dietary intake, diet quality, dietary diversity and food related QoL in a cohort of patients with CD.

17.1.2 Study design

Patients recruited to the OCEaN RCT will be eligible for the embedded COAST study.

17.1.3 Outcomes – Early or late surgery

In COAST, an analysis of a subset of participants from OCEaN with terminal ileal disease will be carried out to determine the impact of surgical timing on quality of life and cost.

- QoL will be analysed at 6 weeks post-operatively as well as over time (CLIQ will be collected fortnightly until 12 weeks post-surgery and then monthly up to 24 weeks post-surgery).
- The EQ-5D-5L questionnaire and an incremental cost-utility analysis will determine the cost per QALY gained over the 52 weeks post-surgery.

17.1.4 Sample size and analysis

We anticipate that 70-80% of participants in OCEaN (n=433 to 494) will have surgery for ileocolonic or terminal ileal disease (38, 75) and will be analysed in COAST. The analysis will divide patients into early surgery versus late surgery. There are no definitions for early and late surgery, thus we propose looking at this in two different ways:

Disease duration before surgery

- Early surgery will be defined as surgery less than 2 years from the time of confirmed diagnosis
- Late surgery will be defined as surgery at least 2 years from the time of confirmed diagnosis

We have chosen a 2-year cut off for early surgery as data from other studies indicates that early surgery can be defined as less than one year and up to 5 years (76-78). We felt that after more than two years, patients may have developed fibrotic disease for which currently there is no medical treatment option (79-81).

Confirmed diagnosis will be defined as time of diagnostic endoscopy or radiology.

Medical treatment before surgery

- Early surgery will be defined as patients who have had no medications or been treated with conventional treatment only (i.e. thiopurine/methotrexate, aminosalicylates) and/or steroids (oral prednisolone or budesonide) and/or one biologic agent (or small molecule).
- Late surgery will be defined as patients who have received the above plus more than one biologic (or small molecule).

We have chosen to include patients who have failed one biologic in the early group as on review of our patients' undergoing surgery, few had surgery prior to receiving any medication (38, 40).

The rationale for using both disease duration before surgery and medical treatment before surgery will enable us to determine whether either or both impact patient outcomes in reference to the timing of surgery. Regression models will be used to assess whether early versus later surgery (based on the above definitions) is associated with better outcome (e.g. QoL, using CLIQ). Analyses will adjust for other important factors (e.g. age, gender, disease phenotype, malnutrition risk at baseline, smoking status) and intervention group.

17.1.5 Outcomes - Nutrition

Nutritional outcomes are not part of the main OCEaN RCT. We therefore propose in the embedded COAST study to collect the following data at baseline i.e., randomisation to OCEaN (week 0), 6 weeks post-surgery and 52 weeks post-surgery:

- Energy, nutrient and food group intake, and dietary patterns evaluation – using the EPIC food frequency questionnaire. The EPIC FFQ is a validated tool to measure dietary intake and comprises approximately 200 food items and nine frequency of intake categories (82).
- Diet quality and dietary diversity - using the Diet Quality Index-Revised Dietary Diversity Score (83) and the Dietary Diversity Score (84). Data from food categories collected using the EPIC FFQ will be recoded to enable scoring of these indices.
- Food-related quality of life – using an IBD specific food related quality of life (FR-QOL) assessment tool. The FR-QOL is a validated tool and comprises 29 questions using a 5-point Likert scale (85).

17.1.6 Samples size and analysis

200 participants (100 in each group) will provide 90% power to be able to detect correlations of >0.3 (moderate correlation) between dietary intake (e.g. fibre, calcium, iron) and food-related quality of life in each group separately. Further analyses using multivariable models adjusting for other important factors (e.g. age, gender, disease phenotype, malnutrition risk at baseline, smoking status, and previous surgery) and intervention group will also be undertaken.

17.2 MICROBIOME

17.2.1 Background

The gut microbiome is strongly implicated in the underlying aetiology of CD and disease severity and phenotype, and in particular through its interaction with host diet. (86, 87) There is also good evidence to suggest that the mode of action of EEN is mediated by the extensive modulation that the treatment induces on the human gut microbiome. In our previous research, we have shown that decrease in gut inflammation was related with changes in certain microbes and diet-originated metabolites which collectively explained 78% of the variance in faecal calprotectin levels. (88) As therapeutic response to EEN varies among patients, identification of pre-treatment predictors is of great interest for the clinical practitioner, so that the right treatment is provided to the right patient, as in the paradigm of precision medicine. In a paper in Press (Gerasimidis et al. Microbiome 2022) using a multi-omics dataset and machine learning, we have identified a pre-treatment microbiome signature which was able to distinguish treatment responders from non-responders with an "out of box (OOB)" error of ~90%, and a sensitivity and specificity rate greater that 85% and 92%, respectively. Noteworthy, disease characteristics and routinely collected biomarkers (e.g., disease phenotype, behaviour, severity etc.) were unable to prognosticate successful response to EEN treatment.

17.2.2 Aims

The microbiome sub-study of OCEaN aims to identify microbial compositional and metabolomic signatures which will predict improvement of disease activity after 6-week treatment with EEN and the risk of development of post-surgical complications and disease recurrence at follow-up.

17.2.3 Methods

We will perform microbiome analysis on the same samples that we will collect for measurement of EEN compliance using GIP. Analysis of these samples will take place at UoG. Genomic DNA will be extracted from samples using the bead-beating method coupled with enzymatic lysis and chemical extraction. (89) The V4 region of the 16S rRNA gene will be sequenced (NovaSeq,) in a sequencing centre (e.g., Novogene, Edinburgh Genomics) in the UK ensuring best value for money. The absolute concentration of short chain fatty acids (SCFA), branched chain fatty acids, and medium chain fatty acids will be measured in faeces, using gas chromatography and untargeted metabolomics as service. (52)

17.2.4 Microbiome data analysis

Microbiome analysis will be performed as described previously. (52, 90 - 92) Statistical analysis will be performed using R packages in conjunction with scripts that have been coded in-house specifically for use with this dataset. The gut microbiome will be represented using an amplicon sequence variant (ASV) table generated using the most up to date version of the dada2 pipeline. Data will be explored both in terms of alpha diversity and overall community composition, visualised using non-metric multidimensional scaling (NMDS) of Bray-Curtis and UniFrac distance matrices, and

evaluated using permutation Analysis of Variance (ANOVA). We will correct for multiple testing using the Benjamini-Hochberg method. Changes in microbiome composition over time will be assessed using the R package, splinectomeR, designed for use with real longitudinal data which may have noisy biological variability. To evaluate the microbiome as a predictor of EEN response and complications machine learning will be applied to the data for each patient at baseline with classification based on the outcome determined at the end of the study. Metabolomic peaks will be fragmented and we will use probabilistic quotient normalization for univariate differential analysis, and square-root transformation with Pareto-scaling for multivariate analysis.

Random forest classification models will be implemented to assess prediction accuracy of the microbiome versus outcome measures (e.g., reduction in faecal calprotectin levels, disease recurrence, surgical complications). Performance of these models will be assessed using the "Out-of-box (OOB)" error rate and receiver operating characteristic (ROC) analysis. Models will be optimised, and the most influential taxa/variables identified using the mean reduction in Gini importance coefficient. The mainstream statistical analysis above will be complimented with Bayesian methods when needed. Data will be analysed within Professor Gerasimidis group at the UoG (The BINGO Group).

17.2.5 Sample biobank

Leftover stool samples will be biobanked at the OCEaN dedicated freezer at University of Glasgow, Glasgow Royal Infirmary for future research within ethically approved studies and following participants written informed consent.

18. TRIAL ORGANISATIONAL STRUCTURE

18.1 Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

18.2 Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

18.3 Trial Management Group (TMG)

The TMG comprises individuals responsible for the day-to-day management of the trial: the CIs, statisticians, trial team leader, trial manager, data manager, qualitative researcher, dietitian, health economist, nutrition experts, IBD and surgical experts and patient representative. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

18.4 Co-investigator group

The Co-investigator group, an extended TMG, will comprise all members of the co-applicant group and the members of the TMG to review progress, troubleshoot and plan strategically.

18.5 Trial Steering Committee (TSC)

A TSC, comprising independent and non-independent members, will be established for the OCEaN trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC. The TSC will operate in accordance with a trial specific TSC Charter.

18.6 Data Monitoring Committee (DMC)

The role of the independent DMC is to monitor the trial data and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

18.7 Finance

The research costs of the trial are funded by the NIHR Health Technology Assessment (HTA) grant awarded to Dr Rachel Cooney, University Hospitals Birmingham NHS Foundation Trust. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess intervention costs associated with the trial, e.g., gaining consent, are estimated in the Schedule of Events Cost Attribution Template (SoECAT). These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network (LCRN).

19. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include Data Protection Act 2018; and Human Tissue Act 2004; and the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the REC prior to the start of the trial. All correspondence with the REC will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

20. DATA PROTECTION AND CONFIDENTIALITY

Personal and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). Personal data categories that will be collected and analysed include Name, NHS/CHI/H&C Number, gender, date of birth, telephone/mobile number, email and postal address, health information and medical history.

Participants will only be identified by their unique trial identification number, initials and partial date of birth on CRFs and on any correspondence with the Trial Office. Participants will acknowledge the transfer and storage of their ICF to the Trial Office, this will be conducted as part of the electronic consent process. This will be used to perform central monitoring of the consent process.

Participants will also acknowledge the transfer of their personal data for the purpose of medical research and analysis to the University of Birmingham, University of Glasgow, and King's College London who will be processing data on behalf of the trial. This will be fully explained to the participant in the PIS and requires participants to acknowledge a specific statement on the ICF if they agree to this.

Recordings and transcriptions for the qualitative interviews will be identified by using the participant's Trial number, which they are allocated at point of trial entry (i.e. Randomisation); centre initials, and the date of recording. There will be no participant identifiers in files, databases, or transcripts, which will only be labelled with participant's Trial Number. All recordings will be securely transferred to a University of Birmingham approved transcription company or transcriber that has signed the required confidentiality agreements. All transcripts will be anonymised upon receipt. The anonymised interview data (transcripts only) will be uploaded to a 'controlled access' data repository, subject to individual written informed consent from the participants. This has been

fully explained in the Qualitative study PIS and requires participants to initial a specific statement on the Qualitative study consent form (if they agree).

In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the OCEaN trial team and sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The Trial Office will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party.

21. FINANCIAL AND OTHER COMPETING INTERESTS

This is a trial funded by the HTA programme of the NIHR. There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

22. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Resolution.

23. POST TRIAL CARE

At the end of the trial, all participants will continue to receive standard medical care as provided by the NHS following participation in the clinical trial, and as deemed appropriate by their responsible clinician and usual clinical care team.

24. ACCESS TO FINAL DATASET

The final dataset will be available to members of the TMG and co-applicant group who need access to the data to undertake the final analyses.

Any requests for data generated during this trial will be considered by the BCTU Data Sharing Committee. Data will typically be available 6 months after the primary publication, unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CIs and Co lead applicant, where appropriate (or in absence of the CIs) any of the following: the Trial Sponsor, the TMG, and/or the independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved, and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

25. PUBLICATION PLAN

On completion of the trial, the data will be analysed, and a Final Study Report prepared. Results of this trial will be submitted for publication in a peer reviewed journal and the findings of the trial will be made public. This manuscript will be prepared by the CI and members of the TMG and submitted to the whole TMG in a timely fashion and in advance of being submitted for publication to allow time for review.

Outputs from this trial will be published under a corporate authorship group. Each publication will include a detailed description of the exact contributions of each person, following accepted guidelines for collaborative authorship models.

Any secondary publications and presentations prepared by investigators must be reviewed and approved the TMG. Manuscripts should be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues.

In all publications, authors must acknowledge that the trial was performed with the support of NIHR, University Hospitals Birmingham and the University of Birmingham (the Sponsor) and Birmingham Clinical Trials Unit. Intellectual property rights will be addressed in the OCEaN Clinical Trial Site Agreement between Sponsor and site.

Participants can request the published trial results from their PI once available.

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