Project Title: MEsenteric Excision and Kono-S Anastomosis Trial
Statistical Analysis Plan
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Roles and Responsibilities

This SAP was initially drafted by Ines Rombach (MEErKAT trial statistician) and Esther Herbert (MEErKAT trial statistician), with input from Stephen Walters (senior statistician) and the trial team.

SAP Revision History

Version Number	Revision Date	Timing Within Trial	Description/Justification
n/a -this is version 1.0			

List of Abbreviations and Definitions of Terms

ADDQoL-14	**Audit of Diabetes Dependent Quality of Life (14 items)**
AE	Adverse Event
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
DVT	Deep Vein Thrombosis
EEN	Exclusive Enteral Nutrition
ER	Endoscopic Recurrence
EQ-5D-5L	EuroQol - 5 Dimensions - 5 Levels
GCP	Good Clinical Practice
GLM	Generalised Linear Model
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
ICC	Intra-class Correlation Coefficient
IQR	Inter Quartile Range
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention To Treat
LRT	Likelihood Ratio Test
MDAI	Mesenteric Disease Activity Index
MUST	Malnutrition Universal Screening Tool
NHS	National Health Service
OR	Odds Ratio
PE	Pulmonary Embolism
PP	Per Protocol
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee

SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

Contents

1. INTRODUCTION

1.1. Background and Rationale

Crohn's disease is an inflammatory condition of the gastrointestinal tract affecting 300 per 100,000 population (200,000 in the UK)[1]. It follows a chronically relapsing pattern despite advances in medical therapy. Almost all patients eventually require resection of diseased bowel. Even after surgery over one third of patients need further surgery within 10 years[2].

Two resection techniques have gained traction based on poor evidence but apparent spectacular reduction in recurrence[3]. The Kono-S anastomosis takes into account the predisposition for mesenteric border recurrence by proposing an antimesenteric anastomosis. High quality data is needed to establish whether this technique is as effective as suggested; some comparative studies are ongoing [4]. An interesting component of the technique is the proposal that the mesentery is essentially preserved. The other school of thought proposes the mesentery as the driver of disease, requiring a more extended resection of diseased mesentery, with the anastomosis irrelevant to recurrence [5,6]. Evidence for this technique is poor but comparative studies are ongoing [7]. Despite the contrasting techniques, there may be commonalities that explain why both are effective. Both aim to isolate the anastomosis from diseased mesentery. Kono-S does this by a totally antimesenteric anastomosis as far away as possible from the mesentery; extended mesenteric resection by removing the theoretical disease driver. A combination of techniques is possible and may increase efficacy.

1.2. Objectives

<u>The primary objective of the trial is to:</u>

The main aim of the study is to compare recurrence after standard mesenteric excision or extended excision and standard anastomosis or Kono-S anastomosis (with or without extended mesenteric excision).

The secondary objectives are:

Clinical objectives

- Assessment of endoscopic recurrence (Rutgeerts score ≥i2) and severe endoscopic recurrence (Rutgeerts score ≥i3) after around 12 (window -6 months/+3 months) months of follow-up, with a potential for patients to have endoscopic assessment at up to 3 years (if clinically indicated).
- Assessment of symptomatic recurrence and assess the time to recurrence using Inflammatory Bowel Disease (IBD) Control [8] and Crohn's Disease Activity Index [9].
- Assessment of surgical recurrence
- Assessment of complications for each intervention
- Assessment of need for escalating medical therapy

Mechanistic objectives

- Investigate the locality of endoscopic recurrence in relation to the mesenteric border.
- Investigate the degree and anastomotic locality of mucosal T cell clonality and exhaustion, especially CD8+ T cells and fibrocyte alterations
- Investigate changes in antigen presentation in the mesentery, blood and mucosa.

The study also includes an internal pilot to assess feasibility of a full-scale trial. Assessments on feasibility will be made based on recruitment, eligibility to consent rate, and equipoise. These assessments are not included in this statistical analysis plan.

2. TRIAL METHODS

2.1. Trial Design

The study is a UK multicentre, superiority, 2 × 2 factorial, randomised, open-label trial with a one-year follow-up (-6 months/+3 months). Participants will be randomised (1:1:1:1) to one of four groups:

(1) Kono-S + extended mesenteric resection;

(2) Kono-S + close mesenteric resection;

(3) Standard anastomosis + extended mesenteric resection;

(4) Standard anastomosis + close mesenteric resection.

Endoscopic recurrence will be evaluated at the post-surgery/randomisation endoscopic follow up visit. The locality of recurrence will be investigated using colonoscopic assessment of mucosa relative to mucosal tattoos placed at the time of operation. A mechanistic component will determine in those that develop endoscopic recurrence, the locality of that recurrence. For those patients who do not have endoscopic recurrence at their endoscopy follow up visit, their notes will be reviewed again up to 3 years post-surgery/randomisation for evidence of endoscopic and surgical recurrence.

Extended mesenteric resection: mesenteric resection resecting all macroscopically abnormal tissue and dividing the mesentery up to the origin of the ileocolic trunk [7,10] with preservation of the main ileocolic vessels.

Close mesenteric resection: the mesentery is resected within 3 cm of the border of the bowel, leaving most of the mesentery in situ.

Kono-S: Resected bowel stapled perpendicular to the mesentery and the stapled ends sutured together. 7cm antimesenteric enterotomies are made 1-1.5cm from the stapled resection margin and a side to side anastomosis created by suturing the enterotomies together.

2.2. Randomisation and Blinding

Participants will be allocated using a computer generated pseudo-random list, stratified by centre, with random permuted blocks of varying sizes. The sequence will be restricted by authorisation until analyses are complete.

As there is no difference between the interventions in abdominal access or closure it is easy to blind the participant. Those assessing the 12 month (window -6 months/+3 months) endoscopic outcomes will be blinded to the allocation. Colonoscopists may recognise the Kono-S anastomosis in the bowel configuration, but will not be directly involved in the study. The degree of mesenteric excision will not be apparent during colonoscopy.

The trial statistician will be blinded until the final data lock; the senior statisticians may be unblinded after approval of the statistical analysis plan (SAP). Statisticians may see blinded data prior to final data lock to prepare code in advance.

2.3. Sample Size

The primary outcome will be the time to endoscopic recurrence (ER) post-randomisation (Rutgeerts score >= i2). All participants will be followed up for a minimum of 6 months post-randomisation and up to a maximum of 3 years. The best existing data indicates ER rates of approximately 65% on conventional surgery and 24% on Kono-S surgery at 12 months [11]. Other published data on the rate of endoscopic recurrence after conventional surgery varies from 58-93% [12-16]. The systematic review unfortunately found no published data on the ER rates after close or extended mesenteric resection [3]. In a survey of 34 surgeons, 71% were persuaded to change practice based on a reduction in endoscopic recurrence to 30% or less after 12 months.

The sample size calculation for the 2 x 2 factorial design assumes: 90% power; 5% (two-sided) significance level; and estimated 1-year endoscopic recurrence rates of 65% in the standard anastomosis/close mesenteric resection group; 40% in the standard anastomosis and extended mesenteric resection group (for a combined ER rate of 52.5% on standard anastomosis) ; 40% in the Kono-S and close mesenteric resection group and a 25% recurrence rate in the Kono-S and extended mesenteric resection group (estimated assuming no interaction) for a combined ER rate of 32.5% on Kono-S. Based on a reduction in the 1-year ER rate from 52.5% to 32.5%, equivalent to a hazard ratio of 0.528, a total of 112 recurrences are required (using the Freedman method) or a sample size of 130 patients per group (260 in total) of Kono-S versus standard anastomosis (or extended mesenteric resection vs close resection).

To account for surgeon effects we assume each of 12 sites would have 2 surgeons and an ICC of 0.01 (surgical procedures are well-developed, standardized and performed by experienced surgeons; the ICC from HubBLe was <0.0001 [17]) and 15 patients per surgeon (equivalent to design effect of 1.14), the number was increased to 149 per group. Based on a further 3% attrition we require 308 patients (77 per group; 154 per group for the factorial design). We are assuming there is no interaction between the two treatments (i.e. extended resection of the mesentery in addition to Kono-S surgery

does not change the effect of Kono-S surgery and vice versa). The trial is not powered to assess any observed interaction, which would require a fourfold increase in size to N~1200, not achievable in a reasonable time scale or resource envelope.

Table 1: Estimated 1-year post randomisation endoscopic recurrence rates for 2 x 2 factorial design

	Factor B		
Factor A	**Extended mesenteric resection**	**Close mesenteric resection**	***Total***
Kono-S	25%	40%	*32.5%*
Standard anastomosis	40%	65%	*52.5%*
Total	*32.5%*	*52.5%*	

estimated assuming no interaction, that is additive independent effects.

2.4. Trial Framework

The primary aim of this trial is to conduct a superiority 2x2 factorial RCT comparing Kono-S vs. standard anastomosis, and extended mesenteric resection vs. close mesenteric resection to detect a minimum clinically significant hazard ratio of 0.528 between each of the two groups after a maximum follow-up of three years.

2.5. Trial Monitoring and Management

In compliance with Sheffield CTRU's SOPs, the following committees will be established to govern the overall conduct and supervision of the trial:

- Trial Steering Committee (TSC)
- Data Monitoring and Ethics committee (DMEC)
- Trial Management Group (TMG)

The trial will be supervised on a day-to-day basis at Sheffield CTRU by the Trial Manager with supervision from the Chief Investigator, co-Chief Investigators, and an Assistant Director of the CTRU.

2.6. Interim Analysis and Stopping Rules

There are no interim analyses or early stopping planned for this trial, hence no stopping rules are applicable.

2.7. Timing of Final Analysis

The final analysis will take place after the last participants have completed their 12-month follow-up visit, and sufficient time has been allowed for data chasing and data cleaning. All data will be analysed collectively at this time point.

2.8. Timing of Outcome Assessments

Table 1 below shows the biomedical and psychological outcome measures, and the different time-points outcomes are measured. A detailed description of the outcome assessment is found under section 5.

Table 2: Outcomes measures within the trial and time points they will be collected at

	Baseline	Operation	6 wks.	12 months (-6 to + 3 months	Study end (up to 3 years)
Eligibility Assessment	X[1]	X[1]			
Consent	X				
Medical History	X				
Concomitant Medications	X		X	X	X
Demographics	X				
IBD-Control	X		X	X	
CDAI	X[2]		X	X	
EQ-5D	X		X	X	
Randomisation		X			
Mesenteric disease activity index		X			
Adverse Events		X	X	X	
Colonoscopy				X	X[3] (via note review)
Blood samples	X[4]			X[4]	
Mucosal/mesenteric biopsies		X[5]		X[5]	
Surgical recurrence				X	X (via note review)

[1] General eligibility assessment will be done at baseline to assess patient is suitable for trial; however, formal eligibility assessment can only be carried out at surgery when surgeon physically observes the gut
[2] CDAI patient diary should be started 7 days prior to a patient's day of surgery
[3] Data will be collected on any additional colonoscopies participants receive as part of their standard care
[4] Patients in (optional) mechanistic sub-study only
[5]Biopsies standard for main trial patients. Patients in (optional) mechanistic sub-study will have extra samples taken

3. STATISTICAL PRINCIPLES

This statistical analysis plan (SAP) is written in conjunction with the International Conference of Harmonisation topic E9 [18], applicable Standard Operating Procedures (SOP) from the Sheffield Clinical Trials Research Unit (CTRU) (ST001 and ST006).

3.1. Confidence Intervals and P Values

All statistical tests will be completed at the 5% significance level and estimates of the treatment effect will be reported with their associated 95% confidence intervals. All tests completed will be two-sided. The results of the trial are focussed on the primary endpoint for each of the two separate comparisons (time to endoscopic recurrence) so no adjustment for multiple testing and control of the type 1 error rate is required.

3.2. Adherence and Protocol Deviations

Adherence to the trial procedures is defined as:

- Randomised procedure was performed as intended

The number (and percentage) of participants who are adherent with the trial procedures will be presented, together with details on non-adherence, i.e. which alternative procedures these participants received.

The number (and percentage) of patients with major and minor protocol deviations will be summarised by treatment group with details of type of deviation provided. No formal statistical testing will be undertaken between the two groups.

3.3. Analysis Populations

The primary analysis set will be that defined in Intention To Treat (ITT) on the primary outcome. Additional analysis populations, such as Per Protocol (PP), will be used as sensitivity analyses. Table 3 defines each of the analysis sets.

Table 3: definitions of the analysis set

Analysis Set	Outcomes	Participant Inclusion Criteria
Intention to treat (ITT)	Primary outcome & other time to event outcomes	Randomised participants, analysed according to their randomisation allocation, regardless of their adherence to the eligibility criteria, intervention received. For time-to-event outcomes, all randomised participants will be included in the analysis and censored at appropriate time points, for continuous or categorical secondary outcomes, participants with available follow-up data will be included in analyses.

Per protocol (PP)	Primary outcome only	All randomised participants excluding those who did not adhere to the assigned intervention as defined by section 3.2, or who were found to be ineligible for the trial.

4. SCREENING, RECRUITMENT, DEMOGRAPHICS AND WITHDRAWAL

4.1. Eligibility Criteria

Inclusion criteria

- Patients aged 18 years and over
- Patients undergoing ileocaecal resection for primary/recurrent Crohn's disease where an anastomosis is carried out.

5.2 Exclusion criteria

- Patients with markedly extensive inflammation affecting the vascular root of the mesentery seen on imaging or at operation
- Patients undergoing stoma formation
- Patients who have contraindication to subsequent colonoscopy
- Patients unable to give full informed consent
- Patients who are pregnant (as ascertained by standard pregnancy tests undertaken at pre-operative visits/ as per standard clinical care)
- Patients who, in the opinion of the principal investigator, to not meet the criteria for relevant surgery

In a very small subset of patients, it may be the case that extensive mesenteric inflammation (an exclusion criteria) is only seen once undergoing surgery. Usually, this degree of inflammation would be picked up prior to surgery via relevant scans. In the case when it is only found at operation and the surgeon is unwilling to do a extended mesenteric excision, the patient would not be eligible for the trial. This decision is based on the surgeon's usual practice and standard of care. Participants should therefore not undergo randomisation until such time as the diseased area can be visually assessed at operation.

4.2. Consolidated Standards of Reporting Trials (CONSORT)

Using guidelines from the CONSORT statement [19], the summaries outlined Table 4 will be calculated in order to construct a CONSORT flowchart (see Figure 7.1 and Figure 7.2). Data will be presented overall and by treatment allocation.

Table 4: CONSORT summary

Screening Data	• Number of participants assessed for eligibility at screening • Number ineligible including reasons • Number eligible but declined to participate including reasons
Recruitment Data	• Number of participants randomised to each of the 4 treatment combinations • Number and percentage of those received their randomised intervention
Lost to Follow Up/Withdrawal Data	• Number and percentage of participants who dropped out or withdrew before the one-year follow-up, and during the additional follow-up
Analysis Population Data	• Number of those included in primary ITT analysis (primary endpoint) • Number of those included in PP population (primary endpoint)

4.3. Withdrawal of Participants

The analysis plan will include summaries of withdrawals from follow-up, including number and percentage of participants who have withdrawn from follow-up, and reasons for withdrawal.

Participant-requested withdrawals from the intervention only are not expected, as randomisation takes place during the surgery, when participants are under general anaesthetic. It is anticipated that once surgeons have confirmed eligibility and randomised participants during their surgery, it will only rarely be clinically necessary to deviate from the assigned surgical procedures. (See section 3.2 for adherence summaries.)

4.4. Baseline Characteristics

Baseline characteristics will be summarised for the main comparisons (Kono-S vs. standard anastomosis and extended mesenteric resection vs. close mesenteric resection), as well as for the four distinct treatment combinations (Kono-S + extended mesenteric resection vs. Kono S + close mesenteric resection vs. Standard anastomosis + extended mesenteric resection vs. Standard anastomosis + close mesenteric resection).

At the participant level, the variables shown below, as captured at baseline, will be presented. Categorical variables will be presented using counts and percentages, continuous variables will be

presented with means and standard deviations, median, inter-quartile range ad range. No statistical significance testing will be used to test baseline imbalances between groups, but any noteworthy differences will be descriptively reported.

Table 5: Baseline variables

- **Demographics**
  - Age (years)
  - Sex (female/ male)
  - Ethnicity
    - White
      - English / Welsh / Scottish / Northern Irish / British
      - Irish
      - Gypsy or Irish Traveller
      - Any other White background*
    - Asian/ Asian British
      - Indian
      - Pakistani
      - Bangladeshi
      - Chinese
      - Any other Asian background*
    - Mixed / multiple ethnic groups
      - White and Black Caribbean
      - White and Black African
      - White and Asian
      - Any other mixed / multiple ethnic background*
    - Black / African / Caribbean / Black British
      - African background*
      - Caribbean
      - Any other Black / Black British or Caribbean background*
    - Other ethnic background
      - Arab
      - Any other ethnic group*

      **additional details will be provided*
- **Smoking history**
  - Smoking status (never vs. current vs. previous smoker)
    - If current: product type (cigarettes, cigars, tobacco, e-cigarettes; categories not mutually exclusive)
    - If previous smoker: when did they stop (within last year, 1-5 years ago, 5+ years ago)
- **Medical history**
  - Age at Crohn's Disease (CD) onset (years)
  - Time from CD onset to randomisation into trial (years or months, as appropriate)

- Location of CD (L1 Terminal ileum vs. L2 Colon vs. L3 Ileocolon)
  - L4 Concomitant upper GI disease (yes vs. no)
- Behaviour of CD (B1 non-stricturing, non-penetrating vs. stricturing vs. penetrating)
  - B4 concomitant perianal disease (yes vs. no)
- Length of bowel affected (cm)
- Family history of inflammatory bowel disease (yes vs. no)
  - If yes: type of family history (ulcerative colitis, Crohn's disease, not mutually exclusive)
- Participant required radiological intervention for drainage of abdominal abscess before surgery (yes vs. no)
- Participant received a prescription for exclusive enteral nutrition (EEN) within the ten weeks prior to their consent to the study (yes vs. no)
  - If yes: duration of EEN (weeks), time from end of EEN to surgery (ongoing, 1 week prior to surgery, 2 weeks prior, 3 or more weeks prior [additional categories may be added as appropriate])
- Previous use of biologics medication for CD
  - Adalimumab (yes vs. no)
  - Infliximab (yes vs. no)
  - Ustekinumab (yes vs. no)
  - Vedolizumab (yes vs. no)
  - Other* (yes vs. no)
    **details will be provided*
- Previous use of immunosuppressant medication for CD
  - Azathioprine (yes vs. no)
  - Cyclosporine (yes vs. no)
  - Mercaptopurine (yes vs. no)
  - Methotrexate (yes vs. no)
  - Mycophenolate (yes vs. no)
  - Other (yes vs. no)
    **details will be provided*

- **Surgical history**
  - Previous surgery (none, strictureplasty, small bowel resection, ileocolic resection, segmental colonic resection, other; these categories are not mutually exclusive)
- **Clinical and patient reported scores**
  - Crohn's Disease Activity Index (CDAI) score
  - EuroQol - 5 Dimensions - 5 Levels (EQ-5D-5L) index and Visual Analogue Scale (VAS)
  - IBD Control questionnaire score
  - Mesenteric disease activity index (MDAI – scored 1 vs. 2 vs. 3 vs. 4)
  - Malnutrition Universal Screening Tool (MUST) (0-6, or low, medium, high risk)
- **Laboratory tests**

- Albumin
  - Albumin levels (g/l)
  - Number and percentage of participants outside normal local range (yes vs. no)
  - Clinically significant (yes vs. no)
- C-reactive protein
  - Albumin levels (mg/l)
  - Number and percentage of participants outside normal local range (yes vs. no)
  - Clinically significant (yes vs. no)
- Haemoglobin
  - Haemoglobin levels (g/l)
  - Number and percentage of participants outside normal local range (yes vs. no)
  - Clinically significant (yes vs. no)
- White cell count
  - White cell count levels ($x10^9$/L)
  - Number and percentage of participants outside normal local range (yes vs. no)
  - Clinically significant (yes vs. no)

4.5. Surgery details (trial surgery)

Details of the trial surgery will be summarised for the main comparisons (extended mesenteric resection vs. Close mesenteric resection and Kono-S vs. Standard anastomosis), as well as for the four distinct treatment combinations (Kono-S vs. standard anastomosis and extended mesenteric resection vs. close mesenteric resection), as well as for the four distinct treatment combinations (Kono-S + extended mesenteric resection vs. Kono S + close mesenteric resection vs. Standard anastomosis + extended mesenteric resection vs. Standard anastomosis + close mesenteric resection).

The following variables, as captured on the surgery case report form (CRF), will be presented. Categorical variables will be presented using counts and percentages, continuous variables will be presented with means and standard deviations, median, inter-quartile range ad range. No statistical significance testing will be used to test imbalances between groups, but any noteworthy differences will be descriptively reported.

Table 6: Trial surgery details

- Days between randomisation and surgery[1]
- Primary procedure for which participant was admitted (Ileocaecectomy vs. right hemicolectomy vs. Ileocolic resection for recurrent disease)
- ASA score (I vs. II vs. III vs. IV vs. V vs. VI)

[1] To confirm that randomisation and surgery were on the same day.

Trial procedure

- Participant free of markedly extensive inflammation affection the vascular root of the mesentery (yes vs. no)
- Prophylactic antibiotics given (yes vs. no)
- Participant taking prednisolone on day of surgery (yes vs. no)
    - If yes: dose (mg)
- Trial procedure performed (Kono-S + extended mesenteric resection vs. Kono S + close mesenteric resection vs. Standard anastomosis + extended mesenteric resection vs. Standard anastomosis + close mesenteric resection)
    - Deviations from Kono-S or Standard anastomosis (end to end vs. end to side vs. side to site (isoperistaltic) vs. side to site (antiperistaltic) vs. other)
- Mode of access (open vs. robotic vs. laparoscopic)
    - Conversion to open (for robotic and laparoscopic) (yes vs. no)
- Anastomosis performed (intracorporeal vs. extracorporeal)
- Anastomotic technique (suture/ handsewn vs. staple)
- Extraction site (midline vs. Pfannenstiel vs. other)
    - Details for other will be provided
- Additional procedures performed (multiple choice)
    - Strictureplasty (yes vs. no)
    - Adhesiolysis (yes vs. no)
    - Additional bowel resection (yes vs. no)
      (additional details provided where available)
    - None (yes vs. no)
- Trial procedure successfully completed (yes vs. no)
    - If no: reason (procedure abandoned vs. procedure changed from protocol vs. other [details provided])

Interoperative findings

- Were there any operative findings (yes vs. no)
  If yes:
    - Ileocolic disease – inflammatory only (yes vs. no)
    - Ilecolic disease – structuring (yes vs. no)
        - If yes: length of stricture (cm)
    - Ileocolic disease – penetrating (yes vs. no)
        - If yes: presence of fistulation (yes vs. no)
            - If yes: organ(s) involved:
                - Bladder (yes vs. no)
                - Colon (yes vs. no)
                - Small bowel (yes vs. no)
                - Duodenum (yes vs. no)
                - Uterus (yes vs. no)
                - Vagina (yes vs. no)
    - Presence of additional stricture(s) (yes vs. no)
        - If yes:
            - length of stricture (cm)

- location of stricture (free text)
- Presence of bowel dilatation (yes vs. no)
- Presence of skip lesions (yes vs. no)
- Presence of perforation(s) (yes vs. no)
- Presence of intra-abdominal contamination (yes vs. no)
- Presence of intra-abdominal abscess (yes vs. no)
- Other abnormal or unexpected findings (yes vs. no)
  - If yes: details provided as free text

Intraoperative complications

- Intra-operative complications occurred (yes vs. no)
  If yes:
  - Intraoperative MI (yes vs. no)
  - Intraoperative PE (yes vs. no)
  - Intraoperative transfusion (yes vs. no)
  - Physiological instability (haemodynamic instability requiring inotrope vasopressor support) (yes vs. no)
  - Other intraoperative complication (yes vs. no)
    - If yes, details provided (free text)

Resection details

- Small bowel length (cm)
- Colonic length – tip of caecum to resection staple line (cm) [not available for recurrent disease and no caecum]
- Colonic length – Distal ileum to resection staple line (cm) [for recurrent surgery]

Histology

- Resection margin positive (yes vs. no)
- Granuloma(s) present (yes vs. no)

Mesenteric disease

- Mesenteric disease activity index (Fat wrapping minimal, mesenteric thickening minimal vs. Fat wrapping <25% circumference of bowel, thickening of vascular pedicle only vs. Fat wrapping <25% circumference of bowel, pan mesenteric thickening vs. Fat wrapping >25% circumference of bowel, pan mesenteric thickening)

Surgeon details

- Number of surgeons by site (mean, median, inter quartile range (IQR), minimum, maximum)
- Average number of surgeries per surgeon (mean, median, IQR, minimum, maximum)

Similar summaries will also be provided for additional surgeries performed during the trial follow-up.

5. OUTLINE OF STATISTICAL ANALYSIS

Binary and categorical variables will be presented as the number of observations and proportions in each category, by treatment group and overall.

Continuous variables will be summarised and presented by treatment group and overall as mean and standard deviation (SD) for normal distribution.

Median, Inter-Quartile Range (IQR), minimum and maximum may also be provided for non-parametric data.

5.1. Outcome Measures

5.1.1. Primary Outcome

The primary outcome is the time to endoscopic recurrence (ER) up to a maximum of three years of follow-up, defined as a Rutgeerts score ≥i2.

For the primary analysis, the following definition of ER is used:

Participants will be classed as having had ER if they had an endoscopy for which a Rutgeerts score ≥i2 is reported during their follow-up[+]. The date of the corresponding endoscopy, or the date of the earliest endoscopy if a Rutgeerts score ≥i2 was found at more than one endoscopy for the same participant, is used in the time-to-event analysis. Time to ER is calculated as the time from randomisation to ER.

Participants will be censored at the earliest of:

- at the end of the study follow-up*, if at least one endoscopy was performed, and no Rutgeerts score ≥i2 reported
- date of withdrawal (if no prior Rutgeerts score ≥i2 available)
- date of death (if no prior Rutgeerts score ≥i2 available)
- day after randomisation if no endoscopies are recorded over the follow-up (i.e. these participants are essentially lost to follow-up)

***Definitions:**

End of study follow-up: The end of the trial is defined as the date of the last recruited participant's 1 year (window -6 months/+3 months) post-surgery follow-up visit.

Length of follow-up: The last participant recruited to the trial will be followed up for 12 months (window -6 months/+3 months). Other participants will be followed up for longer, i.e. until the earliest of 42 months post their randomisation, or the end of the study follow-up, as defined above.

Note:

- The primary endpoint definition does not consider other ER purely based on endoscopic evidence, and may miss cases where no endoscopy data are available, but surgical or symptomatic recurrence has been reported. These cases are part of the secondary endpoints, will be reported as such.
- ER may be missed where an endoscopy has been performed, but no Rutgeerts score is available. It is expected this will happen very infrequently in the trial, and the potential impact of this will be considered in sensitivity analyses (see Section 5.5).

Sensitivity analysis including surgical recurrence in the endpoint:
Within this trial, it is unlikely that participants will progress to surgical recurrence without documented evidence of a Rutgeerts score ≥i2 from an endoscopy. If any such cases exist, the primary analysis will be repeated, this time also counting surgical recurrences reported at least 6 months after randomisation. The date of surgery will then be used in the time to event analysis.
(See below for the definition of surgical recurrence)

In line with the above, the date of the ER event is calculated as the earliest date of either the endoscopy resulting in a Rutgeerts score of ≥i2, or the date of the surgical recurrence.

5.1.2. Secondary Outcomes

- **Severe endoscopic recurrence (Rutgeerts score ≥i3)**
  Definition of endpoint as per primary endpoint, except that only Rutgeerts score ≥i3 are classed as events of interest (instead of Rutgeerts score ≥i2).

- **Clinician and patient-reported symptomatic recurrence up to 12 months and at the end of the trial (Best, Becktel et al. 1976, Bodger, Ormerod et al. 2014)**
  Symptomatic recurrence is defined as:
  - surgical re-intervention in combination with histological confirmation of recurrence (as collected on Îsurgical recurrence CRF"); **OR**,
  - change of medical strategy for recurrence (excluding changes for safety/tolerability); **OR,**
  - IBD Control >13; **OR**,
  - CDAI >220.

  IBD Control and CDAI will only be collected up to 12 months and will not be used in the derivation of the endpoint thereafter.

  Time to symptomatic recurrence will be calculated as the time from randomisation to the date of the first of these events.
  As above, participants without an event will be censored at the earliest of:

  - at the end of the study follow-up
  - date of withdrawal
  - date of death

  IBD control
  All 13 individual items are scored as follows: zero points for least favourable response; one point for intermediate or indeterminate response; two points for most favourable response. The IBD-Control-8 is calculated by adding up scores for Q1a, Q1b, Q3a, Q3b, Q3c, Q3d, Q3e and Q3fm and ranges from 0 (worst control) to 16 (best control)[8]. The reference paper does not clarify how missing items should be handled, and no IBD-Control score will be calculated for participants for whom at least one of the eight relevant items is missing.

A separate visual analogue scale (VAS) ranges from 0 (worst possible control) to 100 (best possible control).

Crohn's Disease Activity Index (CADI)

The CADI is calculated in line with the scoring manual [9] as the sum of the following subtotals:

1. Liquid stools: total number of liquid or very soft stools over the last 7 days * 2
2. Abdominal pain is rated as 0 = none, 1 = mild, 2 = moderate, 3 = severe.
   The pain Likert scores over the last 7 days are added up, and the total is multiplied by 5.
3. General wellbeing is rated as 0 = generally well, 1 = slightly under par, 2 = poor, 3=very poor, 4 = terrible
   The pain Likert scores over the last 7 days are added up, and the total is multiplied by 7.
4. The number of symptoms over the last 7 days are added up and multiplied by 20
   Relevant symptoms are:
   a) Arthritis / arthralgia
   b) Iritis / uveitis, erythema nodosum or pyoderma gangrenosum
   c) Aphthous ulcers
   d) Anal fissure, fistula, abscess
   e) Other fistula
   f) Fever over 37.8°C (100° F)
5. Anti-diarrhoeal drug therapy.
   30 points are added to the score if the participant received Anti-diarrhoeal drug therapy
6. Abdominal mass
   20 points are added to the score if the participant has a questionable abdominal mass, 50 points if the participant has a definitive abdominal mass
7. Anaemia
   For women: (42 – haematocrit %) * 6
   For men: (47 – haematocrit %) * 6
8. Body weight:
   (standard weight - actual weight)/ standard weight * 100%
   (maximum weight reduction is 10 points)

Lower scores indicate less Crohn's disease activity.
The total score is capped at 0, i.e. negative scores are reported as 0.

- **Quality of life (EQ-5D-5L)**

  The EQ-5D-5L consists of a utility score, generated from the responses to the five questions on mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression, we well as a separate visual analogue scale (VAS), ranging from 0-100.
  The utilities will be generated based on the current NICE (National Institute for Health and Clinical Excellence) guidance[20].

  At the time of writing this SAP, NICE recommended that the mapping function developed by Hernández Alava et al[21] is used for economic evaluations.

- **Surgical recurrence up to three years (clinician and patient reported);**

Surgical recurrence is defined as another surgery for Crohn's disease at the site of the initial operation.

The time to surgical recurrence is calculated as the time from randomisation to (the first) surgical recurrence.
The following rules will be applied for censoring:
Participants who with no record of surgical recurrence will be censored at the earliest of:

- at the end of the study follow-up
- date of withdrawal (especially from the collection of information contained in their medical notes)
- date of death

- **Radiological and surgical anastomotic leak as defined by the latest consensus (van Helsdingen, Jongen et al. 2020); other complications for each intervention;**

Radiological anastomotic leak will be defined as:
  - extravasation of endoluminal-administered contrast;
  - collection around the anastomosis;
  - perianastomotic air;
  - free intra-abdominal air (depending on the number of post-operative days).

Surgical leak will be defined as:
  - necrosis of the anastomosis
  - signs of peritonitis
  - dehiscence of the anastomosis

Data on anastomotic leak are collected on the surgical follow-up form (collected at six weeks), and do not distinguish between surgical and radiological anastomotic leaks. Events of Clavien-Dindo grade 2 and above are reported for this secondary endpoint.

Summaries of all other complications, as reported on the surgery form and the six-week surgical follow-up form, together with their Clavien-Dindo grades, will be reported separately.

- **Adverse events (AEs) reported during the follow-up**

Only related AEs will be reported for this trial; unrelated events will not be reported. The following events have been highlighted in the protocol as associated with the trial interventions:

  - Anastomotic leak.

Other complications of surgery may include:

  - haemorrhage; ileus/bowel obstruction; wound infection;
  - urinary tract infection;
  - cardiac events;
  - pulmonary embolism (PE)/ deep vein thrombosis (DVT); and,
  - respiratory insufficiency/pneumonia.

Late postoperative complications may include:

- trocar-site and incisional hernia;
- ureteral stenosis (retroperitoneal fibrosis).

Additionally, occurrences of the following complications of anaesthesia will be recorded: nausea, vomiting, sore throat, dizziness, blurred vision, headaches, bladder problems, damage to lips or tongue, itching, aches and pains, pain during injection for drugs, bruising and soreness, confusion, memory loss, chest infection, muscle pains, slow breathing, damage to teeth, worsening of existing medical conditions, damage to the eyes, heart attack or stroke, serious allergy to drugs, nerve damage, equipment failure and death.

Events are classed as AEs or serious AEs (SAEs), and will be categorised as expected or unexpected.

5.1.3. Other Measurements/Scores

- **mesenteric disease activity index** [22]
  The index is scored as follows as per the table below. It is collected at the time of the operation, and scored by the surgeon at site.

Mesenteric disease score	Severity	Stage	Score
FW minimal, MT minimal	Mild	One	1
FW <25%, MT adipovascular pedicle only	Moderate I	Two A	2
FW <25%, pan-mesenteric MT	Moderate II	Two B	4
FW >25%, pan-mesenteric MT	Severe	Three	6

FW, fat wrapping; MT, mesenteric thickening
Table reproduced from the Coffey et al paper referenced above.

5.2. Analysis of Primary Outcome

The primary outcome is the time to endoscopic recurrence (ER), which is calculated as described in section 5.1.1. The principal analysis will be based on the ITT population.
The number and percentage of participants who have experienced an outcome will be presented for the main comparisons (Kono-S yes vs. no) and extended mesenteric resection yes vs. no), as well as for the four randomisation combinations (extended mesenteric resection and Kono-S vs. extended mesenteric resection and Standard anastomosis vs. Close mesenteric resection and Kono-S vs. Close mesenteric resection and Standard anastomosis).

Primary estimands for the MEErKAT trial

Estimand attribute	Description
Population	Patients undergoing ileocecal resection for primary/recurrent Crohn's disease
Treatment(s)	(1) Kono-S + extended mesenteric resection in addition to usual post operative care followed by any subsequent therapy/treatment (as needed); (2) Kono-S + close mesenteric resection in addition to usual post operative care followed by any subsequent therapy/treatment (as needed) in addition to usual care followed by any subsequent therapy/treatment (as needed); (3) Standard anastomosis + extended mesenteric resection in addition to usual post operative care followed by any subsequent therapy/treatment (as needed) ; (4) Standard anastomosis + close mesenteric resection in addition to usual post operative care followed by any subsequent therapy/treatment (as needed) .
Outcome (endpoint)	Time to endoscopic recurrence (ER) post-randomisation
Handling Intercurrent events	1. Stopping randomised treatment/surgery for any reason – treatment policy (as part of treatment) 2. Switching surgical treatments – treatment policy (as part of treatment) 3. Changing randomised treatment or not receiving randomised treatment - treatment policy (as part of treatment) 4. Use of other medications/treatments/therapy - treatment policy (as part of treatment) 5. Death – while alive
Summary measures	**Hazard Ratio for the risk of ER post-randomisation between** 1) (Kono-S yes vs. no) and 2) extended mesenteric resection yes vs. no) groups.

Strategies:

Treatment policyÎ Ì regardless of any post randomisation events, the treatment effect is described from the final outcome measure in all patients. Note that this approach cannot be used for truncated events, for example, where a variable cannot be measured due to death"[23]

While alive – data up to death will be included and patients will be censored at date of death if ER hasnÑ occurred before

Research questions answered by the estimands framework:

In patients undergoing ileocaecal resection surgery for primary/recurrent CrohnÑs disease what is the between group difference in the time to endoscopic recurrence expressed as a hazard ratio, between patients/participants randomised to receive Kono_S surgery/procedure/treatment, performed with or without extended or closed mesenteric resection, in addition to usual post-surgery care followed by any subsequent therapy/treatment (as needed) compared with patients randomised to receive treatment no Kono_S (or standard anastomosis) surgery, (with or without extended or closed mesenteric resection) followed by any subsequent therapy/treatment (as needed), up to 3 years after randomisation, or until death (whichever occurs first), regardless of study treatment compliance/discontinuation?

In patients undergoing ileocaecal resection surgery for primary/recurrent CrohnÑs disease what is the between group difference in the time to endoscopic recurrence expressed as a hazard ratio, between patients/participants randomised to receive extended mesenteric resection surgery/procedure/treatment, performed with Kono-S or standard anastomosis, in addition to usual post-surgery care followed by any subsequent therapy/treatment (as needed) compared with patients randomised to receive closed mesenteric resection, performed with Kono-S or standard anastomosis followed by any subsequent therapy/treatment (as needed), up to 3 years after randomisation, or until death (whichever occurs first), regardless of study treatment compliance/discontinuation?

<u>Process of choosing primary treatment effects:</u>

Analysis of the primary endpoint will be by mixed-effects parametric survival model with random effects for centre and surgeon and fixed effects for Kono-S (yes vs. no) and extended mesenteric resection (yes or no), as well as for important prognostic factors (see below). The model will be implemented using a Weibull survival distribution, and an exchangeable variance-covariance structure of the random effects. An accelerated failure time model will be considered if the data suggest a different hazard function.

Prognostic factors:

- Smoking status at randomisation (yes vs. no)
- Previous abdominal surgery for Crohn's (yes vs. no)
- Degree of visceral fat (fat wrapping minimal, mesenteric thickening minimal vs. fat wrapping <25% circumference of bowel, thickening of vascular pedicle only vs. fat wrapping <25% circumference of bowel, pan mesenteric thickening vs. fat wrapping >25% circumference of bowel, pan mesenteric thickening)
- Resection margin positivity (yes vs. no)
- Behaviour or CD (B1 non-stricturing, non-penetrating vs. stricturing vs. penetrating)

Initially, an interaction effect between the Kono-S and the extended mesenteric resection will be added to the above-described model.

We will report the estimate of the interaction term and its associated 95% confidence interval (CI).

- If the CI for the HR for the interaction term includes one (no evidence of an interaction) then we will analyse the data without the interaction term.
  The hazard ratios (HRs), corresponding 95% confidence intervals and p-values will be presented for the Kono-S vs. standard anastomosis contrast and extended mesenteric resection vs. close resection contrasts will be reported from this simpler model.
- If the CI for the HR for the interaction term excludes one (i.e. evidence of an interaction) then we will analyse the data using the four randomised groups (1. Kono-S + extended mesenteric resection; 2. Kono-S + close mesenteric resection; 3. Standard anastomosis + extended mesenteric resection; 4. Standard anastomosis + close mesenteric resection) separately. The hazard ratios (HRs), corresponding 95% confidence intervals and p-values will be presented for the following comparisons by changing the reference category in the model:
  - Kono-S + Extended mesenteric resection vs. Kono-S + Close mesenteric resection
  - Kono-S + Extended mesenteric resection vs. Standard anastomosis + Extended mesenteric resection
  - Kono-S + Extended mesenteric resection vs. Standard anastomosis + Close mesenteric resection
  - Kono-S + Close mesenteric resection vs. Standard anastomosis + Extended mesenteric resection
  - Kono-S + Close mesenteric resection vs. Standard anastomosis + Close mesenteric resection
  - Standard anastomosis + Extended mesenteric resection vs. Standard anastomosis + Close mesenteric resection
  - Standard anastomosis + Close mesenteric resection vs. Standard anastomosis + Extended mesenteric resection

Three Kaplan Meier plots, of the time to ER, will be shown for the primary analysis for all four randomised groups and for the factorial design main comparisons (Kono-S yes vs. no) and extended mesenteric resection yes vs. no).

5.2.1. Model Checking

Model assumptions will be assessed graphically using the following methods:

- We will present log-log plots (−ln(−ln(survival)) vs. ln(analysis time) for each of the treatment variables outlined in the analysis model above.
  Lines need to be approximately parallel for the model to be deemed appropriate.
- We will compare predicted and observed values graphically.

5.3. Sensitivity Analyses of the Primary Outcome

Using the analysis model selected for the primary endpoint, a number of sensitivity analyses will be performed, and treatment effects and 95% CIs will be generated for

- An alternative definition of the primary endpoint, i.e. ER including surgical recurrence, as defined in section 5.1.1
- The PP population.

5.4. Subgroup Analyses

The following sub-group analysis will be completed on an ITT basis. Subgroup effects will be shown for the anastomosis procedure (Kono-S vs. standard anastomosis), and separately for the mesenteric resection type (extended mesenteric resection vs. close mesenteric resection) comparisons.
The analysis will be the same model as the primary analysis with the addition of an interaction term between the relevant treatment variable and subgroup to assess the stability of the result in different populations.
*Note: two separate models will be run to, including the interactions between anastomosis procedure by subgroup and mesenteric resection type by subgroup in turn.

Treatment effect estimates with 95% confidence intervals will be calculated for each sub-group.

a) Smoking status (current vs. previous vs. never)
b) Family history of inflammatory bowel disease (none vs. ulcerative colitis vs. CD)
c) Penetrating CD (yes vs. no)
d) Recurrent CD (yes vs. no)
e) Presence of perianal disease (yes vs. no)
f) Resection margin positivity (yes vs. no)
g) Presence of granulomas (yes vs. no)
h) Extensive small bowel disease (yes vs. no)
   Extensive small bowel disease is present if any of the following apply: extensive bowel disease is met if any of the following apply:
   - >50cm of small bowel length resected
   - Strictureplasty (under additional procedures performed)
   - Additional bowel resection (under additional procedures performed)
i) Degree of visceral fat (fat wrapping minimal, mesenteric thickening minimal vs. fat wrapping <25% circumference of bowel, thickening of vascular pedicle only vs. fat wrapping <25% circumference of bowel, pan mesenteric thickening vs. fat wrapping >25% circumference of bowel, pan mesenteric thickening)
j) Previous abdominal surgery for Crohn's disease (yes vs. no)
k) Location of CD (L1 Terminal ileum vs. L2 Colon vs. L3 Ileocolon)
l) L4 Concomitant upper GI disease (yes vs. no)
m) Behaviour or CD (B1 non-stricturing, non-penetrating vs. stricturing vs. penetrating)
n) B4 concomitant perianal disease (yes vs. no)
o) Anastomotic technique (suture/handsewn vs. stapled)

Results from the subgroup analyses will be displayed graphically, using Forest Plots or similar graphs. Subgroup effects will be presented. No statistical testing for subgroup effects will be performed.

5.5. Handling Missing Data

Missing observations can occur for numerous reasons (e.g. attrition) which can shrink the sample size, affects the precision of confidence intervals, reduce statistical power and, crucially, may bias parameter estimates [24]. Appropriately handling of missing observations requires careful examination of data to identify the type and pattern of missingness.

In the MEETKAT study, we expect rates of missing data for the primary endpoint, ER, to be low as data collection is based on routine clinical care, and results can be obtained from medical notes. Therefore, the vast majority of participants will be conclusively identified as either having ER or not.
The primary analysis model handles missing data via censoring, which is appropriate under the assumptions that missing data are non-informative, or missing at random, that is that the probability of data being missing is unrelated to the (unobserved) ER after accounting for the covariates included in the analysis model.
However, the assumptions about missing data cannot be tested, and this sensitivity analysis explores the impact of alternative assumptions on the conclusions of the trials.

In a worst-case sensitivity analysis scenario, the following participants with missing data for ER in the primary analysis will be assumed to have had an ER in this sensitivity analysis:

- Participants without data for a Rutgeerts score will be assumed to have had a Rutgeerts score ≥i2 at the corresponding endoscopy
- Participants without an endoscopy at the protocol stipulated follow-up (approximately 6 to 15 months post surgery), and no subsequent endoscopies with a Rutgeerts score <i2 will be assumed to have an ER (Rutgeerts score ≥i2) at 12 months post randomisation

In a best-case sensitivity analysis scenario, participants who were censored before the end of the study will be assumed to not have had ER (Rutgeerts score ≥i2) until the end of the study, or until their date of death.

5.5.1. Partial Dates

If there are any issues with partial dates in the database, the following approaches will be used to deal with them and therefore still allow derived time variables to be calculated with sufficient precision:

If only month and year are available ("MM/YYYY"), replace with "15/MM/YYYY".

Dates with missing months cannot be used in the analyses.

5.6. Analysis of Secondary Outcomes

5.6.1. Time-to-event outcomes

All secondary time-to-event outcomes will be analysed using the statistical model chosen for the primary endpoint.

Variables analysed as outlined above are:

- Time to Severe ER (Rutgeerts score ≥i3)
- Time to clinician and patient-reported symptomatic recurrence

- Surgical recurrence

Mean and median survival times will be presented.

5.6.2. Binary outcomes

The variables analysed as time to event data will also be considered as binary outcomes in additional analyses.

For each time-to-event outcome, two binary variables will be generated, one indicating if an event occurred within one year (15 months will be used as a cut-off, in line with the time window around assessments as outlined in the protocol), and one if an event occurred at any time during the follow-up.

Variables are coded as follows:

- 1 – event occurred – if the event occurred within the relevant time period
- 0 – no event – if no event was reported within the relevant time period, and the participant was not censored within that time period
- Missing – if no event was reported within the relevant time period, and the participant was censored within that time period.

Variable	Event occurred	Event did not occur	Variable missing
ER within one year from randomisation	Rutgeerts score ≥i2 within 15 months* from randomisation.	No Rutgeerts score ≥i2 recorded within 15 months* from randomisation, and at least one valid Rutgeerts score post-randomisation available	No valid Rutgeerts scores available
ER at any time during the follow-up	Rutgeerts score ≥i2 at any point during the follow-up	No Rutgeerts score ≥i2 recorded, and at least one valid Rutgeerts score post-randomisation available	No valid Rutgeerts scores available
Severe ER within one year from randomisation	Rutgeerts score ≥i3 within 15 months* from randomisation	No Rutgeerts score ≥i3 recorded, and at least one valid Rutgeerts score available	No valid Rutgeerts scores available
Severe ER at any time during the follow-up	Rutgeerts score ≥i3 at any point during the follow-up	No Rutgeerts score ≥i3 recorded, and at least one valid Rutgeerts score available	No valid Rutgeerts scores available

Clinician and patient-reported endoscopic recurrence within one year from randomisation	If, within 15 months* from randomisation, the participant meets at least one of these criteria: •surgical re-intervention in combination with histological confirmation of recurrence •change of medical strategy for recurrence (excluding changes for safety/tolerability) •IBD Control >13 •CDAI >220	If, within 15 months* from randomisation, the participant meets at none of these criteria: •surgical re-intervention in combination with histological confirmation of recurrence •change of medical strategy for recurrence (excluding changes for safety/tolerability) •IBD Control >13 •CDAI >220	No event reported, but missing data in at least one of the variables.
Surgical recurrence within one year from randomisation	Surgical recurrence (as defined above) within 15 months* from randomisation	No surgical recurrence within 15 months, and no withdrawal from follow-up before 15 months	No surgical recurrence within 15 months, and withdrawal from follow-up before 15 months
Surgical recurrence at any time during the follow-up	Surgical recurrence (as defined above) from randomisation	No surgical recurrence, and no withdrawal from follow-up before end of study	No surgical recurrence, and withdrawal from follow-up before end of study

*15 months are used to include the time-window stipulated in the protocol (12 months [-6 months/+3 months])

The frequency and proportion of participants with the relevant event will be presented for each of the four treatment combinations, as well as for main comparisons, i.e. Kono-S vs standard anastomosis and extended vs close mesenteric resection.
Odds ratios and 95% CIs for the comparisons between the two factors (1: Kono-S vs standard anastomosis and 2: extended vs close mesenteric resection) will be generated from multi-level mixed effects logistic regression models with adjustment for baseline covariates in line with the primary analysis model. Interaction terms between the surgeries will not be included for secondary analyses.
Absolute risk differences with 95% Cis will also be presented.

Variables analysed as outlined above are:

- ER (Rutgeerts score ≥i2)
- Severe ER (Rutgeerts score ≥i3)
- Clinician and patient-reported symptomatic recurrence
- Surgical recurrence

Data for the different components of the endpoints listed above (i.e. surgical re-intervention in combination with histological confirmation of recurrence, change of medical strategy for recurrence

(excluding changes for safety/tolerability), IBD Control >13, CDAI >220) will also be reported at the relevant follow-up times.

5.6.3. Continuous outcomes

Summary statistics, including means and standard deviations, will be presented for each of these variables at baseline, and six weeks and 12-months follow-up.

Mean differences and 95% CIs for the comparison between the two factors (1: Kono-S vs standard anastomosis and 2: extended vs close mesenteric resection) will be generated from multi-level mixed effects regression model with adjustment for baseline covariates in line with the primary analysis model. Interaction terms between the surgeries will not be included for secondary analyses. The model will include repeated measures of the continuous variables (level 1) nested within participants (level 2) and adjusted for recruitment centre as a random effect (level 3). Time will be included in the model as a categorical variable (factor variable), indicating the protocol stipulated follow-up time point, and a treatment by time interaction.

Variables analysed as outlined above are IBD Control, CDAI, Quality of life (EQ-5D-5L index and VAS). Time to endoscopic recurrence will not be analysed as a continuous outcome. Instead, mean and median survival times will be presented.

5.6.4. Model Checking

Frequency graphs and the ratio of the variance to the mean will be used to assess the distribution of severe hypoglycaemia episodes. Failure to properly address existing over dispersion leads to serious underestimation of standard errors and misleading inference for the treatment effect. The Deviance and Likelihood Ratio Test (LRT) will be employed to assess goodness of fit of the Poisson linear regression model against two specific alternatives: a) a zero-inflated Poisson Generalised Linear Model (GLM) (in the case of overdispersion due to excess zeros, or participants who experienced no episodes), and b) negative binomial regression for more general overdispersion. Further model diagnostics including measures of influence such as Cook's Distance will be undertaken for sensitivity analysis.

Unlike linear regression where graphical diagnostic displays can be very useful, for logistic regression models, the discreteness of binary data makes it difficult to interpret such displays. Three methods will be used for diagnostic checking of logistic regression models. Local mean deviance plots for detecting overall lack of fit, empirical probability plots to point out isolated departures from the fitted model and partial residual plots (smoothed) to identify specific causes of lack of fit.

5.7. Mediation analysis

A separate analysis plan will be written for the mediation analysis.

5.8. Safety Outcomes

Adverse Events (AE) will be recorded throughout the trial and are defined as any unwanted medical occurrences. Serious Adverse Event (SAE) will also be recorded throughout the trial and are defined

as AEs which result in hospitalisation or have a risk to life. A detailed description of AEs and SAEs can be found in the protocol.

Summary measures will be presented by treatment group as the number and percentage of participants reporting an AE/SAE as well as the total number of AE/SAEs reported and will be on an ITT basis. No formal statistical testing will be undertaken.
Rates of SAEs per person year will also be presented.

5.9. Statistical Software

This analysis will be carried out using any suitable packages such as R [25] or STATA [26].

6. REFERENCES

6.1. Documents

Title	Version	Date	Location
Trial Protocol	2.0	28-06-2023	[redacted]
Data Management Plan			
ST001 The Statistical Analysis Plan	6	10-12-2021	[redacted]
ST006 Undertaking a Statistical Analysis	3	08-02-2021	[redacted]
DM012 Study Database Lock and Retention	6	22-03-2022	[redacted]

6.2. Publications

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7. APPENDICES

7.1. Example CONSORT flowcharts

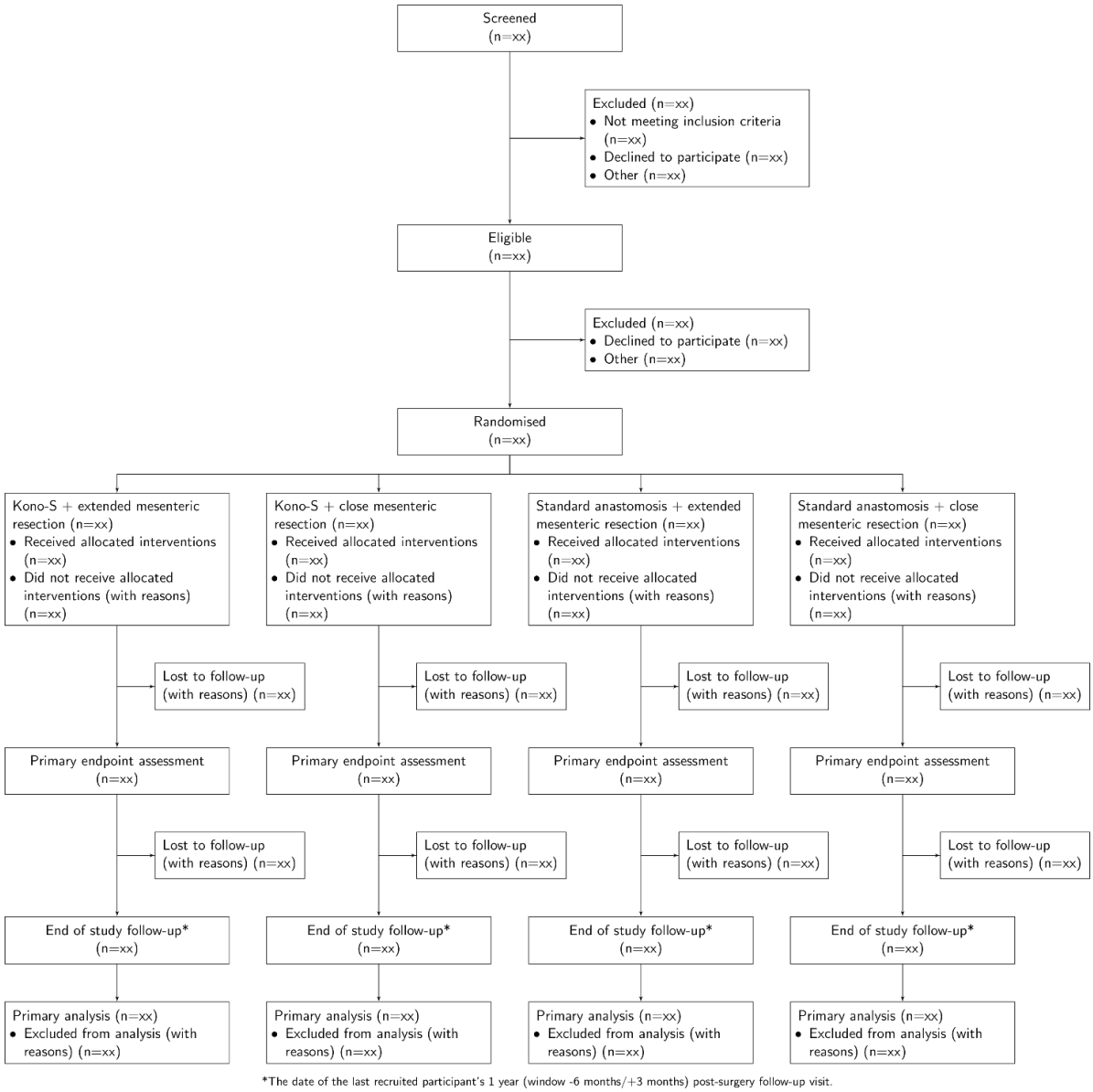

Figure 7.1 Example CONSORT flowchart for the randomisation arms.

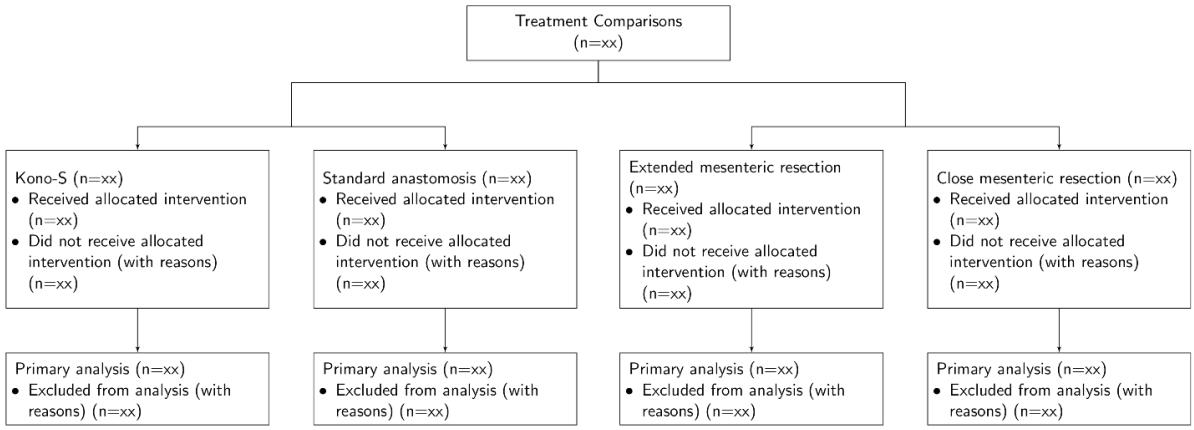

Figure 7.2 Example CONSORT flowchart for the treatment comparisons.