Optimisation before Crohn's surgery using Exclusive enteral Nutrition:

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BACKGROUND & RATIONALE

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract, with a significant burden amongst young patients. Medication such as oral immunosuppressants and biologics are the mainstay of treatment for CD, however surgery continues to have a role in disease management. Exclusive Enteral Nutrition (EEN) is widely used in paediatric CD as first line therapy for the induction of remission without the use of steroids. To date, there have been no randomised controlled trials 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.

Research Question:

Is pre-operative Exclusive Enteral Nutrition (EEN) more clinically and cost-effective compared with usual diet in patients undergoing surgery for Crohn's disease (CD)?

TRIAL DESIGN

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.

Intervention: Six weeks of EEN prior to surgery vs usual diet as per local standard care.

Target 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.

OBJECTIVES

Primary objective: 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: 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 index 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

Economic objective: 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.

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

ELIGIBILITY CHECKLIST

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

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 or follow up

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OUTCOMES

Primary outcomes:

Dual primary outcomes at 6 weeks post-surgery:

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

Secondary outcomes:

Patient reported outcomes:

- Quality of life over time using CLIQ which will be collected 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)

Clinical outcomes:

- 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
- Number of participants requiring stoma formation
- Number of participants who develop an anastomotic leak
- Number of participants who required expedited surgery
- Number of participants re-admitted within 30 days of discharge
- Number of participants requiring re-operation within 30 days of index surgery
- Number of participants who develop enterocutaneous fistulae within 90 days of surgery
- Number of participants who develop clinical recurrence of their CD at 24 and 52 weeks as assessed by Crohn's disease activity index
- Number of participants who develop endoscopic disease recurrence at 24-52 weeks
- Number of participants on steroids at baseline who were able to wean off steroids prior to surgery
- Safety assessed through adverse event and serious adverse event reporting
- Number of participants whose planned surgery did not proceed due to clinical improvement

Economic outcome:

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

Qualitative outcome:

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

KEY POINTS

- Pragmatic study designed in line with current clinical practice and patient visits.
- The trial utilises remote consent.
- All data entry is electronic.
- Co-enrolment with MEERKAT is permitted.
- The trial includes the COAST (Crohn's Optimisation and Surgical Timing) sub study.
- The trial supports the NIHR Associate PI scheme.
- Additional funding will be made available for patients randomised to the EEN arm and we suggest that this may be best used to support the dietetic service.

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INTERNAL PILOT OBECTIVES

Stop/Go Traffic light system criteria:

After 9 months of recruitment the stop/go criteria will be assessed. At this point, we anticipate that we will have recruited 100 participants from 20 trial sites.

Progression criteria for Pilot	Red *(stop)*	Amber *(modify)*	Green *(go)*
Acceptance rate (% eligible who agree to take part in the study)	<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%

CURRENT STATUS

REC approval received in July 2023. Planned start date for recruitment is January 2024.

STUDY REFERENCE INFORMATION

Sponsor: University of Birmingham

Sponsor Ref no: RG_23-020

REC: London City & East REC

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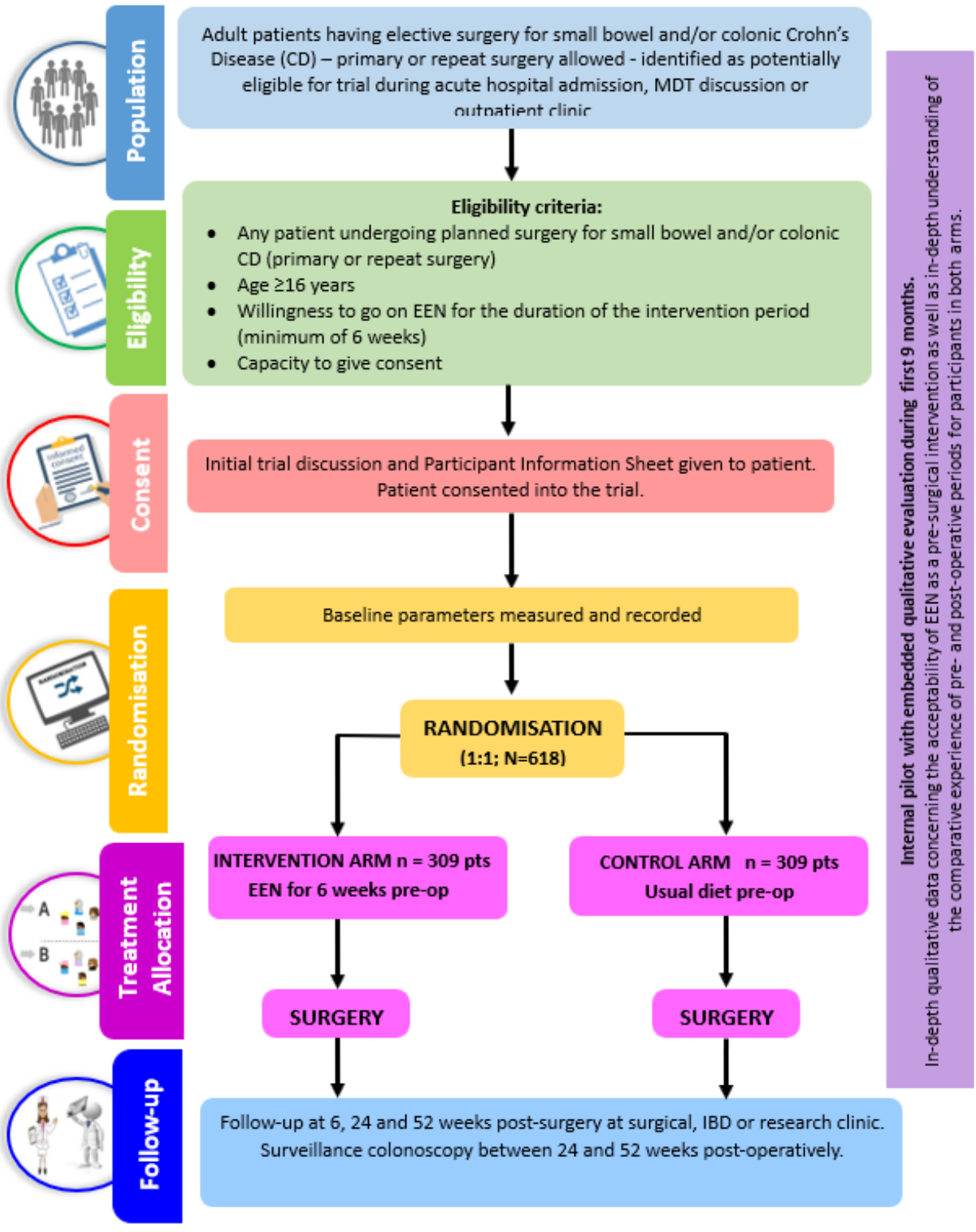
TRIAL SCHEMA



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