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# Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Title:	Clinical effectiveness of elemental nutrition for the maintenance of
	remission in Crohn's disease: a systematic review and meta-analysis
Produced by:	Warwick Evidence
	Division of Health Sciences
	Warwick Medical School
	University of Warwick
	Coventry
	CV4 7AL
Authors:	Alexander Tsertsvadze, Senior Research Fellow <sup>1</sup>
	Tara Gurung, Research Fellow <sup>1</sup>
	Rachel Court, Information Specialist <sup>1</sup>
	Aileen Clarke, Professor of Public Health and Health Services
	Research and Director for Warwick Evidence <sup>1</sup>
	Paul Sutcliffe, Associate Professor and Deputy Director for Warwick
	Evidence <sup>1*</sup>
<sup>1</sup> Warwick Evidence, Divis	ion of Health Sciences, Warwick Medical School, University of Warwick,
Coventry, CV4 7AL	

*Corresponding author:	Dr Paul Sutcliffe
	Warwick Evidence
	Division of Health Sciences
	Warwick Medical School
	University of Warwick
	Coventry
	CV4 7AL
Tel:	02476 150189
Fax:	02476 528375
Email:	p.a.sutcliffe@warwick.ac.uk

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#### **Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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#### **Contributions of authors**

Paul Sutcliffe (Associate Professor) coordinated the report. Alexander Tsertsvadze (Senior Research Fellow), Tara Gurung (Research Fellow) and Paul Sutcliffe conducted the systematic review, this included: screening and retrieving papers, assessing against the inclusion criteria, appraising the quality of papers and abstracting data from papers for synthesis. Rachel Court (Information specialist) developed the search strategy and undertook searches. Aileen Clarke (Professor) wrote sections of the abstract, executive summary and discussion and provided comments throughout. All authors were involved in writing the draft and final versions of the report.

### ABSTRACT

**Background:** Although enteral nutrition has been shown to be a viable treatment option for the management of active Crohn's Disease (CD), the evidence regarding its clinical benefits compared to standard treatments (e.g., steroids) for maintaining remission in patients with CD has been inconsistent. If enteral nutrition was to be effective, the use of drugs such as steroids and immunosuppressive drugs could be reduced, thereby reducing the likelihood of adverse events associated with these medications.

**Objectives:** This systematic review aimed to assess the effectiveness and cost-effectiveness of elemental nutrition (a type of enteral nutrition) for maintenance of remission in patients with CD.

**Methods:** Electronic searches of major databases (e.g., MEDLINE, EMBASE, CDSR), not limited by study design, language, or publication date were carried out. Websites for relevant organisations and references of included studies were checked. Randomised and non-randomised experimental controlled trials (RCTs and non-RCTs) reporting clinical effectiveness and/or cost-effectiveness of elemental nutrition in the maintenance of remission in patients with CD were eligible. Study selection, data extraction, and risk of bias assessment were performed independently. Risk ratios (RRs) and mean differences (MDs) were pooled using a random-effects model. Heterogeneity was assessed via forest plots, Cochran's Q and the I<sup>2</sup> statistics. Overall quality of evidence for each outcome was rated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

**Results:** Twelve of 36 potentially relevant papers were included in the review (representing three RCTs and five non-RCTs). RCTs indicated a significant benefit of elemental nutrition vs. no intervention (an unrestricted diet) in maintaining remission at 24 months (one RCT; RR=2.06, 95% CI: 1.00, 4.43; very low grade evidence) and preventing relapse at 12-24 months post-baseline (two RCTs; pooled RR=0.57, 95% CI: 0.38, 0.84; high grade evidence). Similarly, three non-RCTs showed significant benefits of elemental nutrition over no intervention in maintaining remission at 12-48 months and preventing relapse at 12 months post-baseline (MD=1.20 months, 95% CI: 0.35, 2.04). Incidence of mucosal healing between intervention and control groups was not significantly different (RR=2.70, 95% CI: 0.62, 11.72). Adherence was significantly worse for an elemental compared to polymeric nutrition (RR=0.68, 95% CI: 0.50, 0.92). When compared to other active treatments (medications, polymeric nutrition, or a combination), elemental nutrition yielded non-significant results

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with wide 95% CIs, rendering these results inconclusive. Complications and adverse events were too sparse to allow meaningful comparisons. None of the studies reported cost-effectiveness of elemental nutrition.

**Limitations:** The findings warrant cautious interpretation given the limitations of the evidence in methodological quality (small samples, short follow-up) and the risk of bias in individual studies (lack of blinding, confounding). Due to scarcity of data, no subgroup or sensitivity analysis was performed.

**Conclusions:** Limited evidence indicates potential benefits of elemental nutrition against no intervention in the maintenance of remission and prevention of relapse in adult patients with CD. There was lack or insufficient evidence on adverse events and complications. Future large and long-term randomised trials are warranted to draw more definitive conclusions regarding the effects of elemental nutrition in maintaining remission in CD.

# PLAIN ENGLISH SUMMARY

We conducted a systematic review of eight prospective controlled experimental trials which examined the effectiveness of elemental nutrition for the maintenance of remission in patients with Crohn's disease (CD). Based on the limited amount of evidence, elemental nutrition was more beneficial than an unrestricted diet for the maintenance of remission and prevention of relapse in the short-term. Evidence comparing the benefits of elemental nutrition to other treatment options (standard medication, polymeric nutrition) for maintaining remission was uncertain, and therefore, inconclusive. There was insufficient information on adverse events and complications. This review identified methodological shortcomings of individual studies (small samples, short follow-up, bias) and gaps in evidence (no cost-effectiveness studies of elemental nutrition for maintenance of remission; no studies of elemental nutrition in children or young adults in remission). Future large and long-term randomised trials are warranted to draw more definitive conclusions regarding the effects of elemental nutrition in maintaining remission in CD.

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# GLOSSARY

# **Enteral nutrition**

A method of delivering nourishment through a tube placed in the nose (nasogastric or nasoenteral tube), the stomach (gastrostomy or percutaneous endoscopic gastrostomy tube), or the small intestine (jejunostomy or percutaneous endoscopic jejunostomy tube). Enteral nutrition varies in the protein and fat content and can be classified as elemental, semi-elemental, polymeric or specialised.

# **Elemental nutrition**

Elemental nutrition is a liquid monomeric amino-based formula, which contains individual amino acids, glucose polymers, and is low in fat with about 2% to 3% of calories derived from long chain triglycerides (LCT). Elemental nutrition formula does not contain antigens.

# **Semi-elemental nutrition**

Semi-elemental nutrition is liquid oligopeptide formula that contains peptides of various chain lengths, simple sugars, glucose polymers or starch and fat, mainly as medium chain triglycerides (MCT).

## **Polymeric nutrition**

Polymeric nutrition is a liquid whole-protein based formula that contains intact proteins (sources: milk, meat, egg, soy), complex carbohydrates and mainly LCTs.

## **Specialised nutrition**

Specialised nutrition is liquid formula that contains biologically active substances or nutrients such as glutamine, arginine, nucleotides or essential fatty acids.

# Parenteral nutrition and total parenteral nutrition

Parenteral nutrition involves feeding via the blood stream intravenously, total parenteral nutrition means feeding solely via the intravenous route.

# LIST OF ABBREVIATIONS

AST	Aspartate transaminase
ASA	Amino-salicylic acid
BMI	Body Mass Index
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CICRA	Crohn's in Childhood Research Association
CI	Confidence interval
CRP	C - reactive protein
CCTs	Controlled clinical trials
DARE	Database of Abstracts of Reviews of Effects
ED	Elemental Diet
EMBASE	Excerpta Medica Database
EEN	Exclusive enteral nutrition
ESR	Erythrocyte sedimentation rate
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HR	Hazard ratio
HQOL	Health-related quality of life
IBD	Inflammatory bowel disease
IOIBD	International Organization for the Study of Inflammatory Bowel
	Disease
ICER	Incremental cost-effectiveness ratio
LCT	Long chain triglycerides
MCT	Medium chain triglycerides
MD	Mean difference
MP	Mercaptopurine
MEDLINE	Medical Literature Analysis and Retrieval System Online
nRCT	Non randomised controlled trial
NACC	National Association for Colitis and Crohn's Disease
NA	Not applicable
NG	Nasogastric
NICE	National Institute for Health and Clinical Excellence

NI	No intervention
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NS	Not significant
NR	Not reported
OR	Odd ratio
PEN	Partial Enteral Nutrition
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QOL	Quality of life
QALYs	Quality-adjusted life-years
RR	Risk ratio (relative risk)
RCT	Randomised controlled trial
ROB	Risk of bias
SD	Standard deviation
SE	Standard error
SS	Statistically significant
SROB	Summary risk of bias
TNF	Tumor necrosis factor
UK	United Kingdom
UKCRN	UK Clinical Research Network
WHO	World Health Organisation
WHO ICTRP	WHO International Clinical Trials Registry Platform

# **EXECUTIVE SUMMARY**

## Background

Crohn's disease (CD) is a relapsing-remitting condition which causes chronic inflammation of the gastrointestinal tract. Frequent symptoms of CD include malnutrition, abdominal pain, diarrhoea, and weight loss. The objective of CD management is to induce and maintain remission of disease by controlling inflammation, reducing clinical symptoms, and preventing complications. The management of children with CD involves additional goals to promote normal growth and pubertal development. The choice of therapy depends on the extent of inflammation, the disease severity, and complications.

None of the currently available therapeutic options including medical (e.g., corticosteroids, biologics, antibiotics), surgical (e.g., bowel resection), and nutritional (e.g., enteral/parenteral feeding, restricted diet) leads to complete cure of CD. Although corticosteroids are the most widely used drugs for the treatment of active CD and their use has been shown to be associated with short-term remission, they are also associated with steroid dependency, impairment in growth, and risk of infection. Tumour necrosis factor inhibitors are also used but there are safety concerns with their long-term use.

Recently, enteral nutrition has been shown to be a viable treatment option in the management of active forms of CD. But evidence regarding the efficacy of an enteral nutrition relative to standard treatment (i.e., steroids) has been inconsistent. For example, one meta-analysis showed that enteral nutrition was at least as effective as steroids in inducing remission in children and young adults with active CD. In contrast, a more recent meta-analysis indicated that enteral nutrition was less beneficial compared to steroids in inducing remission in adults with active CD. In Japan, enteral nutrition is recommended as the first-line treatment in the management of active CD.

Evidence for the efficacy of different types of enteral nutrition (i.e., elemental, semi-elemental, polymeric) in maintaining remission in CD has been insufficient and is less clear. Most of the comparative evidence on the maintenance of remission rests on a few retrospective observational cohort studies and prospective non-randomised controlled trials (non-RCTs). If enteral nutrition proves to be as effective as conventional medications, its use might minimize or replace the use of conventional drugs (e.g., steroids).

# **Objectives**

This review aimed to evaluate clinical effectiveness and cost-effectiveness of elemental nutrition (a type of enteral nutrition) for the maintenance of remission in CD. The specific aims of this review were to explore:

- The clinical effectiveness and cost-effectiveness of elemental nutrition compared to other interventions (e.g., placebo, unrestricted diet, standard drug treatment, or other types of enteral nutrition such as polymeric and semi-elemental) for maintaining remission in patients with quiescent CD.
- Whether the treatment effect of elemental nutrition on the maintenance of remission varies across groups defined by dose/duration of elemental nutrition, sex (males, females), age (adults, adolescents, and children), and type of induction therapy (medically-, nutritionally-, surgically-induced).
- Additional outcomes for patients with CD: adherence to elemental nutrition, CD activity index (CDAI), incidence of mucosal healing, quality of life (QOL), adverse events, gain in body weight (or body mass index [BMI]), growth, and pubertal development.

## Methods

#### Search strategy and data sources

Electronic searches were carried out in MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE (via OVID); CDSR, CENTRAL, DARE, NHS EED, HTA database (via the Cochrane Library); Science Citation Index and Conference Proceedings (via Web of Knowledge); WHO ICTRP; UKCRN Study Portfolio. The searches were not limited by study design, language, or publication date. Websites for relevant organisations as well as references of included studies were checked for relevant studies. All the retrieved records were collected and then de-duped using a specialized database.

#### Study eligibility criteria

English publications of RCTs and non-RCTs comparing clinical effectiveness and/or costeffectiveness of elemental nutrition to no intervention (restricted/unrestricted diet) or other types of treatment (e.g., placebo, semi-elemental/polymeric nutrition, standard drug therapy) in patients with CD in remission at baseline were eligible for inclusion. Reviews, meta-analyses, observational cohort studies, case-reports, case-series, editorials, or comments were excluded.

#### **Outcomes of interest**

Primary review outcomes were maintenance of remission (% patients maintaining remission, cumulative probability of remission, and duration of remission), development of relapse (% patients developing relapse, time to relapse), and incidence of mucosal healing (% patients with endoscopic mucosal healing). Secondary outcomes were adherence to elemental nutrition, need for surgery, withdrawals from steroids, CDAI score, QOL, gain in body weight or BMI, pubertal development, adverse events, and complications.

#### Study selection and data extraction

Two independent reviewers used a pre-piloted form to screen the identified records for title/abstract. Afterwards, full text reports of all potentially relevant abstracts were retrieved and examined independently. Disagreements were resolved via discussions and consensus agreement.

Two reviewers using a pre-piloted form independently extracted relevant data on study (e.g., author, country, design, sample size), participant (e.g., age, sex, type of induction therapy), intervention (e.g., type, mode/dose of administration, concomitant diet or medications), and outcome characteristics (e.g., scale of measurement, assessment timing, definition of CD relapse). The extracted data were cross-checked by second reviewer and any disagreements were resolved by discussion.

#### **Risk of bias assessment**

Two reviewers independently assessed risk of bias of individual studies. We used the Cochrane Collaboration Risk of Bias (ROB) tool to assess RCTs which rates risk of bias (high, low, and unclear) across selection, performance, detection, attrition, and reporting domains. Non-RCTs were assessed using a modified Cochrane ROB tool in which the domain of selection bias was evaluated in regards to baseline between-group imbalance for important prognostic factors. Disagreements on extractions were resolved by a third reviewer through discussion.

The quality of economic analyses of the included studies was planned to be assessed using the Drummond 10-item checklist.

#### Data synthesis and overall quality of evidence

Study, treatment, population, and outcome characteristics were summarised in text and summary tables. The data on effectiveness of elemental nutrition for each outcome of interest were compared qualitatively and quantitatively in text and summary tables. Results for each outcome were stratified

by a comparison of elemental nutrition to no intervention (i.e., restricted/unrestricted diet), drug alone, combination of elemental nutrition and drug, and other types of enteral nutrition.

The decision to pool data was based on a degree of similarity with respect to methodological and clinical characteristics of studies. Post-treatment mean differences for continuous and risk ratios for binary measures were planned to be pooled using a DerSimonian and Laird random-effects model. The degree of heterogeneity was determined through inspection of the forest plots, Cochran's Q and the I<sup>2</sup> statistics. The heterogeneity was judged according to pre-determined levels of statistical significance (Chi<sup>2</sup>-based p<0.10 and/or I<sup>2</sup>>50%). Study-level clinical and methodological sources of heterogeneity was planned to be explored through a priori defined subgroup (i.e. age, sex, induction therapy) and sensitivity analysis. Publication bias was planned to be assessed through visual inspection of funnel plots for asymmetry and use of linear regression tests.

Results were rendered inconclusive in cases of missing/partially reported data (undetermined effect measures, 95% confidence intervals) or statistically non-significant effect estimates with great uncertainty (i.e., sufficiently wide intervals that include moderate to large effect size treatment effects in both directions compatible to either benefit or harm of elemental nutrition).

The overall quality of evidence (high, moderate, low, very low grade) for pre-selected gradable outcomes (e.g., maintenance of remission, risk of relapse) was assessed using an approach developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org).

#### Results

A total of 630 records were identified and screened, of which 594 were excluded at title/abstract level. Of the remaining 36 records screened at full-text level, 12 were included in the review (representing three RCTs and five non-RCTs).

Out of eight studies, six were conducted in Japan and two in the UK. The sample size ranged from 33 to 95 participants. The mean age ranged from 22 to 44 years and length of follow-up from 12 to 48 months. Type of induction therapy in most studies was medical (standard drugs, enteral or parenteral nutrition). Elemental nutrition was given in addition to unrestricted/restricted diet through tube infusion and/or oral intake. Participants in the control groups received either unrestricted diet (no intervention), standard drug (e.g., 6-MP, infliximab, prednisolone) or polymeric nutrition.

RCTs indicated a significant benefit of elemental nutrition vs. no intervention (unrestricted diet) in maintaining remission after 24 months of follow-up (one RCT; RR=2.06, 95% CI: 1.00, 4.43; very low grade evidence) and preventing relapse at 12-24 months of follow-up (two RCTs; pooled RR=0.57, 95% CI: 0.38, 0.84; high grade evidence). The 6-12 month maintenance rate was not significantly different (RR=1.37, 95% CI: 0.86, 2.17; very low grade evidence; inconclusive result due to wide 95% CIs).

Similarly, three non-RCTs showed significant benefits of elemental nutrition over no intervention (unrestricted diet) in maintaining remission and preventing the occurrence of relapse at 12 months. In one non-RCT, the use of elemental nutrition was associated with a significantly longer time to relapse compared to no intervention (MD=1.20, 95% CI: 0.35, 2.04). Incidence of mucosal healing between elemental nutrition vs. no intervention (unrestricted diet) groups at 12 months was not significantly different (inconclusive results; RR=2.70, 95% CI: 0.62, 11.72).

There was a significantly worse adherence rate to elemental nutrition compared to an unrestricted diet or polymeric nutrition (RR=0.68, 95% CI: 0.50, 0.92).

In general, effects of elemental nutrition vs. active treatments (medications, polymeric nutrition, or combination) yielded statistically non-significant results across outcomes with wide 95% CIs including moderate to large treatment effects in both directions and compatible with both benefit or harm of elemental nutrition (inconclusive results). Data on complications and adverse events were too sparse (e.g., zero events, low counts) to derive effect estimates and 95% CIs or to permit any meaningful comparison between the treatments.

There was no evidence for children with CD. Likewise, none of the studies reported costeffectiveness of elemental nutrition.

Due to scarcity of data, no subgroup or sensitivity analysis could be performed.

#### Discussion

Evidence from two RCTs and three non-RCTs demonstrated short-term benefits of elemental nutrition for the maintenance of remission and prevention of relapse compared to no treatment (i.e., unrestricted diet). Adherence rates were lower in the elemental vs. no intervention or polymeric nutrition groups. This finding may be explained by the inconvenience of nasogastric feeding, poor palatability, and/or higher cost of elemental nutrition compared to an unrestricted diet or polymeric

nutrition. One RCT showed no difference in QOL between elemental nutrition and no intervention (unrestricted diet).

Generally, differences across outcomes between elemental nutrition and active treatments (i.e., medications, polymeric nutrition, or combination) were not statistically significant. These results should not be interpreted as the treatments being equivalent (or the absence of effect of elemental nutrition). The associated 95% CIs were wide and uninformative suggesting both benefit and harm of elemental nutrition. Therefore, these results are inconclusive.

The data on complications and adverse events was too sparse to permit any meaningful comparison between the treatments. It is unclear whether insufficient evidence on adverse events and complications is due to the absence or rarity of these events or it is simply due to underreporting of such events.

The review findings warrant cautious interpretation given the limitations of evidence in terms of methodological quality (small samples, short follow-up) and risk of bias in individual trials (lack of blinding, confounding). Non-RCTs in particular may have been biased because of the possibility of uneven distribution of known (e.g., location of the lesion, disease duration) or unknown prognostic factors between groups. In some non-randomised trials, patients with 'good compliance' were assigned to elemental nutrition and those with 'poor compliance' to the control treatment. It is hard to predict the direction of bias (if any), if good and poor compliers differed systematically.

Future research using long-term large RCTs would fill-in gaps in evidence (e.g., studies in young adolescents and children; effects of exclusive elemental nutrition; effects of elemental nutrition in subgroups) and improve reporting practices in relation to trial methodology and completeness of reported data for better interpretability of evidence. More research exploring better tasting elemental nutritional formulas to maximize the adherence rate to elemental nutrition is also warranted.

# Conclusions

There is limited evidence indicating benefits of elemental nutrition in the maintenance of remission and prevention of relapse in adult patients with CD. There was lack or insufficient evidence on adverse events and complications. Methodological shortcomings of individual studies and gaps in evidence have been identified. Future large and long-term randomised trials are warranted to draw more definitive conclusions regarding the effects of elemental nutrition in maintaining remission in CD.

## **1 BACKGROUND**

## **1.1 Description of health problem**

#### 1.1.1 Health problem

Crohn's disease (CD), a form of inflammatory bowel disease (IBD), is a chronic relapsing-remitting condition which causes chronic inflammation of the gastrointestinal tract. CD can affect any part of the digestive tract, from the mouth to the anus.<sup>1</sup> Usually, CD involves both the superficial and deep layers of the intestine.<sup>2</sup> CD may be characterized by location (terminal ileal, colonic, ileocolic, upper gastrointestinal) and/or pattern of disease (inflammatory, perforating, or stricturing).<sup>3</sup> The most frequently reported symptoms of CD include malnutrition, abdominal pain, diarrhoea, weight loss, fever, and rectal bleeding.

The disease can occur at any age from early childhood to late adulthood. However, it is more common among age group between 15 and 25 years. Male and female are affected equally.<sup>4, 5</sup> Around one third of people with CD are diagnosed before 21 years of age.

#### 1.1.2 Aetiology of CD

The aetiology of CD is unknown. It is hypothesized that CD may result due to interactions amongst genetic, immunological and environmental factors.<sup>6</sup> Smoking and genetic predisposition are the two important factors thought to play a key role in the aetiology of CD.<sup>7</sup>

#### 1.1.3 Clinical features of CD

The clinical course of CD is characterised by exacerbations and remission.<sup>3</sup> The clinical presentation depends on the part of the affected intestine and varies from mild to severe malnutrition, abdominal pain, diarrhoea, weight loss, fever, and rectal bleeding.<sup>5, 8</sup> The symptom pattern in children is different to that of adults, and is instead characterized by anaemia, fever, growth failure and/or delayed puberty.<sup>8</sup>

#### 1.1.4 Diagnosis of CD

Initial assessment of patients with suspected CD includes history taking, physical findings and routine blood and stool tests. Further examinations including plain abdominal radiography, colonoscopy, flexible sigmoidoscopy, endoscopy or barium x-ray are also performed. The diagnosis of CD depends upon the pathological findings of focal, asymmetric, transmural, or often granulomatous inflammation. Upper or lower gastrointestinal endoscopy should be performed to confirm the diagnosis of CD and assess disease location.<sup>8-10</sup>

#### 1.1.5 Prognosis of CD

CD is considered a serious disease which needs extensive and long-term treatment with continuous monitoring.<sup>11</sup> Quality of life is reduced for CD patients during relapse but patients with few relapses or with continuous mild symptoms manage to lead a normal life.

CD patients are affected not only physically, but also mentally (for example with depression) impacting on both their personal and professional lives. Patients with CD take more time off work and may change their time schedules at work as a direct result of their disease.<sup>12-14</sup>

As the disease progresses, patients develop complications such as strictures, perforation, and/or fistula formation, from 50% to 80% of whom will eventually require surgical interventions.<sup>7</sup>

The mortality rate amongst patients diagnosed with CD has been shown to be greater for those diagnosed at an earlier age. For example, a study by Canavan et al. reported a standardised mortality ratio (SMR) among CD patients and showed that younger patient had a worse prognosis compared to older patients (overall SMR=1.29, 95% CI: 1.12, 1.45). The SMR for patients aged 10–19 years was 16.95 (95% CI: 14.99, 18.91) compared to an SMR of 0.92 (95% CI: 0.65, 1.19) for patients aged 75 years or older. Compared to the general population, mortality of patients with CD is also significantly higher in the first 3 years after diagnosis or for patients who have had the disease for 13 years or more. Actual cause of death could be anything directly related to the disease or as a consequence of the disease such as surgery, malnutrition, colorectal cancer, electrolytes imbalance or massive haemorrhage.<sup>13, 14</sup>

#### 1.1.6 Epidemiology of CD

CD has become an important health threat in the West and industrialised countries.<sup>15</sup> The areas with the highest incidence rate are the United Kingdom (UK), North America, and northern Europe.<sup>16</sup> The annual incidence of CD in Europe and North America has been increasing over time and is estimated to be around 2 to 8 per 100,000 population. Similarly, the prevalence of the disease in the Western world has been estimated as approximately 60 per 100,000.<sup>4</sup>

In the UK, CD is one of the most common causes of gastrointestinal morbidity. In the North of England and Scotland, more recent estimates of the prevalence of CD indicate it to be between 145 and 157 per 100,000.<sup>17</sup> Scotland has a higher incidence rate compared to London and Wales. In the UK, there are currently at least 115,000 people with CD.<sup>7</sup>

Approximately 80% of CD patients will require surgery over their lifetime.<sup>18</sup> Between 1990 and 2000, the rate of hospital admissions rose from 7,648 to 8,834 in England (16% increase). The age standardised admission rate for CD increased from 15.5 to 17.6 per 100,000 (14% increase). The hospital admission rate (in 1999-2000) was higher in females than in males, with a female to male ratio of 1.5. According to age specific admission rates however the hospital admission rate was higher for the 25-34 age groups with a more equal distribution between males and females.<sup>19</sup>

#### 1.1.7 Impact of CD

CD typically affects people during their economically productive adult life and many require life-long medical and surgical interventions over several decades. The financial burden due to the management of CD is very large.<sup>20</sup> Bassi et al (2004) reported a detailed micro-costing analysis of costs of illness for IBD in inner city patients for the UK National Health Services. Using hospital records, the authors identified and followed up 479 patients who had received some form of secondary care for IBD for up to 6 months. The mean six-month cost per patient for CD was found to be £1,652.00 (95% CI: 1,221, 2,239). Similarly, costs for ambulatory and hospitalisation groups were £516.00 (95% CI: 452, 618) and £6,923.00 (95% CI: 5415, 8919), respectively.<sup>21</sup>

#### 1.1.8 Measurement of disease

The most widely used tool for characterising the activity (i.e., severity) of CD is the Crohn's Disease Activity Index (CDAI).<sup>8</sup> Patients with CDAI score < 150 are often classified as having a quiescent or non-active (i.e. in remission) form of disease. A CDAI score  $\geq$  150 is indicative of an active form of the disease.<sup>22</sup> CDAI is also used in conjunction with additional parameters/markers such as erythrocyte sedimentation rate (ESR) and C Reactive Protein (CRP).<sup>23</sup>

#### **1.1.9** Current service provision

#### Management of CD

According to the current NICE guideline, the management of CD consists of smoking cessation, treatment with drugs, nutritional support, and surgery (in severe or chronic cases). The aim of treatment is mainly to reduce symptoms by inducing and maintaining remission so that quality of life improves.<sup>7</sup>

The treatment of CD can be categorised as non-surgical and surgical.

- a) Non-surgical interventions include:
- Smoking cessation

- Pharmacological (Corticosteroids, biologics, aminosalicylates, immunosuppressants, tumour necrosis factor inhibitors, antibiotics)
- Nutritional (enteral feeding, restricted diet, parenteral feeding) alone or, as an adjuvant therapy
- b) Endoscopic/surgical interventions (indicated for complications such as bowel obstruction, high grade dysplasia, abscess, internal fistulas, and cancer)

The treatment is chosen after considering a balance between individual response in terms of beneficial effects, treatment-related adverse events, and long term complications.<sup>23, 24</sup> Corticosteroids are most widely used for the management of active CD. However, their use is associated with high risk of relapse, low rates of mucosal healing, steroid dependency, and other adverse events (e.g., growth impairment in children, increased risk of infection). There have been safety concerns with long term use of other agents such as tumour necrosis factor (TNF) inhibitors.<sup>1</sup> A summary of the relevant national guidelines, including National Service Frameworks are provided in Table 1.

### Table 1: Relevant national guidelines, including National Service Frameworks

### NICE Guideline (NICE clinical guideline 152) 2012<sup>7</sup>

• First line therapy in children and young people to improve growth and development

## BSG Guidelines 2011 (British Society of gastroenterology)<sup>25</sup>

- Usually used as an alternative therapy to corticosteroid for active CD
- 60 -80% effective on inducing remission for small and large bowel disease

## ESPEN guideline 2006 (European Society for Clinical Nutrition and Metabolism)<sup>26</sup>

- First line induction therapy for children with CD
- Liquid diet only as sole therapy in adult when treatment with corticosteroid is not possible

• In case of persistent intestinal inflammation for patient with steroid dependent EN is used in the maintenance of remission

# Inflammatory Bowel disease (IBD) Working Group of the British Society of Paediatric Gastroenterology, Hepatology and Nutrition<sup>3</sup>

- First line induction therapy for small and large bowel disease
- To improve nutritional and growth status
- Both polymeric and elemental nutrition are of similar effect at inducing remission

## 1.2 Description of technology under assessment

#### **1.2.1** Summary of intervention

Enteral nutrition has played an important but controversial role in the alleviation of malnutrition and control of disease activity in patients with active CD. Enteral nutrition formulas vary in the protein and fat content and are classified as elemental (amino-acid), semi-elemental (oligopeptide), polymeric (whole protein) or specialised diet.<sup>27, 28</sup> Enteral nutrition is a method of delivering nourishment through a tube placed in the nose (nasogastric or nasoenteral tube), the stomach (gastrostomy or percutaneous endoscopic gastrostomy tube), or the small intestine (jejunostomy or percutaneous endoscopic jejunostomy tube).

Elemental nutrition is a liquid formula that contains individual amino acids, glucose polymers, and is low in fat with approximately 2% to 3% of calories derived from long chain triglycerides (LCT). In many elemental products, medium chain triglycerides (MCT) are the main fat source, and are absorbed directly across the small intestinal mucosa into the portal vein in the absence of lipase or bile salts. Semi-elemental nutrition contains peptides of various chain lengths, simple sugars, glucose polymers or starch and fat. Polymeric nutrition contains intact proteins, complex carbohydrates and mainly LCTs. Specialised nutritional formulas contain biologically active substances or nutrients such as glutamine, arginine, nucleotides or essential fatty acids.<sup>28, 29</sup>

The mechanism of action of enteral nutrition on CD is not known. Several hypothesised mechanisms underlying the proposed benefits of enteral nutrition in CD include reduced gut activity, include reduction of antigenic load, nutritional effects, anti-inflammatory effects, or modulation of immune system and gastrointestinal flora.<sup>30-33</sup>

#### 1.2.2 Types and route of administration

- As exclusive enteral nutrition (EEN): provided especially as a sole dietary source and a primary medical therapy to induce remission
- As partial enteral nutrition (PEN): given additionally to normal unrestricted/restricted diet, to improve nutritional status and /or to maintain remission

Both EEN and PEN may be administered either orally or with nasogastric (NG) tube.<sup>34</sup>

#### **1.2.3** Enteral nutrition as induction therapy

There is some evidence of clinical benefit and long term safety of enteral nutrition in inducing remission in patients, especially children and young adults with active CD<sup>35, 36</sup> and in maintaining the

remission of quiescent CD.<sup>30</sup> For example, in Japan, enteral nutrition is recommended as the first-line treatment in the management of active CD.<sup>33, 37</sup> It has also been recommended as first line therapy in children and young adults with concerns about growth and side effects. Although enteral nutrition has been shown to be an effective and safe intervention for induction of remission in patients with active CD, withdrawal from enteral nutrition and resumption of normal diet would often be followed by reoccurrence of gastrointestinal symptoms and use of corticosteroids.<sup>38</sup> Evidence comparing clinical effectiveness of enteral nutrition to corticosteroids for the induction of remission has been inconsistent, with one meta-analysis showing no difference between the two,<sup>36</sup> and a more recent meta-analysis indicating a superiority of corticosteroids over enteral nutrition.<sup>27</sup>

#### **1.2.4** Enteral nutrition as maintenance therapy

Evidence of the efficacy of different types of enteral nutrition (i.e., elemental, semi-elemental, polymeric) in maintaining remission in CD has been insufficient and less clear.<sup>1, 3, 4, 15</sup>

NICE recommends that enteral nutrition should not be used as maintenance therapy after surgery.<sup>7</sup> Moreover, use of enteral nutrition as maintenance therapy is challenging due to compliance issues.<sup>1</sup> Most evidence on the comparative clinical effectiveness of enteral nutrition in the maintenance of CD remission rests upon retrospective observational cohort studies and prospective non-randomised controlled experimental trials.<sup>1, 3, 15</sup>

# **2** DEFINITION OF THE DECISION PROBLEM

# 2.1 Decision problem

Crohn's disease (CD) is a chronic relapsing-remitting inflammatory disease affecting the gastrointestinal tract.<sup>1</sup> Currently, none of the available therapeutic options (e.g., medical, surgical, or nutritional) lead to complete cure of CD. The management of the disease usually involves the induction and then maintenance of remission of disease activity by controlling the extent of inflammatory process, correcting malnutrition, and reducing symptoms as well as the occurrence of complications.<sup>23, 24</sup> In children, the additional aim of the treatment is to promote healthy growth and development.

Enteral nutrition is one of the available treatment options in the management of CD and has been shown to be beneficial in inducing remission and improving nutritional status in adults and children diagnosed with active CD.<sup>31, 37</sup> There is less clarity of the role of enteral nutrition in maintaining remission in patients with quiescent CD.

If enteral nutrition is at least as effective as standard medical treatments, it could potentially replace or minimize the use of steroids and/or other pharmaceutical agents, thereby prevent the occurrence of adverse events, complications, steroid dependence, and growth retardation in both adults and children with CD.

The objective of this systematic review was to identify, appraise and evaluate the evidence on clinical effectiveness and cost-effectiveness of elemental nutrition for the maintenance of remission in CD.

# 2.2 Overall aims and objectives of assessment

- To evaluate the clinical effectiveness and cost-effectiveness of elemental nutrition administered alone or in combination with other interventions (e.g., diet, standard drug treatment) compared to other intervention(s) (e.g., placebo, diet, standard drug treatment) for maintaining remission in patients with CD.
- To compare the clinical effectiveness and cost-effectiveness of elemental nutrition with other types of enteral nutrition (semi-elemental, polymeric nutrition), duration, and dose in regards to maintaining remission and adherence.
- To explore subgroup effects of elemental nutrition on maintenance of remission (i.e., risk of relapse or recurrence). Specifically, to examine if the treatment effect of elemental nutrition varies across groups defined by sex (males, females), age (adults, adolescents, and children), and type of induction therapy (medically-, nutritionally-, surgically-induced).
- To evaluate additional outcomes for patients with CD such as adherence to elemental nutrition, CD activity index (CDAI), incidence of mucosal healing, quality of life, adverse events, gain in body weight (or BMI), growth, and pubertal development.

# **3 METHODS**

The review protocol is provided in Appendix I and is registered on PROSPERO International prospective register of systematic reviews (CRD42013005134; available from http://www.crd.york.ac.uk/PROSPERO/display\_record.asp?ID=CRD42013005134).

# 3.1 Search strategies

Using an iterative procedure an experienced librarian developed the search strategy with input from clinical advisors and previous systematic reviews.<sup>37-39</sup>

Comprehensive electronic searches were conducted to identify all references relating to elemental nutrition, maintenance of remission, and CD. Searches were undertaken in August 2013 in MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE (via OVID); CDSR, CENTRAL, DARE, NHS EED, HTA database (via the Cochrane Library); Science Citation Index and Conference Proceedings (via Web of Knowledge); WHO ICTRP; UKCRN Study Portfolio. The databases were searched from 1947 to August 2013; the actual data range for each of the databases searched depended on the coverage of the individual database. The electronic searches were not limited by study design, language, or publication date.

Citation searches of included studies were undertaken using the Web of Science citation search facility.

Two supplementary database searches using limits were undertaken. The first, combining CD with the concept of nutrition therapy and limited to systematic reviews or cost-effectiveness, aimed to capture any articles that included the assessment question as part of a broader systematic review or cost study. The second, combining CD with the concept of elemental nutrition and limited to relevant study types aimed to capture any articles that involved the current included population (see section 3.2) as part of a controlled clinical trial of both active CD and CD in remission.

Websites such as Crohn's and colitis UK (NACC);<sup>5</sup> Crohn's nutricia;<sup>40</sup> and Children with Crohn's and Colitis (CICRA)<sup>41</sup> were also checked.

In addition, experts in the field were contacted and references of included studies were also checked for potentially relevant studies. All the retrieved records were collected in a specialised database. Duplicate records were identified and removed from the database.

Details of the electronic search strategies used for the review of the clinical effectiveness are given in Appendix II.

# 3.2 Study inclusion criteria

### **Type/language of publication:**

English full text and abstracts (only if companion publications to full text included studies).

### Study design:

RCTs and non-randomised controlled clinical trials.

#### **Population:**

Adults, young people, or children with CD in remission (inactive, quiescent CD) at the time of study baseline.

#### Main intervention:

Elemental nutrition alone via oral passage, nasal passage (naso-gastric tube, naso-jejunal tube, nasoduodenal tube), or direct passage via the abdomen (gastrostomy tube, jejunostomy tube).

Elemental nutrition in combination with other intervention(s) (e.g., standard drug therapy any other type of treatment).

#### **Comparator:**

Enteral nutrition (elemental, semi-elemental, or polymeric nutrition) alone, normal unrestricted/restricted diet alone (i.e., no intervention), standard drug therapy alone, any other intervention, or placebo.

Enteral nutrition (elemental, semi-elemental, or polymeric nutrition) in combination with other intervention(s) (e.g., standard drug therapy, any other intervention or placebo).

Standard drug therapy in combination with any other intervention, and/or placebo.

# 3.3 Study exclusion criteria

- Induction studies (patients with active CD at baseline) with or without follow up of remitted patients continuing to receive maintenance therapy
- Studies of parenteral (intravenous) nutrition
- Studies of ulcerative colitis
- Studies employing non-concurrent (e.g., historical) controls
- Studies with mixed patient populations (< 80% Crohn's disease)
- Studies comparing different formula/diets of elemental nutrition
- Reviews (systematic or non-systematic), meta-analyses, observational cohort studies, case-reports, case-series, editorials, abstracts, or comments

# **3.4** Outcomes of interest

### **Outcomes – clinical effectiveness:**

Adult populations

- Maintenance of remission (% patients in remission at end of follow-up, cumulative probability of maintaining remission [Kaplan Meier estimate of survival], and duration of remission) primary outcome
- Development of relapse/recurrence (proportion of patients developing relapse/recurrence [n/N], time to relapse/recurrence [mean # of months]) primary outcome
- Incidence of mucosal healing (n/N) primary outcome
- Need for surgery (n/N)
- Withdrawal from steroids (n/N)
- Steroid dose tapering (n/N)
- CDAI score (mean endpoint or mean change from baseline)
- Health related quality of life (mean score: endpoint or mean change)
- Adverse events (n/N)
- Complications of CD (n/N)
- Gain in body weight or BMI (mean change in kg or  $kg/m^2$ )
- Adherence (n/N)

Younger populations (e.g., adolescents, paediatric)

- Maintenance of remission (% patients in remission at end of follow-up, cumulative probability of maintaining remission [Kaplan Meier estimate of survival], and duration of remission) primary outcome
- Development of relapse/recurrence (proportion of patients developing relapse/recurrence [n/N], time to relapse/recurrence [mean # of months]) primary outcome
- Incidence of mucosal healing (n/N) primary outcome
- Need for surgery (n/N)
- Withdrawal from steroids (n/N)
- Steroid dose tapering (n/N)
- CDAI score (mean endpoint score or mean change score from baseline)
- Health related quality of life (mean score: endpoint or mean change)
- Adverse events (n/N)
- Complications of CD (n/N)
- Gain in body weight or BMI (mean change in kg or  $kg/m^2$ )
- Adherence (n/N)
- Growth (mean change score/any growth measure from baseline)
- Pubertal development

#### **Outcomes – cost-effectiveness:**

- Costs (no efficacy measures: cost-minimisation analysis)
- Costs and efficacy measures clinical and quality-adjusted life years (QALYs) (full economic analysis)
- Incremental cost-effectiveness ratios (ICERs) (full economic analysis)
- Results from cost-effectiveness acceptability curves (CEACs)

# 3.5 Study selection strategy

Two independent reviewers using a pre-piloted screening form screened all identified bibliographic records for title/abstract. Full text reports of all potentially relevant records were then retrieved and examined independently. Disagreements were resolved via discussions and consensus agreement (either between the two reviewers or via a third party).

The study flow and reasons for exclusion of full text papers were documented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram.<sup>42</sup>

#### **3.6 Data extraction strategy**

Two reviewers independently extracted relevant data using a pre-defined pre-piloted extraction sheet (Appendix III). The extracted data included details about study (e.g., author, country, design, sample size, follow-up duration, risk of bias items), participant (e.g., age, sex, inclusion/exclusion criteria, CD activity index, clinical/endoscopy definitions of CD remission, type of induction therapy), intervention/comparator (brand name/manufacturer of elemental nutrition; type, mode, duration, and dose of administration of elemental nutrition, any concomitant diet or dietary restriction, and other co-intervention such as medications), and outcome characteristics (e.g., type and scale of measurement, timing of assessment, definition of CD relapse/recurrence). The extracted data were cross-checked by second reviewer and any disagreements were resolved by discussion. Further discrepancies were resolved by a third reviewer, if necessary.

For individual studies, the dichotomous and continuous summary clinical effectiveness outcome measures of association were summarized as risk/odds ratio, mean difference, and measures of variability (p-value, 95% confidence interval). We tried to calculate missing statistical parameters (e.g., risk ratios, mean differences, standard deviations, standard errors, and 95% confidence intervals [CIs]) for clinical outcomes of interest (e.g., maintenance of remission, risk of relapse, time to relapse, incidence of mucosal healing, need for surgery, withdrawals, adherence, adverse events, and complications). All calculated parameters were entered into the data extraction sheets and marked as 'calculated'.

### **3.7** Risk of bias assessment strategy

Two reviewers independently assessed the methodological and reported quality of included individual studies. Any disagreements between the two reviewers were resolved by a third reviewer through discussion.

RCTs were quality-assessed using the Cochrane Collaboration Risk of Bias (ROB) tool<sup>43</sup> which covers the following domains of threat to internal validity: selection bias (randomisation sequence generation, treatment allocation concealment), performance bias (blinding of participants/personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data primary outcome), reporting bias (selective outcome/analysis reporting), and other pre-specified bias (e.g., funding source, adequacy of statistical methods used, type of analysis, baseline between-group imbalance in important prognostic factors).

The risk of bias assessment falls into three categories of high, low, and unclear risk of bias. The assessments were provided in ROB tables and summary graphs. Non-randomised controlled clinical

trials were assessed using a modified Cochrane ROB tool in which the domain of selection bias was evaluated in regards to baseline between-group imbalance for important prognostic factors instead of randomisation sequence generation and treatment allocation concealment. For each study (RCT or non-RCT), the risk of performance, detection, and attrition bias domains for subjective (e.g., patientadministered clinical or quality of life scores) and objective (e.g., additional laboratory criteria used in the definition of remission/relapse, weight gain, mucosal healing, growth, adverse events) outcomes were assessed separately. Afterwards, within-study summary ROB ratings across all domains were derived for subjective and objective outcome groups separately. At data synthesis stage, across-study average summary ROB ratings were determined and assigned to each outcome of interest (Appendix IV).

The quality of economic analyses of the included studies was planned to be assessed using the Drummond 10-item checklist.<sup>44</sup>

#### **3.8 Data synthesis**

Study, treatment, population, and outcome characteristics were summarised in text and summary tables. The study results on the relative effectiveness of elemental nutrition for each outcome of interest were compared qualitatively and quantitatively in text and summary tables.

In the clinical effectiveness part of the review, results for any given outcome measures were presented separately stratified by a comparison category: a) elemental nutrition vs. no intervention (i.e., restricted/unrestricted diet alone), b) elemental nutrition vs. drug (standard therapy), c) elemental nutrition vs. combination of elemental and drug, d) elemental nutrition combination with drug vs. drug alone, and e) elemental nutrition vs. other type of enteral nutrition.

The decision to pool individual study results was based on a degree of similarity with respect to methodological and clinical characteristics of studies under consideration (e.g., design population, comparator treatment, and outcome). Estimates of post-treatment mean difference for continuous outcomes and RRs for binary outcomes (except for rare events) of individual studies were pooled using a DerSimonian and Laird random-effects model.<sup>45</sup> Dichotomous outcomes with low event rates (5.0% - 10.0%) were pooled as RR using a Mantel-Haenszel fixed-effects model. Dichotomous outcomes for studies with very low event rates ( $\leq 5.0\%$ ) or zero events in one of the treatment arms were pooled as odds ratio (OR) using a Peto fixed-effects model.<sup>46</sup> Trials were not pooled if the mean and/or standard deviation for the continuous outcome of interest could not be ascertained.

The degree of statistical heterogeneity across pooled studies was determined through inspection of the forest plots, Cochran's Q and the I<sup>2</sup> statistics. The heterogeneity was judged according to predetermined levels of statistical significance (Chi<sup>2</sup>-based p<0.10 and/or I<sup>2</sup>>50%). If data allowed, study-level clinical and methodological sources of heterogeneity of effect estimates across studies was explored through a priori defined subgroup analysis (i.e., age, sex, induction therapy) and sensitivity analysis (risk of bias item-specific ratings, intention-to-treat vs. per protocol analysis). Given a sufficient number of data points, publication bias was planned to be assessed through visual inspection of funnel plots with respect to plot asymmetry and use of linear regression tests.<sup>47</sup>

Results for individual studies were rendered inconclusive in cases of missing/partially reported data (e.g., missing/undetermined summary effect measures and/or corresponding 95% CIs, only p-value reported) or statistically non-significant effect estimates with great uncertainty (i.e., wide intervals that include moderate to large effect size treatment effects in both directions compatible to either benefit or harm of elemental nutrition).

### **3.9** Overall quality of evidence (GRADE system)

The overall quality of evidence for pre-selected gradable outcome (maintenance of remission, risk of CD relapse/recurrence, mucosal healing, need for surgery, adherence, and adverse events) across studies was assessed using the systematic approach developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org).

The GRADE approach<sup>48</sup> indicates level of confidence in the observed treatment effect estimate(s) and is based on assessments across five domains: a) summary ROB across studies per gradable outcome (internal validity across studies; study limitations), b) consistency of results (heterogeneity), c) directness of the evidence (applicability of the results), d) precision of the results (the width of 95% CI around the estimate), and e) publication/reporting bias (detection of asymmetry in the funnel plot; selective outcome reporting). The overall quality of evidence was rated as high, moderate, low, or very low grade. Initial grade of RCTs was rated as high and downgraded by one point (e.g. from high to moderate) if any of the five criteria was not met. Initial grade for non-RCTs was to be rated as low and upgraded by one point (e.g. from low to moderate) if any of the three criteria for upgrading a grade was met (e.g., dose-response gradient, large magnitude of effect, and adjustment for confounders).<sup>49</sup>

# **4 RESULTS**

# 4.1 Literature search

A total of 1,222 records was identified through electronic searches. Four additional records were identified from other sources. The removal of duplicates left 630 records to be screened, of which 594 were excluded at title/abstract level as obviously irrelevant. The remaining 36 records were examined for full-text, of which 12 (representing eight unique studies) were included in the review.<sup>30, 50-60</sup>

Of the eight included studies, one RCT<sup>52, 53</sup> and one non-RCT<sup>30, 59, 60</sup> were represented in multiple publications. Throughout this review, these two studies will be cited according to their corresponding original publications.<sup>30, 52</sup>

The search of on-going trials in Clinical Trials.gov, Current Controlled Trials, UKCRN Portfolio, and WHOICTRP databases (carried out in September 2013) retrieved 26 potentially relevant records, none of which was deemed relevant for inclusion in the review.

The study flow diagram outlining the process of identifying relevant literature and eight included studies<sup>30, 50-52, 55-58</sup> along with reasons for exclusion is given in Figure 1. More details on exclusions can be found in Appendix V.
### Figure 1: Study Flow Diagram



## 4.2 Trial characteristics

This review included three randomised controlled trials (RCTs)<sup>50, 52, 55</sup> and five non-randomised controlled trials (non-RCTs).<sup>30, 51, 56-58</sup>

### 4.2.1 Randomised controlled trials (RCTs)

The study and participant characteristics of the three included randomised controlled trials (RCTs)<sup>50, 52, 55</sup> are summarised in Table 2. Of three RCTs, two were conducted in Japan<sup>50, 52</sup> and one in the UK.<sup>55</sup> A total of 179 participants was randomised across three RCTs with individual trial sample size ranging from 33<sup>55</sup> to 95<sup>50</sup> participants. The mean age of participants across the three trials ranged from 29<sup>52</sup> to 44 years<sup>55</sup> and the proportion of females from 23%<sup>52</sup> to 68%.<sup>55</sup> The length of follow-up of the studies ranged from 12<sup>52, 55</sup> to 24 months.<sup>50</sup> In most participants CD was located in both the small and large intestines. Induction therapies included parenteral nutrition,<sup>50, 52</sup> central venous feeding,<sup>50</sup> prednisolone,<sup>50, 55</sup> infliximab,<sup>50, 52</sup> 6-MP,<sup>50</sup> enteral nutrition,<sup>52</sup> or surgery.<sup>52</sup> Only two studies<sup>52, 55</sup> reported criteria used for the diagnosis of CD. The diagnosis of CD included clinical, endoscopic, radiological, and/or histological criteria.

In all three trials, the elemental nutrition was given in addition to unrestricted diet (i.e., normal/free diet) through self-inserted feeding tube<sup>50, 52</sup> or oral intake.<sup>50, 52, 55</sup> In one trial,<sup>52</sup> participants in the elemental nutrition group were asked to take half of the daily calories through elemental nutrition (i.e., 'half-elemental diet') and the other half from unrestricted diet. Participants in the control groups were assigned to receive unrestricted diet (no intervention),<sup>50, 52</sup> drug (6-MP),<sup>50</sup> or polymeric nutrition.<sup>55</sup>

Remission was defined using CDAI score of  $\leq 150$  either alone or with additional clinical criteria (e.g., absence of diarrhoea and abdominal pain or, ESR<20 mm/h).<sup>55</sup> Similarly relapse was defined as either a CDAI score  $\geq 200$  alone or with additional criteria (e.g., the need for an additional medication to suppress worsening symptoms,<sup>50, 52</sup> CDAI score increase by 100 points from baseline).<sup>55</sup>

Table 2: Study and	l participant char	acteristics (randomised controlled trials)

Author	Study details	Inclusion/	Interventions	ns Patient characteristics			
year Ref ID Country		exclusion criteria			Element al nutritio	Control 1	Control 2
					n		
Hanai	Aim: To	Inclusion	Elemental	Patients randomised (n)	32	30	33
2012 Japan	evaluate the	criteria: age	nutrition:	Age (years) - Mean	30.1	32.5	29.8
Japan	elemental diet	$\geq$ 10 years with achieved	(Ajinomoto	(SD/range)	(7.7) 10/32	(8.9)	(10.5)
	and 6-MP vs.	remission	Tokvo) at	Sex - Jemaie M/IV (76)	(31.2)	(23.3)	(24.2)
	no intervention	(CDAI < 150)	$\geq$ 900 kcal/day,	Weight (kg) - Mean	NR	NR	NR
	as maintenance	within 30 days	taken via self-	(SD/range)			
	therapy in CD	of entry to this	inserted	BMI (kg/m <sup>2</sup> ) - Mean	NR	NR	NR
		trial	feeding tube (2	(SD/range)			
	Study setting:	Evolution	pts) or by oral	Smoking n/N (%)	18/32	15/30	18/33
	specialty clinic	Exclusion criteria	Restricted diet:		(56.2)	(50.0)	(54.5)
	Length of	Patients with	patients were	Duration of CD (mo) -	(60.6)	67.2	58.8
	follow up (#	abdominal	allowed an	CDAL score- Mean	103.4	(80.4)	(73.0)
	months): 24	abscess,	intake of 3.5-	(SD/range)	(21.4)	(27.8)	(30.1)
		stricture (B1 of	4.0 kcal/kg/day	Location of CD - $n/N$ (%)	(=111)	(1/10)	(0011)
	Funding: NR	Vienna and	from food as	Ilio-colic type	19/32	21/30	19/33
		Montreal	recommended	Ileal type	(59.4)	(70.0)	(57.6)
		classification),	by a qualified	Colic type	8/32	8/30	11/33
		women	uleticiali		(25.0)	(26.7)	(33.3)
		patients with	Control 1:		3/32	2/30	3/33
		cardiovascular	Drug [6-MP	Provide housed respection	(9.4) ND	(0.7) ND	(9.1) ND
		disorders and	20-80 mg/day]	n/N (%)		INIX	INIX
	6-MP Unrestricted normal diet Control 2: No intervention Unrestricted normal diet	Type of induction therapy ( (70/95 [73.7]), central venous prednisolone (9/95 [9.5]), inf [14.7]) Total N received induction Total N achieving remission Total N allocated to mainte Diagnostic criteria used for Co-interventions: 5-ASA (2 Sulphasalazine (3000 mg/day Outcome definitions applie Relapse/recurrence (CDAI ≥ medication to suppress worse Outcomes reported: Mainter relapse, adverse events, comp	(n[%]): para s feeding (2. liximab (4/9 therapy: Ni n after indu nance treat CD: NR 250–3000 n (7) d: Remissio 200 or the n ening sympt nance of rep blications, n	enteral nutri 5/95 [26.3]) 95 [4.2]), 6-1 R action thera ment: 95 mg/day), n (CDAI < eed for an acoms) mission, risk eed of surge	tion , MP (14/95 <b>py</b> : 105 150), dditional c of ery		
Takagi	Aim: To	Inclusion	Flemental	Patients randomised (n)	26	25	
$2006^{52-54}$	compare	criteria: CD	nutrition:	Age (years) - Mean	30.8	28.9 (8.1)	
Japan	relapse rates in	patients if they	Elental	(SD/range)	(11.1)	20.7 (0.1)	
	patients with inactive CD	had just undergone	(AJINOMOTO PHARMA	Sex - female n/N (%)	6/26 (23.1)	8/25 (32.0	))
	receiving half elemental	induction of remission	Co., Tokyo, Japan) through	Weight (kg) - Mean (SD/range)	NR	NR	

			16		00.1	
	nutrition		a self-inserted	BMI (kg/m²) - Mean	20.1	20.0 (3.6)
	(elemental	Exclusion	tube and/or	(SD/range)	(3.1)	
	nutrition +	criteria: NR	oral intake	Smoking n/N (%)	NR	NR
	unrestricted			Duration of CD (mo) -	49.2	67.2 (78.0)
	diet) vs. no		Patients took	Mean (SD/range)	(50.4)	
	intervention		half the	CDAI score- Mean	101.8	86.4 (31.3)
	(unrestricted		amount of their	(SD/range)	(34.1)	
	diet)		daily	Location of CD - n/N (%)		
			allowance of	Small bowel only	8/26	7/25 (28.0)
	Study setting:		calories by	Colon only	(30.7)	6/25 (24.0)
	specialty clinic		elemental	Both	3/26	12/25 (48.0)
			nutrition and		(11.5)	
	Length of		the remaining		15/26	
	follow up (#		half by usual		(57.7)	
	months): 12		unrestricted	Previous bowel resection	11/26	11/25 (44.0)
			meals	n/N (%)	(42.3)	
	Funding: no			Type of induction therapy (	(n[%]): eler	nental enteral
	external		Control: No	nutrition 22/51 [43 1] (1800-	-2100  kcal/d	lav) for 6–8 weeks
	funding		intervention;	total parenteral nutrition 25/5	51 [49 0] (15	500-2100  kcal/day
	received		patients took	for 6–8 weeks: oral/IV predn	isolone 1/51	1 [2 0] (40  mg/day)
			all nutrients	then tapered down every 2 w	eeks by 5–1	(10  mg) aug, $(10  mg)$
			via their usual	infliximab 3/51 [5 9] and/or	surgery (5/5	51 [7 9])
			un-restricted		surgery (5/2	)1 [ <i>1</i> ./])
			meals	Total N received induction	therany <sup>,</sup> 87	)
				Total N achieving remission	n ofter indu	- iction therapy: 56
				Total N allocated to mainta	nonco troot	mont: 51
				1 otal N anocateu to mainte	nance treat	linent. 51
				Diagnostia aritaria usad far	CD. alinia	ally and a conically
				Diagnostic criteria used for		any, endoscopicany,
				radiologically and/or histolog	gically (diag	nostic criteria as
				defined by the Ministry of He	ealth, Labou	ir and Welfare of
				Japan)		
				Co-interventions: Mesalazir	ne (2250–30	00 mg/day),
				Azathioprine (50 mg/day)		
				Outcome definitions applie	d: remission	n (CDAI<150),
				relapse/recurrence (CDAI > 2	200, or the r	need for therapy to
				induce remission)		
				Outcomes reported: risk of	relapse, HQ	OL, adherence
					1	T
Verma	Aim: To	Inclusion	Elemental	Patients randomised (n)	19	14
200155	compare safety	criteria:	nutrition:			
UK	and efficacy of	inactive CD	Orally taken	Age (years) - Mean	41.7	44.1 (3.2)
	elemental and	and steroid	(EO28,	(SD/range)	(5.4)	
	polymeric	dependency for	Scientific	Sex - female n/N (%)	13/19	9/14 (64.3)
	nutrition for	maintaining	Hospital		(68.4)	
	the	clinical	Supplies Ltd,	Weight (kg) - Mean	62.4	71.4 (7.7)
	maintenance of	remission and	Liverpool,	(SD/range)	(3.4)	
	remission, risk	two previous	UK); sachets	BMI (kg/m²) - Mean	21.8	24.4 (1.6)
	of relapse, and	unsuccessful	containing	(SD/range)	(1.2)	
	intolerance	attempts to	powdered feed	Smoking n/N (%)	NR	NR
		withdraw	mixed with tap	Duration of CD (mo) -	154.4	123.6 (26.4)
	Study setting:	steroid that	water (20	Mean (SD/range)	(37.2)	. ,
	specialty clinic	prompted	g/100 ml); the	CDAI score- Mean	106.4	90.4 (17.8)
		recurrence	mean daily	(SD/range)	(14.9)	
1	1			1~~~/	(****/)	1

Length of dr	uring or after	intake 730	Location of $CD - n/N$ (%)							
follow up (# 30	0 d of	(range 600–	Small bowel	7/19	6/14 (42.8)					
months): 12 w	vithdrawal	1017) Kcal	Large bowel	(36.8)	4/14 (28.6)					
		Unrestricted	Mixed anastamotic	4/19	0/14 (0.0)					
Funding: NR E	Exclusion	normal diet		(21.0)						
c,	riteria:			2/19						
re	ecurrent	Control:		(10.5)						
SI	mall-bowel	Orally taken	Previous bowel resection	NR	NR					
lo	bstruction due	Polymeric	n/N (%)							
tc	o Crohn's	nutrition (Fortisip, Nutricia, UK);			1 : 1 (22 [1000/])					
st	strictures, significant		Type of induction therapy (	$\mathbf{n}[\%]$ : prec	(33[100%])					
si				41 NI	D					
S€	epsis	ready-to-drink	Total N achieving remission after induction therapy: NR Total N achieving remission after induction thera							
in	ncluding	cartons (200								
po	erianal	ml); the mean	Total N anocated to mainte	enance treatment: 33						
di	isease,	sease, daily intake								
pr	revious	730 (range	Diagnostic criteria used for	<b>CD</b> : standa	iru ciinicai,					
in	ntolerance to	600–1017)	radiological, endoscopic and histological criteria							
ei	nteral feeding	Kcal	Co interventions: Staroids/r	radnicalana	(6571mg)					
0	r unwilling to	Unrestricted	Azethiopring (dose: NP) 5	S A (doso)	(0.3-7.1 mg),					
gi	ive formal	normal diet	Azamiophile (dose. INK), 3-A	ISA (dose. 1	NK)					
W	ritten consent		Outcome definitions applies	d. romission	(absonoo of					
			diarrhoas and abdominal pair	a. remission	0 in the 2 weeks					
			preseding the study and ESE	$1, CDAI \leq 13$	v miline 2 weeks					
			(CDAI > 200  or increased by)	100 points f	from baseline)					
			(CDAI ≥200 of increased by	100 points i	ioni basenne)					
			Outcomes reported. Mainte	nonco of ror	nission risk of					
			relance adherence withdraw	al from stor	oide					
relapse, adherence, withdrawal from steroids										
$\Delta S \Delta = 3m_1n_0s_0 l_1c_V l_1c_0 s_0 l_0$	=hody mass ind	ev: CD=Crohn's I	Disease: mo=month(s): CDAI=	Crohn's Di	sease Activity Index.					

#### 4.2.2 Non-randomised controlled trials (non-RCTs)

The study and participant characteristics of the five included non-randomised controlled trials (non-RCTs)<sup>30, 51, 56-58</sup> are summarised in Table 3. Of five studies, four were conducted in Japan<sup>30, 51, 57, 58</sup> and one in the UK.<sup>56</sup> A total of 236 participants were assigned to the study treatments. The number of participants across the studies ranged from 39<sup>56</sup> to 61.<sup>51</sup> The mean age in the studies ranged from 22<sup>51</sup> to 42 years<sup>56</sup> and the proportion of females from 13%<sup>51</sup> to 72%.<sup>56</sup> The length of follow up ranged from 12<sup>30, 57</sup> to 48 months.<sup>51</sup> One trial included exclusively those participants who had earlier undergone bowel resection surgery for CD.<sup>30</sup> The majority of participants had both small and large bowel involvement of CD. Only one study reported the diagnostic criteria of CD.<sup>51</sup> Induction therapies were prednisolone,<sup>56, 57</sup> azathioprine,<sup>56</sup> 5-ASA,<sup>30, 56, 57</sup> infliximab,<sup>57, 58</sup> corticosteroid,<sup>30</sup> bowel resection,<sup>30</sup> parenteral nutrition,<sup>57</sup> and elemental nutrition.<sup>51, 57</sup>

In all five trials, the elemental nutrition was given in addition to either restricted<sup>30, 51, 57, 58</sup> or unrestricted diet (i.e., normal/free diet)<sup>56</sup> through feeding tube infusion<sup>30, 51, 57, 58</sup> or oral intake.<sup>56</sup> Participants in the elemental nutrition groups were asked to take half of the daily calories through elemental nutrition.<sup>30, 57, 58</sup> The elemental nutrition groups received either elemental nutrition alone<sup>30, <sup>51, 56, 57</sup> or elemental nutrition with drug (sulfasalazine/prednisolone<sup>51</sup> or infliximab<sup>58</sup>). Participants in the control groups were assigned to receive unrestricted/restricted diet (no intervention),<sup>30, 51, 56, 57</sup> drug only (sulfasalazine/prednisolone<sup>51</sup> or infliximab<sup>58</sup>).</sup>

Remission was defined clinically using CDAI score<150 alone<sup>30, 56-58</sup> or with additional clinical/endoscopic criteria such as normal values of IOIBD, erythrocyte sedimentation rate (ESR) and CRP scores<sup>51</sup> or Rutgeerts score<2.<sup>30, 57</sup> Relapse/recurrence was defined by subjective/objective symptoms (increase of the IOIBD score by  $\geq$ 2, enhanced ESR/CRP;<sup>51</sup> increase in CDAI by >100 points after baseline, or final CDAI score >150, need of surgery, or increased doses of steroids;<sup>56</sup> or CDAI scores  $\geq$  150).<sup>30, 57, 58</sup>

	Table 3: Study and	l participant o	characteristics	(non-randomised	controlled	trials)
--	--------------------	-----------------	-----------------	-----------------	------------	---------

Author	Study	Inclusion/	Interventio	o Patient characteristics					
year	details	exclusion	ns		Eleme	Contr	Contr	Contr	
Ref ID		criteria			ntal	ol 1	ol 2	ol 3	
Countr					nutriti				
У					on				
Hiraka	Aim: To	Inclusion	Elemental	Patients assigned (n)	25	22	8	6	
wa	compare the	criteria:	nutrition:	Patients analysed (n)	22	17	8	6	
1993 <sup>51</sup>	effects of	patients	Elemental	Age (vears) - Mean	27.0	26.6	21.9	25.7	
Japan	elemental	with CD in	nutrition	(SD/range)	(7.4)	(2.4)	(2.6)	(5.0)	
	nutrition	remission	(Brand: NR)	Sex - female n/N (%)	3/22	6/17	3/8	2/6	
	alone,		via		(13.6)	(35.3)	(37.5)	(33.3)	
	combinatio	Exclusion	nasoenteral	Weight (kg) - Mean	NR	NR	NR	NR	
	n of	criteria:	tube (with	(SD/range)					
	elemental	patients	restricted	$BMI (kg/m^2)$ - Mean	NR	NR	NR	NR	
	nutrition	with active	diet)	(SD/range)					
	and drugs,	CD		Smoking n/N (%)	NR	NR	NR	NR	
	drugs alone,		Control 1:	Duration of CD (mo) -	NR	NR	NR	NR	
	and no		Elemental	Mean (SD/range)					
	intervention		nutrition +	CDAI score- Mean	61.6	56.0	68.5	69.3	
	on		Drug	(SD/range)	(29.2)	(26.6)	(30.2)	(52.1)	
	maintenanc		[sulfasalazin	Location of CD - n/N (%)					
	e of		e 3g/d or	Small bowel	5/22	0/17	0/8	0/6	
	remission in		prednisolon	Large bowel	(22.7)	(0.0)	(0.0)	(0.0)	
	CD patients		e 10 mg/d]	Small and large bowel	1/22	3/17	2/8	0/6	
	C4 J		(with		(4.5)	(17.6)	(25.0)	(0.0)	
	Study		restricted		16/22	14/17	6/8	6/6	
	setting:		diet)		(72.7)	(82.3)	(75.0)	(100.0	
	prinnary		(100)					)	
	care			Previous bowel resection	NR	NR	NR	NR	
	Length of			n/N (%)					
	follow up		Control 2:	Type of induction therapy	( <b>n</b> [%]): e	elemental	nutrition (	25/53	
	(# months):		Drug	[47.1]), elemental nutrition	and drugs	(23/53 [4]	3.4]), drug	s alone	
	48		[sulfasalazin	(5/53 [9.4])					
			e 3g/d or						
	Funding:		prednisolon	Total N received induction	therapy:	84		-	
	NR		e 10mg/d]	Total N achieving remissio	on after in	iduction t	herapy: 6	)/	
			(with	Total N allocated to maint	enance tr	eatment:	61		
			restricted			(	т	<b>G</b>	
			diet)	Diagnostic criteria used io	r CD: Cn	teria of th	e Japanese	Society	
				Co interventions: NP					
				Co-muerventions: INK					
			Control 2.	Outcome definitions appli	d. remise	ion IOIPI	Score (1	alue	
			No	NR) and normal values of ESR and CRP. relapse/recurrence of					
			intervention	ntion subjective/objective symptoms (increase of the IOIBD score by					
			(with	Solution Subjective Symptoms (increase of the forbb) score by >2. enhanced ESR. and positive CRP)					
			restricted	$\geq 2$ , elinanced ESK, and positive CKF)					
			diet)	Outcomes reported: cumu	lative cont	inuous rei	mission ra	te	

Author	Study details	Inclusion/ exclusion	Interventions	Patient chara	cteristics		
year Ref ID Country		criteria			Elemental nutrition	Control 1	Control 2
Verma 2000 <sup>56</sup>	Aim: To evaluate	<b>Inclusion criteria:</b> Patients with guiescent	Elemental nutrition:	Patients assigned (n)	21	18	NA
UK	clinical effectiveness of adding	disease defined by the absence of bowel symptoms and	Elemental nutrition "EO28 Extra"	Patients analysed (n)	17	18	NA
	elemental nutrition taken orally	CDAI<150 who had been treated with either elemental nutrition or	powder taken orally in three separate	Age (years) - Mean (SD/range)	39.2 (3.9)	42.0 (3.3)	NA
	to normal food for	prednisolone as an induction therapy	portions daily (with normal	Sex - female n/N (%)	14/21 (66.6)	13/18 (72.2)	NA
	maintaining remission in patients with	within preceding 12 months	unrestricted diet)	Weight (kg) - Mean (SD/range)	59.4 (2.9)	62.7 (2.8)	NA
	quiescent CD over 12 months	Exclusion criteria: CDAI>150, sepsis, bowel strictures leading to recurrent	<b>Control 1:</b> No intervention (i.e., normal	BMI (kg/m <sup>2</sup> ) - Mean (SD/range)	20.0 (2.2)	22.9 (0.9)	NA
	Study setting:	attacks of small bowel obstruction or previous	unrestricted diet)	Smoking n/N (%)	NR	NR	NA
	specialty clinic	intolerance to enteral feeding	Control 2: NA	Duration of CD (mo) - Mean	60.3 (18.4)	91.0 (14.8)	NA
	Length of follow up (#			(SD/range) CDAI	112.8	94.6	NA
	months): 24			score- Mean (SD/range)	(11.5)	(7.1)	
	NR			Location of CD - n/N (%) Small bowel Large bowel Mixed bowel Anastomotic <b>Previous</b>	10/17 (58.8) 5/17 (29.4) 6/17 (35.3) 0/17 (0.0) NR	7/18 (38.8) 5/18 (27.7) 3/18 (16.6) 3/18 (16.6) NR	NA
				bowel resection n/N (%)			

Author	Study details	Inclusion/ exclusion	Interventions	s Patient characteristics			
year		criteria			Elemental	Control	Control
Ref ID					nutrition	1	2
Country				<b>T 0 • 1</b>		( [0/])	1. 1
				Type of indu	ction therapy	/ (n[%]): n 5 ASA)	nedical
				(predifisoione Total N recei	, azatmoprine	, J-ASA) n therenv:	46
				Total N recei	veu muuchol ving remissi	on after in	duction
				therapy: 39	ving remissi		uution
				Total N alloc	ated to main	tenance tre	eatment:
				39			
				Diagnostic cr	iteria used fo	or CD: star	ndard
				clinical, endos	scopic, radiol	ogical, and	when
				possible, histo	ological criteri	a	
				Co intomiont	iong. Dradnig	long (mag	n rongo;
				10 5-17 5 mg/	d) azathioprir	ne (dose: N	R)
				5-ASA (dose: NR)			
				Outcome def	initions annli	ed: remissi	ion
				CDAI<150, re	elapse/recurre	nce increas	e in
				CDAI by >10	0 points since	baseline of	r final
				CDAI >150 p	oints; need of	surgery; in	creased
				doses of stero	ids		
				Outcomes re	ported: main	tenance of o	clinical
				remission at 12 mo, withdrawal from steroids,			
				and duration of remission at 24 mo			
							1
Yamamoto	Aim: to	Inclusion criteria:	Elemental	Patients	32	24	NA
2010 <sup>-5</sup>	assess the	CD who had achieved	nutrition:	assigned (n)	22	24	NIA
Japan	FN on the	clinical remission	nutrition via	railenis analysed (n)	32	24	INA
	maintenance	(CDAI<150 after	nasogastric	Age (vears)	31.0 (9.0)	33.0	NA
	rate of	infliximab induction	tube infusion	- Mean	51.0 (5.0)	(7.8)	1.11
	clinical	therapy) with time	during night-	(SD/range)		` ´	
	remission in	from the induction of	time (Elental	Sex - female	12/32	8/24	NA
	patients with	remission to entry $\leq 2$	(Ajinomoto,	n/N (%)	(37.5)	(33.3)	
	quiescent CD	weeks; patients who	Tokyo )) +	Weight (kg)	NR	NR	NA
	infliximab as	therapy including	Drug Jinfliximah 5	- Mean			
	maintenance	elemental nutrition	mg/kg] (with	(SD/range) PMI	ND	ND	ΝΔ
	therapy	infusion at least one	restricted low	$(ka/m^2)$	INIX	INIX	INA
	1.0	time before entry; and	fat diet)	(kg/m) - Mean			
	Study	patients who agreed to		(SD/range)			
	setting:	continue with the	Control 1:	Smoking	4/32	4/24	NA
	specialty	assigned treatment	Drug	n/N (%)	(12.5)	(16.6)	
	clinic	(with or without	[Infliximab 5 mg/kg] (with	Duration of	33.0	35.0	NA
	Length of	nutrition) for 56 weeks	unrestricted	CD (mo) -	(24.8)	(19.6)	
	follow un (#	number) for 50 weeks	low fat diet)	Mean (SD/marras)			
	<b>months):</b> 14	Exclusion criteria:	, unet,	(SD/range)	102.1	102.3	ΝΔ
		patients who had	Control 2: NA	Score-	(18.1)	(22.5)	11/1
	Funding: NR	severe anorectal		Mean	(10.1)	(22.3)	
		involvement; patients		(SD/range)			

Author	Study details	udy details Inclusion/ exclusion	Interventions	Patient characteristics			
year Ref ID		criteria			Elemental nutrition	Control 1	Control 2
Country		who had tight bowel strictures or enteric fistulae even if clinical symptoms were quiescent		Location of CD - n/N (%) Small bowel Small bowel and colon Previous	11/32 (34.4) 21/32 (65.6)	11/24 (45.8) 13/24 (54.1) 8/24	NA
				bowel resection n/N (%)	(34.4)	(33.3)	
				<b>Type of indu</b> (infliximab 5	c <b>tion therapy</b> mg/kg)	v ( <b>n[%]):</b> m	nedical
				Total N recei Total N achie therapy: 56 Total N alloc 56	ved induction eving remission ated to maint	n therapy: on after in tenance tre	NR duction eatment:
				Diagnostic cr	iteria used fo	or CD: NR	
				<b>Co-intervent</b> g/day), Azathi	ions: Mesalaz ioprine (Imura	tine (Pentas an 50–100 i	a 3 mg/day)
				Outcome defi < 150, relapse Outcomes rep	initions appli e/recurrence s ported: remis	ied: remissi core CDAI	ion CDAI > 150 enance
Vamamoto	Aim	Indusion oritoria:	Flomontal	Patients	20	20	NA
30, 59, 60	to examine if	patients with	nutrition:	assigned (n)	20	20	
Japan	elemental nutrition	histological diagnosis of CD, aged 15-75 yrs	Elental (Ajinomoto, Tokvo, Japan)	Patients analysed (n)	20	20	NA
	infusion along with low fat diet is	who had resection for ileal and ileocolonic (including ileocaecal)	infused at home	Age (years) - Mean (SD/range)	31.0 (16.5)	33.0 (17.4)	NA
	useful in reducing	CD; received EN therapy including	via self-	Sex - female n/N (%)	8/20 (40.0)	6/20 (30.0)	NA
	clinical and endoscopic recurrence	elemental nutrition infusion at least once before operation;	intubated tube in the night- time 1 week	Weight (kg) - Mean (SD/range)	NR	NR	NA
	rates after resection for CD	agreed to continue assigned treatment (with or without enteral nutrition) for more than	after operation (with restricted food diet)	BMI (kg/m <sup>2</sup> ) - Mean (SD/range)	NR	NR	NA
	Study setting:	1 year after operation	Control 1:	Smoking n/N (%)	2/20 (10.0)	2/20 (10.0)	NA
	specialty clinic	<b>Exclusion criteria:</b> patients with colonic	No intervention	Duration of CD (mo) -	37.0 (31.7)	39.0 (36.7)	NA
	Length of	CD alone or with diffuse small bowel CD	(1.e., normal unrestricted	Mean (SD/range)			

Author	Study details	Inclusion/ exclusion	Interventions	Patient characteristics			
year Ref ID Country		criteria			Elemental nutrition	Control 1	Control 2
Country	follow up (#		diet)	CDAI	NR	NR	NA
	months): 12 Funding: no		Control 2: NA	score- Mean (SD/range)			
	external funding received			Location of CD - n/N (%) Terminal ileum Terminal ileum and colon Ileocolonic anastomosis	5/20 (25.0) 11/20 (55.0) 4/20 (20.0)	7/20 (35.0) 9/20 (45.0) 4/20 (20.0)	NA
				Previous bowel resection n/N (%)	20/20 (100.0)	20/20 (100.0)	NA
				Type of induce resection (40/4 [92.5]), pentast Total N receit Total N achie therapy: NR Total N alloc: 40 Diagnostic er and histologic Co-interventit prophylactic r No corticoster infliximab exc Outcome defit CDAI<150 (c (endoscopic), 12 mo: CDAI	ction therapy 40 [100.0]), c sa (32/40 [77. ved induction eving remission ated to main iteria used for al (no specific ions: Pentasa medication. roid, immunos cept patients v initions appli linical), Rutge relapse/recum	(n[%]): b orticosteroi 5]) n therapy: on after indicesteroi tenance tree or CD: end c criteria re 3000 mg/d suppressive who relapse ed: remissive erts score rence clinic or CDAI>2	owel ds (37/40 NR duction eatment: oscopic ported) ay as a drugs, or d con (2 al (at 6, 200)
				endoscopic (Rutgeerts score≥2) Outcomes reported: clinical and endoscopic recurrence			
Yamamoto	Aim: To	Inclusion criteria:	Elemental	Patients	20	20	NA
Japan	long-term enteral	endoscopic/histological diagnosis of CD in the	nutrition: Elemental	assigned (n) Patients analysed (n)	20	20	NA
	nutrition (vs. no intervention)	terminal ileum and/or the colon; age: 15-75 years; clinical	Elental (Ajinomoto,	Age (years) - Mean (SD/range)	29.0 (17.4)	31.0 (20.1)	NA
	is effective in reducing	remission (CDAI<150) after medical	restricted food	Sex - female n/N (%)	6/20 (30.0)	7/20 (35.0)	NA

Author	Study details	s Inclusion/ exclusion Interventions Patient characteristics					
year Ref ID Country		criteria			Elemental nutrition	Control 1	Control 2
	clinical and endoscopic relapse rates	treatment; the duration from the induction of remission to	diet)	Weight (kg) - Mean (SD/range)	51.1 (8.5)	48.9 (7.6)	NA
	and inhibiting mucosal cytokine production in	entry<8 weeks; patients had experienced enteral nutrition therapy including elemental	<b>Control 1:</b> no intervention (i.e., normal unrestricted	BMI (kg/m <sup>2</sup> ) - Mean (SD/range)	19.2 (1.3)	19.1 (1.8)	NA
	patients with quiescent CD	nutrition infusion at least 1 time before	diet	Smoking n/N (%)	2/20 (10.0)	4/20 (20.0)	NA
	Study setting: NR	entry; patient agreed to continue with assigned treatment (with or without enteral	Control 2: NA	Duration of CD (mo) - Mean (SD/range)	32.0 (35.3)	36.0 (38.9)	NA
	Length of follow up (# months): 12	nutrition) for >1 year; and patient agreed to have ileocolonoscopy with multiple mucosal		CDAI score- Mean (SD/range)	101.0 (28.2)	92.0 (21.5)	NA
	Funding: NR	biopsies even if they did not have any clinical symptoms <b>Exclusion criteria:</b> diffuse jejunoileal or gastroduodenal; severe anorectal stricture or		<i>Location of</i> <i>CD - n/N</i> (%) Terminal ileum Colon Terminal ileum and	7/20 (35.0) 2/20 (10.0) 11/20 (55.0)	8/20 (40.0) 2/20 (10.0) 10/20 (50.0)	NA
		sepsis; tight bowel strictures or enteric fistulae even though clinical symptoms were quiescent; patient had		colon Previous bowel resection n/N (%)	4/20 (20.0)	4/20 (20.0)	NA

Author	Study details	Inclusion/ exclusion	Interventions	Patient chara	octeristics			
year Ref ID Country		criteria			Elemental nutrition	Control 1	Control 2	
ASA=aminos	alicylic acid: BM	received corticosteroids, immunosuppressive drugs, or infliximab at entry	rohn's Disease: m	Type of induce mg/kg x 1 or x pts (prednisolo (prednisolone alone), 36 pts the majority o nutrition at the Total N recei Total N achie therapy: NR Total N alloc: 40 Diagnostic cr and histologic Co-interventi prophylactic r immunosuppr patients who r Outcome defi CDAI<150 (c threshold for t NR), relapse/r NR (endoscop mucosal inflat Outcomes rep proportion of remission (CE disease activit cytokine assay	ction therapy ction therapy x 3 prednisolo one with enter alone), 20 pts (Pentasa 750- f patients requ- e start of the t ved induction eving remission ated to maint riteria used for al (not specific ions: Pentasa medication. N essive drugs, relapsed initions appli linical), NR (of the mucosal in recurrence CD bic; specific the mmation grad ported: CDA patients main DAI=Crohn's	r(n[%]): 4 one, inflixin ral nutrition $ral nutritions(enteral nut-3000 mg/cuired parenreatmentn therapy:on after intenance troor CD: endied)3000 mg/dto corticostor inflixinged: remissiendoscopicofflammatioDAI \ge 150 (ctreshold fore NR)I score, curtaining clintoscopic seflammationDisease Au$	pts (5 nab), 6 i), 10 pts itrition lay), and teral NR duction eatment: oscopic ay as a eroid, ab except ion ; specific n grade linical), : the mulative ical verity of , mucosal	
Index; CRP=0 life; IOBD=Ir	Index; CRP=C-reactive protein; EN=Enteral nutrition; ESR=erythrocyte sedimentation rate; HQOL=health related quality of life; IOBD=International Organization for the Study of Inflammatory Bowel Disease; N=number; NR=not reported;							
pts=patients;	SD=standard devi	lation						

### 4.3 Risk of bias assessment

Risk of bias assessment for the eight included studies (three RCTs<sup>50, 52, 55</sup> and five non-RCTs<sup>30, 51, 56-58</sup>) are presented in risk of bias tables and graphs separately for RCTs (Table 4; Figure 2) and non-RCTs (Table 5; Figure 3).

## 4.3.1 Randomised controlled trials (RCTs)

Overall, two<sup>50, 52</sup> of the three RCTs reported an adequate method for random sequence generation and only one<sup>52</sup> reported adequate treatment allocation concealment (low risk of bias). All three RCTs were rated as having low risk of performance and detection bias for objective (e.g., radiography, endoscopy) vs. subjective (e.g., patient-administered functional scores, CDAI) outcomes. The RCTs failed to report blinding status of the patients and study personnel. But based on the nature of the administered intervention, it is unlikely that study personnel and participants in these studies were blinded. In two RCTs,<sup>50, 55</sup> it was not clear if outcome assessors were blinded. Outcome assessors in one RCT<sup>52</sup> were reported to be blinded. For the three RCTs, the influence of attrition bias was judged at low risk. All three RCTs were judged as being at high risk for selective outcome and/or analysis bias. Risk of other bias (e.g., funding source, balance imbalance in important characteristics, inappropriate analysis) for two RCTs<sup>50, 52</sup> was judged to be low.

### 4.3.2 Non-randomised controlled trials (non-RCTs)

The presence of imbalance in important baseline factors was suspected for two non-RCTs (high risk of bias)<sup>51, 56</sup> and was unclear for the remaining three non-RCTs.<sup>30, 57, 58</sup> In the first trial,<sup>51</sup> there was some between-group imbalance in induction therapy and distribution of the lesion. In the second trial,<sup>56</sup> the elemental nutrition group had a shorter disease duration (60.3 vs. 91.0 months), greater ESR, and a longer steroid use compared to the no intervention group. Four non-RCTs<sup>30, 56-58</sup> were rated as having low risk of performance and detection bias for objective (e.g., radiography, endoscopy) vs. subjective (e.g., patient-administered functional scores, CDAI) outcomes. Three RCTs<sup>51, 56, 58</sup> failed to report blinding status of the patients, study personnel, as well as outcome assessors. Based on the nature of the administered intervention in these studies, it is unlikely that study personnel and participants were blinded. The remaining two non-RCTs<sup>30, 57</sup> explicitly reported that patients and study personnel were not blinded, but outcome assessors were blinded. For four non-RCTs,<sup>30, 56-58</sup> the influence of attrition bias was judged at low risk. Three of the five non-RCTs<sup>30, 57, 58</sup> were judged as being at low risk for selective outcome and/or analysis bias. Risk of other bias (e.g., funding source, balance imbalance in important characteristics, inappropriate analysis) for four non-RCTs<sup>30, 56-58</sup> was judged to be low.

First author, year, study ID	Selection bias Random sequence generation	Selection bias Allocation concealment	Performance bias Subjective (e.g., patient-reported)	Performance bias Objective (e.g., radiography, endoscopy)	Detection bias Subjective (e.g., patient-reported)	Detection bias Objective (e.g., radiography, endoscopy)	Attrition bias Subjective (e.g., patient-reported)	Attrition bias Objective (e.g., radiography, endoscopy)	Reporting bias Selective reporting of the outcome, subgroups, or analysis	Other bias Funding source, adequacy of statistical methods used, type of analysis [ITT/PP], baseline imbalance in important characteristics
Hanai 2012 <sup>50</sup>	+	?	•	+	-	+	+	+	-	+
Takagi 2006 <sup>52-54</sup>	+	+	•	+	-	+	+	+	-	+
Verma 2001 <sup>55</sup>	?	?	•	+	-	+	+	+	-	?
ID=identification; ITT=intention-to-treat; PP=per protocol										
Key:										
	- High risk	of bias	<mark>?</mark> U	nclear risk of bia	IS	+ L	ow risk of bias	NA	Not applicabl	le

### Table 4: Risk of bias for randomised controlled trials: review author's judgments about each risk of bias item

First author, year, study ID	<b>Selection bias</b> The presence/absence of baseline between-group imbalance in important prognostic factors (e.g., age, sex, CDAI, duration of CD, location of CD, complications during induction therapy, type of induction therapy, pre-study compliance, co- intervention, and/or smoking)	Performance bias Subjective (e.g., patient-reported)	<b>Performance bias</b> Objective (e.g., radiography, endoscopy)	Detection bias Subjective (e.g., patient-reported)	Detection bias Objective (e.g., radiography, endoscopy)	Attrition bias Subjective (e.g., patient-reported)	Attrition bias Objective (e.g., radiography, endoscopy)	Reporting bias Selective reporting of the outcome, subgroups, or analysis	Other bias Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]
Hirakawa 1993 <sup>51</sup>	•	NA	+	NA	+	NA	•	-	-
Verma 2000 <sup>56</sup>	•	-	+	-	+	+	+	-	+
Yamamoto 2007a <sup>30,</sup> <sup>60</sup>	?	-	+	-	+	+	+	+	+
Yamamoto 2007b <sup>57</sup>	?	-	+	-	+	+	+	+	+
Yamamoto 2010 <sup>58</sup>	?	-	+	•	+	+	+	+	+
ID=identification; ITT	ID=identification; ITT=intention-to-treat; PP=per protocol								
Key:									

### Table 5: Risk of bias for non-randomised controlled trials: review author's judgments about each risk of bias item



Figure 2: Overall risk of bias assessment: randomised controlled trials





## 4.4 Clinical effectiveness of elemental nutrition

Results of included trials are provided in Table 6 to Table 24. Results reported partially (e.g., missing effect measures, 95% CIs) or statistically non-significant effect measures with wide 95% CIs were considered inconclusive.

#### 4.4.1 Maintenance of Remission

In seven of the eight included trials, the maintenance of remission was reported as the proportion of patients maintaining remission<sup>30, 50, 55-58</sup> and/or cumulative probability of maintaining remission (Kaplan Meier estimates of survival).<sup>50, 51, 57, 58</sup> This outcome was not reported for one trial.<sup>52</sup> None of the trials reported duration of remission. See Table 6 to Table 9.

#### Elemental nutrition vs. No intervention (i.e., unrestricted/free or restricted diet)

#### Randomised controlled trials

In one trial,<sup>50</sup> the post-treatment differences for the maintenance of remission at 6 and 12 months were not statistically significant between the elemental nutrition and no intervention groups [review conclusion: inconclusive]. However, at 24 months of follow-up, elemental nutrition was significantly more beneficial in maintaining remission compared to no intervention (RR=2.06, 95% CI: 1.00, 4.43). The same trial reported statistically significantly greater cumulative probability for being in remission for the participants who received elemental nutrition vs. no intervention at 18 (p=0.04) and 24 months of follow-up (p=0.03) [review conclusion: inconclusive]. See Table 6 and Table 7.

## Non-randomised controlled trials

Two of the three trials,<sup>30, 56, 57</sup> reporting maintenance of remission (i.e., proportion of patients maintaining remission), indicated significantly greater rates of maintenance in favour of elemental nutrition at 12 months post-baseline.<sup>30, 57</sup> For example, in one of these trials,<sup>57</sup> significantly more participants receiving elemental nutrition maintained their remission at 12 months of follow-up (RR=2.14, 95% CI: 1.12, 4.10). The results regarding maintenance of remission reported in one trial<sup>56</sup> and cumulative probability of maintaining remission at 48 months reported in one trial (no intervention: restricted diet)<sup>51</sup> were rendered inconclusive due to wide statistically non-significant 95% CIs<sup>56</sup> and partially reported data (missing effect estimates and 95% CIs), respectively.<sup>51</sup> See Table 8 and Table 9.

#### Elemental nutrition vs. Drug

#### Randomised controlled trials

In one trial,<sup>50</sup> the maintenance rate of remission (i.e., proportion of patients maintaining remission and cumulative probability of maintaining remission) at 6 to 24 months of follow-up was not significantly different between the participants receiving elemental nutrition and 6-mercaptopurine (6-MP). Due to missing effect estimates (for the cumulative probability of maintaining remission) and wide 95% CIs (for the proportion of patients maintaining remission), this result was deemed inconclusive. See Table 6 and Table 7.

### Non-randomised controlled trials

One trial<sup>51</sup> showed significantly greater cumulative probability of maintaining remission in participants receiving elemental nutrition vs. those on sulfasalazine/prednisolone at 48 months of follow-up (63% vs. 0%, p<0.05). However, due to partially reported data (i.e., missing 95% CIs), this result was deemed inconclusive. See Table 8 and Table 9.

### Elemental nutrition vs. Elemental nutrition plus drug

*Randomised controlled trials* No trial with these comparisons

#### Non-randomised controlled trials

In one trial,<sup>51</sup> the cumulative probability of maintaining remission was not significantly different for the participants receiving elemental nutrition vs. elemental nutrition plus sulfasalazine or prednisolone at 48 months of follow-up (63% vs. 66%, p>0.05). Due to partially reported data (i.e., missing 95% CIs), this result was deemed inconclusive. See Table 8 and Table 9.

Elemental nutrition plus drug vs. Drug

Randomised controlled trials

No trial with these comparisons.

### Non-randomised controlled trials

In one trial,<sup>58</sup> the proportion of patients maintaining remission (RR=1.17, 95% CI: 0.83, 1.64) and cumulative probability of maintaining remission (p=0.32) were not significantly different in the elemental nutrition plus infliximab vs. infliximab alone group at 14 months of follow-up [review conclusion: inconclusive]. In contrast, another trial<sup>51</sup> showed a significant effect of adding elemental nutrition to sulfasalazine/prednisolone compared to sulfasalazine/prednisolone alone on the cumulative probability of maintaining remission at 48 months post-baseline (66% vs. 0%, p<0.05) [review conclusion: inconclusive]. See Table 8 and Table 9.

# Elemental nutrition vs. Polymeric nutrition

# Randomised controlled trials

In one trial,<sup>55</sup> the proportion of participants maintaining remission was not significantly different between the groups receiving elemental and polymeric nutrition at 12 months of follow-up (RR=0.98, 95% CI: 0.44, 2.19) [review conclusion: inconclusive]. See Table 6.

*Non-randomised controlled trials* No trial with these comparisons.

	Arm-specific estimates	Difference	# of RCTs	Treatment effect				
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across studies]**	Conclusion*				
Elemental n	Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)							
12 mo	NR <sup>52</sup>	NR	1 [NA]	No evidence				
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)								
	Elemental nutrition vs. 6-MP	Elemental nutrition vs.	1 [high ROB]	Inconclusive				
6 mo	27/32 (84.4) vs. 24/30 (80.0) <sup>50</sup>	6-MP		(elemental				
12 mo	20/32 (62.5) vs. 20/30 (66.7) <sup>50</sup>	RR=1.05 (0.83, 1.33) <sup>£</sup>		nutrition vs. 6-				
24 mo	14/32 (46.9) vs. 17/30 (56.7) <sup>50</sup>	RR=0.93 (0.64, 1.35) <sup>£</sup>		MP)				
		RR=0.77 (0.46, 1.27) <sup>£</sup>						
	Elemental nutrition vs. NI			Inconclusive				
6 mo	27/32 (84.4) vs. 23/33 (69.6) <sup>50</sup>	Elemental nutrition vs.		(elemental				
12 mo	20/32 (62.5) vs. 15/33 (45.5) <sup>50</sup>	NI		nutrition vs. NI at				
24 mo	14/32 (46.9) vs. 7/33 (21.2) <sup>50</sup>	RR=1.21 (0.92, 1.58) <sup>£</sup>		6-12 mo)				
		RR=1.37 (0.86, 2.17) <sup>£</sup>						
		RR=2.06 (1.00, 4.43) <sup>£</sup>		In favour of				
				elemental				
				nutrition (vs. NI)				
				at 24 mo				
Elemental n	utrition (with unrestricted diet) vs. ]	Polymeric nutrition (with u	inrestricted diet)					
12 mo	8/19 (42.1) vs. 6/14 (42.8) <sup>55</sup>	p=NR [NS]	1 [unclear ROB]	Inconclusive				
	(remission: CDAI plus other	RR=0.98 (0.44, 2.19) <sup>£</sup>						
	criteria)							
95% CI=95	percent confidence interval; CDAI=cro	hn's disease activity index;	MP=mercaptopurine; NA=no	t applicable;				
NI=no interv	vention; NR=not reported; NS=statistic	ally not significant; mo=mo	nth(s); RCT=randomised cont	trolled trial;				
RR=risk rati	o (relative risk); SD=standard deviatio	n; SROB=summary risk of b	bias					

Table 6: Proportion of patients maintaining remission $\mathbf{i}$ (n/N) – Randomised controlled tria
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\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
 \*\* Decision was consensus-based
 <sup>f</sup> Calculated
 <sup>g</sup> Remission defined using CDAI only unless specified otherwise (e.g., endoscopic, blood parameter, other criteria in addition)

	Arm-specific Kaplan-Meier	Difference	# of RCTs	Treatment	
Follow-up	survival rate estimates	(p value or 95% CI)	[SROB across studies]**	effect	
				Conclusion*	
Elemental n	utrition (with unrestricted diet) vs.	NI (unrestricted diet)		•	
12 mo	NR <sup>52</sup>	NR	1 [NA]	No evidence	
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)					
	Elemental nutrition vs. 6-MP	Elemental nutrition vs.			
6 mo	$NR^{50}$	6-MP	1 [high ROB]	Inconclusive	
12 mo	$NR^{50}$	p=0.83 [NS]			
18 mo	NR <sup>50</sup>	p=0.54 [NS]			
24 mo	NR <sup>50</sup>	p=0.41 [NS]			
		p=0.31 [NS]			
	Elemental nutrition vs. NI				
6 mo	$NR^{50}$	Elemental nutrition vs.			
12 mo	NR <sup>50</sup>	NI			
18 mo	NR <sup>50</sup>	p=0.19 [NS]			
24 mo	NR <sup>50</sup>	p=0.17 [NS]			
		p=0.04 [SS]			
		p=0.03 [SS]			
Elemental n	utrition (with unrestricted diet) vs.	Polymeric nutrition (with u	unrestricted diet)		
12 mo	NR <sup>55</sup>	NR	1 [NA]	Inconclusive	
95% CI=95	percent confidence interval; mo=montl	n(s); MP=mercaptopurine; N	A=not applicable; NI=no interv	vention; NR=not	
reported; NS	=statistically not significant; RCT=rar	domised controlled trial; RI	R=risk ratio (relative risk); SRO	B=summary risk	
of bias; SS=s	statistically significant				

# Table 7: Cumulative survival rate for being in remission (%) – Randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive \*\* Decision was consensus-based <sup>£</sup> Calculated

# Table 8: Proportion of patients maintaining remission¥ (n/N) – Non-randomised controlled trials

	Arm-specific estimates	Difference	# of non-RCTs	Treatment effect			
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across studies]**	Conclusion*			
Elemental nut	rition (unrestricted diet) vs. NI (unre	estricted diet)					
12 mo	10/21 (47.6) vs. 4/18 (22.2) <sup>56</sup>	p=0.0003 [SS]	1 [high ROB]	Inconclusive			
		RR=2.14 (0.81, 5.67),					
		p=0.18 [NS] <sup>£</sup>					
Elemental nut	Elemental nutrition (restricted diet) vs. NI (unrestricted diet)						
12 mo	19/20 (95.0) vs. 13/20 (65.0) <sup>30</sup>	p=NR					
		RR=1.46 $(1.04, 2.05)^{\text{f}}$	2 [high ROB]	In favour of			
12 mo	15/20 (75.0) vs. 7/20 (35.0) <sup>57</sup>	p=0.01 [SS]		elemental nutrition			
		RR= $2.14 (1.12, 4.10)^{\text{f}}$					
Elemental nut	rition (restricted diet) vs. Elemental	nutrition/Drug <sup><math>\beta</math></sup> (restrict	ted diet) vs. Drug (restricted	diet) vs. NI			
(restricted die	t)						
12, 24, 48 mo	NR <sup>51</sup>	NR	1 [NA]	No evidence			
Elemental nut	rition/Drug <sup>µ</sup> (restricted diet) vs. Dru	ıg <sup>μ</sup> (unrestricted diet)					
14 mo	25/32 (78.1) vs. 16/24 (66.6) <sup>58</sup>	p=0.51 [NS]	1 [high ROB]	Inconclusive			
		RR=1.17 (0.83, 1.64) <sup>£</sup>					
95% CI=95 per	cent confidence interval; CDAI=crohr	n's disease activity index;	mo=month(s); NA=not applic	able; NI=no			
intervention; N	R=not reported; NS=statistically not si	ignificant; RCT=randomis	sed controlled trial; RR=risk r	atio (relative risk);			
SROB=summa	SROB=summary risk of bias; SS=statistically significant						
* Favou	rs elemental nutrition (or comparator treati	ment), no difference, or incom	nclusive				
<sup>£</sup> Calcul	** Decision was consensus-based <sup>£</sup> Calculated						

<sup> $\beta$ </sup> Sulfasalazine (3g/d) or prednisolone (10mg/d)

 <sup>µ</sup> Infliximab (5 mg/kg)
 <sup>¥</sup> Remission defined using CDAI only unless specified otherwise (e.g., endoscopic, blood parameter, other criteria additionally)

	Arm-specific Kaplan-Meier	Difference	# of non-RCTs	Treatment effect
Follow-up	survival rate estimates	(p value or 95% CI)	[SROB across studies]**	Conclusion*
Elemental nut	rition (unrestricted diet) vs. NI (u	nrestricted diet)		
12 mo	NR <sup>56</sup>	NR	1 [NA]	No evidence
Elemental nut	rition (restricted diet) vs. NI (unre	estricted diet)		
6, 12, 60 mo	NR <sup>30</sup>	NR	1 [NA]	No evidence
12 mo	NR <sup>57</sup>	p=0.01 [SS] in favour of	1 [high ROB]	Inconclusive
		elemental nutrition as		
		reported		
Elemental nut	rition (restricted diet) vs. Element	tal nutrition/Drug <sup>β</sup> (restric	ted diet) vs. Drug (restricted	l diet) vs. NI
(restricted die	t)			
12 mo	94% (NR) vs. 75% (NR) vs.	At 48 mo	1 [high ROB]	Inconclusive
	63% (NR) vs. 50% (NR) <sup>51</sup>	p<0.05 [1 vs. 3] SS		
		p<0.01 [1 vs. 4] SS		
24 mo	63% (NR) vs. 66% (NR) vs.	p<0.05 [2 vs. 3] SS		
	42% (NR) vs. 33% (NR) <sup>51</sup>	p<0.05 [2 vs. 4] SS		
48 mo	63% (NR) vs. 66% (NR) vs. 0%	p≥0.05 [1 vs. 2] NS		
	(NR) vs. 0% (NR) <sup>51</sup>			
Elemental nut	rition/Drug <sup>µ</sup> (restricted diet) vs. D	Drug <sup>µ</sup> (unrestricted diet)		
14 mo	NR <sup>58</sup>	p=0.32 [NS]	1 [high ROB]	Inconclusive
95% CI=95 per	rcent confidence interval; mo=mont	h(s); NA=not applicable; NI	=no intervention; NR=not rep	orted; NS=statistically
not significant;	RCT=randomised controlled trial;	RR=risk ratio (relative risk);	SROB=summary risk of bias	; SS=statistically

# Table 9: Cumulative survival rate for being in remission (%) – Non-randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive \*\* Decision was consensus-based

<sup>£</sup> Calculated

significant

<sup> $\beta$ </sup> Sulfasalazine (3g/d) or prednisolone (10mg/d) <sup> $\mu$ </sup> Infliximab (5 mg/kg)

#### 4.4.2 Development of Relapse/Recurrence

In seven of the eight included trials, the development of relapse/recurrence was reported as the proportion of patients developing relapse<sup>30, 50, 52, 55-58</sup> and/or mean time to relapse.<sup>56</sup> All seven studies reported clinical relapse (defined using CDAI alone or with other criteria) and one study<sup>30</sup> additionally reported endoscopic relapse (Rutgeerts score $\geq$ 2). See Table 10 and Table 11.

#### Elemental nutrition vs. No intervention (i.e., unrestricted/free diet)

#### Randomised controlled trials

Our meta-analysis of two  $RCTs^{50, 52}$  indicated a significantly reduced risk of relapse amongst participants receiving elemental nutrition vs. no intervention at 12 to 24 months of follow-up (pooled RR=0.57, 95% CI: 0.38, 0.84; Chi<sup>2</sup>=0.04, p=0.83, I<sup>2</sup>=0%). See Figure 4 and Table 10.

Figure 4: Patients developing relapse/recurrence at 12 to 24 months: elemental nutrition vs. no intervention (unrestricted diet)



## Non-randomised controlled trials

Findings from three trials consistently showed a significant benefit of elemental nutrition vs. no intervention in reducing risk of clinical (RR=0.50, 95% CI: 0.25, 0.98;<sup>56</sup> RR=0.14, 95% CI: 0.02,  $1.00;^{30}$  and RR=0.38, 95% CI: 0.16,  $0.87^{57}$ ) as well as endoscopic relapse (RR=0.42, 95% CI: 0.20,  $0.88)^{30}$  at 12 months post-baseline. In one of the trials,<sup>30</sup> the between-group difference in the risk of endoscopic relapse at 60 months follow-up was not statistically significant (RR=0.68, 95% CI: 0.42, 1.11) [review conclusion: inconclusive]. See Table 11.

In one trial,<sup>56</sup> at 12 months post-baseline, the mean time (in months) to relapse in the elemental nutrition group was significantly longer compared to no intervention group (7.4 vs. 6.2, mean difference: 1.20, 95% CI: 0.35, 2.04). See Table 12.

### Elemental nutrition vs. Drug

### Randomised controlled trials

In one trial,<sup>50</sup> the difference in the occurrence of relapse between participants receiving elemental nutrition and 6-MP after 24 months of follow-up was not statistically significant (RR=1.61, 95% CI: 0.73, 3.53) [review conclusion: inconclusive]. See Table 10.

*Non-randomised controlled trials* Evidence not reported.<sup>51</sup> See Table 11.

Elemental nutrition vs. Elemental nutrition plus drug Randomised controlled trials No trial with these comparisons.

*Non-randomised controlled trials* Evidence not reported.<sup>51</sup> See Table 11.

Elemental nutrition plus drug vs. Drug Randomised controlled trials No trial with these comparisons.

## Non-randomised controlled trials

Of the two available trials with the above-mentioned comparisons,<sup>51, 58</sup> only one reported this outcome.<sup>58</sup> In this trial, the difference in the occurrence of relapse between participants receiving elemental nutrition plus infliximab vs. infliximab alone was not statistically significant (RR=0.65, 95% CI: 0.27, 1.56) [review conclusion: inconclusive]. See Table 11.

## Elemental nutrition vs. Polymeric nutrition

## Randomised controlled trials

In one trial,<sup>55</sup> at 12 months of follow-up, the difference in the occurrence of relapse between participants receiving elemental and polymeric nutrition was not statistically significant (RR=1.18, 95% CI: 0.48, 2.83) [review conclusion: inconclusive]. See Table 10.

# Non-randomised controlled trials

No trial with these comparisons.

	Arm-specific estimates	Difference	# of RCTs	Treatment				
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across studies]**	effect				
				Conclusion*				
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)								
12 mo	9/26 (34.6) vs. 16/25 (64.0) <sup>52</sup>	HR=0.40 (0.16, 0.98)	1 [low ROB]	In favour of				
	(relapse: CDAI plus other criteria)	adjusted estimate		elemental				
				nutrition group				
		RR=0.54 (0.29, 0.99) <sup>£</sup>						
Elemental r	Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)							
	Elemental nutrition vs. 6-MP	Elemental nutrition vs.	1 [low ROB]	Inconclusive				
24 mo	12/32 (37.5) vs. 7/30 (23.3) <sup>50</sup>	6-MP		(elemental				
	(relapse: CDAI plus other criteria)	RR=1.61 (0.73, 3.53) <sup>£</sup>		nutrition vs. 6-				
				MP)				
24 mo	Elemental nutrition vs. NI	Elemental nutrition vs.		In favour of				
	12/32 (37.5) vs. 21/33 (63.6) <sup>50</sup>	NI		elemental				
	(relapse: CDAI plus other criteria)	RR=0.58 (0.35, 0.98) <sup>£</sup>		nutrition group				
				(vs. NI)				
Elemental r	utrition (with unrestricted diet) vs.	Polymeric nutrition (with u	unrestricted diet)					
12 mo	8/19 (42.1) vs. 5/14 (35.7) <sup>55</sup>	p=NR [NS]	1 [high ROB]	Inconclusive				
		RR=1.18 (0.48, 2.83) <sup>£</sup>						
95% CI=95	percent confidence interval; CDAI=cro	ohn's disease activity index;	HR=hazard ratio; mo=month(s)	);				
MP=mercap	topurine; NI=no intervention; NR=not	reported; NS=statistically n	ot significant; RCT=randomised	1 controlled trial;				
RR=risk rati	o (relative risk); SROB=summary risk	of bias						

# Table 10: Proportion of patients developing relapse/recurrence¥ (n/N) – Randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

\*\* Decision was consensus-based
 <sup>f</sup> Calculated
 <sup>g</sup> Relapse defined using CDAI only unless specified otherwise (e.g., endoscopic, blood parameter, other criteria in addition

	Arm-specific estimates	Difference	# of non-RCTs	Treatment effect			
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across	Conclusion*			
			studies]**				
Elemental nutr	ition (unrestricted diet) vs. NI (unrestricted	l diet)	<u> </u>				
12 mo	7/21 (33.3) vs. 14/18 (77.7) <sup>56</sup>	p<0.00001 [SS]	1 [unclear	In favour of			
	(relapse: CDAI plus other criteria)	RR=0.50 (0.25, 0.98) <sup>£</sup>	ROB]	elemental nutrition			
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)							
	Clinical relapse (CDAI≥150/200)	Clinical relapse (12 mo)	1 [high ROB]	Clinical relapse			
12 mo	1/20 (5.0) vs. 7/20 (35.0) <sup>30</sup>	p=0.048 [SS]		In favour of			
60 mo	6/20 (30.0) vs. 12/20 (60.0) <sup>30</sup>	RR= $0.14 (0.02, 1.00)^{\text{f}}$		elemental nutrition			
				(at 12 mo)			
		Clinical relapse (60 mo)					
		p=0.11 [NS]		Inconclusive (at 60			
		RR= $0.50 (0.23, 1.07)^{\text{f}}$		mo)			
	Endoscopic relapse (Rutgeerts score≥2)	Endoscopic relapse (6 mo)	1 [low ROB]	Endoscopic relapse			
6 mo	5/20 (25.0) vs. 8/20 (40.0) <sup>30</sup>	p=0.50 [NS]		In favour of			
12 mo	6/20 (30.0) vs. 14/20 (70.0) <sup>30</sup>	RR= $0.62 (0.24, 1.58)^{\text{f}}$		elemental nutrition			
60 mo	9/16 (56.2) vs. 14/17 (82.3) <sup>30</sup>			(12 mo)			
		Endoscopic relapse (12 mo)					
		p=0.027 [SS]		Inconclusive (at 6 mo			
		RR=0.42 $(0.20, 0.88)^{\text{f}}$		and 60 mo)			
		Endoscopic relapse (60 mo)					
		p=0.21 [NS]					
		RR=0.68 (0.42, 1.11) <sup>£</sup>					
12 mo	5/20 (25.0) vs. 13/20 (65.0) <sup>57</sup>	OR=0.20 (0.04, 0.70),	1 [high ROB]	In favour of			
		p=0.03 <sup>£</sup>		elemental nutrition			
		RR=0.38 (0.16, 0.87) <sup>£</sup>					
Elemental nutr	ition (restricted diet) vs. Elemental nutrition	on/Drug <sup><math>\beta</math></sup> (restricted diet) vs. Dr	ug (restricted diet)	vs. NI (restricted			
diet)							
12, 24, 48 mo	NR <sup>51</sup>	NR	1 [NA]	Inconclusive			
Elemental nutr	ition/Drug <sup>µ</sup> (restricted diet) vs. Drug <sup>µ</sup> (unr	estricted diet)					
14 mo	7/32 (21.8) vs. 8/24 (33.3) <sup>58</sup>	p=0.51 [NS]	1 [high ROB]	Inconclusive			
		RR=0.65 (0.27, 1.56) <sup>£</sup>					
95% CI=95 perc	cent confidence interval; CDAI=crohn's disea	se activity index; mo=month(s); I	NA=not applicable;	NI=no intervention;			
of bias; SS=stati	istically significant	onnised controlled trial; KK=fisk i	and (relative risk);	SNUD-SUIIIIIary fisk			
* Fa	* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive; ** Decision was consensus-based						

Table 11: Proportion of patients developing relapse/recurrence¥ (n/N) – Non-randomised controlled trials

<sup> $\pounds$ </sup> Calculated; <sup> $\beta$ </sup> Sulfasalazine (3g/d) or prednisolone (10mg/d) <sup> $\mu$ </sup> Infliximab (5 mg/kg) ¥ Relapse defined using CDAI only unless specified otherwise (e.g., endoscopic, blood parameter, other criteria additionally)

	Arm-specific estimates	Difference	# of non-RCTs	Treatment effect				
Follow-up	Mean (SD or 95% CI)	(p value or 95% CI)	[SROB across	Conclusion*				
			studies]**					
Elemental nut	Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)							
12 mo	7.4 (0.9) vs. 6.2 $(0.4)^{56}$	p=NR	1 [unclear	In favour of				
		MD=1.20 (0.35, 2.04),	ROB]	elemental nutrition				
		p=0.012 <sup>£</sup>						
Elemental nut	rition (restricted diet) vs. NI (unrestricted diet	)						
6, 12, 60 mo	NR <sup>30</sup>	NR	1 [NA]	No evidence				
12 mo	NR <sup>57</sup>	NR	1 [NA]	No evidence				
Elemental nut	rition (restricted diet) vs. Elemental nutrition/	Drug <sup><math>\beta</math></sup> (restricted diet) vs	. Drug (restricted	diet) vs. NI				
(restricted die	t)							
12, 24, 48 mo	NR <sup>51</sup>	NR	1 [NA]	No evidence				
Elemental nut	rition/Drug <sup>µ</sup> (restricted diet) vs. Drug <sup>µ</sup> (unrest	ricted diet)						
14 mo	NR <sup>58</sup>	NR	1 [NA]	No evidence				
95% CI=95 per	cent confidence interval; mo=month(s); NA=not	applicable; NI=no interve	ntion; NR=not repo	rted;				
RCT=randomis	sed controlled trial; RR=risk ratio (relative risk);	SD=standard deviation; SF	ROB=summary risk	of bias				

# Table 12: Time to relapse/recurrence (mean # of months) – Non-randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive \*\* Decision was consensus-based <sup>*f*</sup> Calculated  $^{\beta}$  Sulfasalazine (3g/d) or prednisolone (10mg/d) <sup>µ</sup> Infliximab (5 mg/kg)

## 4.4.3 Incidence of Mucosal Healing (Endoscopic Remission)

Only one of the eight included trials (non-randomised study)<sup>57</sup> reported this outcome, which was based on mucosal inflammation grade categorized as follows: 0=macroscopically normal, 1= granular mucosa and contact bleeding, 2= erythematous and oedematous mucosa, aphtoid or superficial ulcers, and 3=deep ulcers with slough and inflammatory pseudo polyps. In this non-randomised study, at 12 months of follow-up, the proportion of participants achieving grade 0 between elemental nutrition and no intervention (unrestricted diet) groups was not significantly different (RR=2.70, 95% CI: 0.62, 11.72) [review conclusion: inconclusive]. See Table 13.

	Arm-specific estimates	Difference	# of non-RCTs	Treatment effect		
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across	Conclusion*		
			studies]**			
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)						
12 mo	NR <sup>56</sup>	NR	1 [NA]	No evidence		
Elemental nutr	ition (restricted diet) vs. NI (unrestricte	ed diet)				
6, 12, 60 mo	NR <sup>30</sup>	NR	1 [NA]	No evidence		
12 mo	6/20 (30.0) vs. 2/18 (11.1) <sup>57</sup>	p=NR	1 [low ROB]	Inconclusive		
	(Grade 0: macroscopically normal)	$RR=2.70 (0.62, 11.72)^{f}$				
Elemental nutr	ition (restricted diet) vs. Elemental nut	rition/Drug <sup><math>\beta</math></sup> (restricted diet) vs.	Drug (restricted die	et) vs. NI (restricted		
diet)						
12, 24, 48 mo	NR <sup>51</sup>	NR	1 [NA]	No evidence		
Elemental nutr	ition/Drug <sup>µ</sup> (restricted diet) vs. Drug <sup>µ</sup> (					
14 mo	NR <sup>58</sup>	NR	1 [NA]	No evidence		
95% CI=95 percent confidence interval; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported; RCT=randomised						
controlled trial; RR=risk ratio (relative risk); SROB=summary risk of bias						

## Table 13: Proportion of patients with mucosal healing (n/N) – Non-randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

\*\* Decision was consensus-based

<sup>£</sup> Calculated

 $^{\beta}$  Sulfasalazine (3g/d) or prednisolone (10mg/d)

<sup>µ</sup>Infliximab (5 mg/kg)

## 4.4.4 Need for Surgery

Three of the eight included trials reported this outcome: one RCT<sup>50</sup> and two non-RCTs.<sup>30, 57</sup> See Table 14 and Table 15.

## Elemental nutrition vs. No intervention (i.e., unrestricted/free diet)

## Randomised controlled trials

At 24 months follow-up,<sup>50</sup> the proportion of participants in need of surgery was not statistically significantly different between the elemental nutrition and no intervention groups (RR=1.03, 95% CI: 0.06, 15.79; Fisher's exact test p>0.99) [review conclusion: inconclusive]. See Table 14.

## Non-randomised controlled trials

In two trials,<sup>30, 57</sup> at 12 to 60 months of follow-up, the difference in proportion of participants in need of surgery between the elemental nutrition and no intervention groups was not statistically significant (RR=0.20, 95% CI: 0.02, 1.56) [review conclusion: inconclusive]. See Table 15.

# Elemental nutrition vs. Drug

## Randomised controlled trials

At 24 months follow-up,<sup>50</sup> the difference in proportion of participants in need of surgery between the elemental nutrition and 6-MP groups was not statistically significant (RR=0.93, 95% CI: 0.06, 14.32; Fisher's exact test p>0.99) [review conclusion: inconclusive]. See Table 14.

*Non-randomised controlled trials* Evidence not reported.<sup>51</sup> See Table 15.

	Arm-specific estimates	Difference	# of RCTs	Treatment				
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across studies]**	effect				
				Conclusion*				
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)								
12 mo	NR <sup>52</sup>	NR	1 [NA]	No evidence				
Elemental n	Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)							
	Elemental nutrition vs. 6-MP	Elemental nutrition vs.	1 [low ROB]					
24 mo	1/32 (3.1) vs. 1/30 (3.1) <sup>50</sup>	6-MP		Inconclusive				
		p>0.99 [NS] Fisher's						
		exact test <sup>£</sup>						
		RR=0.93 (0.06, 14.32) <sup>£</sup>						
24 mo	Elemental nutrition vs. NI	Elemental nutrition vs.						
	1/32 (3.1) vs. 1/33 (3.0) <sup>50</sup>	NI						
		p>0.99 [NS] Fisher's						
		exact test <sup>£</sup>						
		RR=1.03 (0.06, 15.79) <sup>£</sup>						
Elemental n	utrition (with unrestricted diet) vs. ]	Polymeric nutrition (with u	unrestricted diet)	I				
12 mo	NR <sup>55</sup>	NR	1 [NA]	No evidence				
95% CI=95	percent confidence interval; mo=mont	h(s); MP=Mercaptopurine; N	NA=not applicable; NI=no inter	vention; NR=not				
reported; NS	=statistically not significant; RCT=rar	ndomised controlled trial; RI	R=risk ratio (relative risk); ROB	=summary risk				
of bias								

# Table 14: Proportion of patients in need of surgery (n/N) – Randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

\*\* Decision was consensus-based <sup>£</sup> Calculated

	Arm-specific estimates	Difference	# of non-RCTs	Treatment effect
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across studies]**	Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	NR <sup>56</sup>	NR	1 [NA]	Inconclusive
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
60 mo	1/20 (5.0) vs. 5/20 (25.0) <sup>30</sup>	p=0.18 [NS]		
		RR=0.20 (0.02, 1.56) <sup>£</sup>	2 [low ROB]	Inconclusive
12 mo	0/20 (0.0) vs. 2/20 (10.0) <sup>57</sup>	p=NR		
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug <sup>β</sup> (restricted diet) vs. Drug (restricted diet) vs. NI				
(restricted diet)				
12, 24, 48 mo	NR <sup>51</sup>	NR	1 [NA]	Inconclusive
Elemental nutrition/Drug <sup>µ</sup> (restricted diet) vs. Drug <sup>µ</sup> (unrestricted diet)				
14 mo	NR <sup>58</sup>	NR	1 [NA]	No evidence
RR=risk ratio (relative risk); SROB=summary risk of bias; SD=standard deviation; 95% CI=95 percent confidence interval;				
NR=not reported; mo=month(s); NA=not applicable; NI=no intervention				

# Table 15: Proportion of patients in need of surgery (n/N) – Non-randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive \*\* Decision was consensus-based <sup>*f*</sup> Calculated  $^{\beta}$  Sulfasalazine (3g/d) or prednisolone (10mg/d) <sup>µ</sup> Infliximab (5 mg/kg)

#### 4.4.5 Adherence

Seven of the eight included trials reported any information on adherence: two RCTs<sup>52, 55</sup> and five non-RCTs.<sup>30, 51, 56-58</sup> See Table 16 and Table 17.

### Elemental nutrition vs. No intervention (i.e., unrestricted/free or restricted diet)

### Randomised controlled trials

In one RCT,<sup>52</sup> the difference in the rates of adherence at 12 months of follow-up between the groups of elemental nutrition and no intervention (unrestricted diet) was not statistically significant (77% vs. 80%; RR=0.96, 95% CI: 0.72, 1.28) [review conclusion: inconclusive]. See Table 16.

#### Non-randomised controlled trials

The rate of adherence reported for two trials<sup>30, 56</sup> was significantly lower in the elemental nutrition vs. no intervention group at 12 months (RR=0.81, 95% CI: 0.65, 0.99)<sup>56</sup> and 60 months (RR=0.80, 95% CI: 0.64, 0.99)<sup>30</sup> after the baseline. For the remaining two trials comparing elemental nutrition to no intervention (unrestricted diet<sup>57</sup> or restricted diet,<sup>51</sup>) the between group differences in adherence were not statistically significant at 12 months (90% vs. 100%, Fisher's exact test p=0.48)<sup>57</sup> and 48 months post-baseline (88% vs. 100%, Fisher's exact test p>0.99)<sup>51</sup> [review conclusion: inconclusive]. See Table 17.

Elemental nutrition vs. Drug Randomised controlled trials No evidence reported.<sup>50</sup>

#### Non-randomised controlled trials

In one trial comparing elemental nutrition to sulfasalazine/prednisolone,<sup>51</sup> the between group differences in adherence at 48 months post-baseline were not statistically significant (88% vs. 100%, Fisher's exact test p=0.84) [review conclusion: inconclusive]. See Table 17.

Elemental nutrition vs. Elemental nutrition plus drug Randomised controlled trials No trial with these comparisons

### Non-randomised controlled trials

In one trial comparing the elemental nutrition to the combination of elemental nutrition and sulfasalazine/prednisolone,<sup>51</sup> the between group differences in adherence at 48 months post-baseline

were not statistically significant (88% vs. 77.3%, Fisher's exact test p=0.55) [review conclusion: inconclusive]. See Table 17.

Elemental nutrition plus drug vs. Drug Randomised controlled trials No trial with these comparisons

## Non-randomised controlled trials

In one trial comparing the combination of elemental nutrition and sulfasalazine/prednisolone to sulfasalazine/prednisolone alone,<sup>51</sup> the between group differences in adherence at 48 months post-baseline were not statistically significant (77.3% vs. 100%, Fisher's exact test p=0.37). Another trial comparing the combination of elemental nutrition and infliximab vs. infliximab alone<sup>58</sup> reported 78% of adherence for the elemental nutrition group. No data was reported for the infliximab group [review conclusion: inconclusive]. See Table 17.

# Elemental nutrition vs. Polymeric nutrition

## Randomised controlled trials

The rate of adherence reported in one trial<sup>55</sup> was significantly lower in the elemental nutrition vs. polymeric nutrition group at 12 months after the baseline (68.4% vs. 100%, RR=0.68, 95% CI: 0.50, 0.92). See Table 16.

*Non-randomised controlled trials* No trial with these comparisons.
# Table 16: Proportion of patients with adherence (n/N) – Randomised controlled trials

	Arm-specific estimates	Difference	# of RCTs	Treatment		
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across studies]**	effect		
				Conclusion*		
Elemental n	Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)					
12 mo	20/26 (77.0) vs. 20/25 (80.0) <sup>52</sup>	RR= $0.96 (0.72, 1.28)^{\text{f}}$	1 [low ROB]	Inconclusive		
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)						
24 mo	NR <sup>50</sup>	NR	1 [NA]	No evidence		
Elemental n	utrition (with unrestricted diet) vs. ]	Polymeric nutrition (with u	unrestricted diet)			
12 mo	13/19 (68.4) vs. 14/14 (100.0) <sup>55</sup>	RR=0.68 (0.50, 0.92) <sup>£</sup>	1 [unclear ROB]	In favour of		
				polymeric		
				nutrition group		
95% CI=95 percent confidence interval; MP=Mercaptopurine; NI=no intervention; NR=not reported; RCT=randomised						
controlled trial; RR=risk ratio (relative risk); SD=standard deviation; SROB=summary risk of bias						

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive \*\* Decision was consensus-based <sup>f</sup> Calculated

	Arm-specific estimates	Difference	# of non-RCTs	Treatment effect			
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across	Conclusion*			
			studies]**				
Elemental nu	Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)						
12 mo	17/21 (80.9) vs. 18/18 (100.0) <sup>56</sup>	p=NR	1 [unclear	In favour of NI group			
		RR= $0.81 (0.65, 0.99)^{\text{f}}$	ROB]				
Elemental nu	utrition (restricted diet) vs. NI (unrest	ricted diet)					
12 mo	20/20 (100.0) vs. 20/20 (100.0) <sup>30</sup>	p=NR		In favour of the NI (60			
60 mo	16/20 (80.0) vs. 20/20 (100.0) <sup>30</sup>	RR= $0.80 (0.64, 0.99)^{\text{f}}$	2 [low ROB]	mo)			
12 mo	18/20 (90.0) vs. 20/20 (100.0) <sup>57</sup>	p=0.48 Fisher's exact test <sup>£</sup> NS		Inconclusive			
Elemental nu	utrition (restricted diet) vs. Elemental	nutrition/Drug <sup><math>\beta</math></sup> (restricted diet)	vs. Drug (restricte	d diet) vs. NI			
(restricted d	iet)						
48 mo	22/25 (88.0) vs. 17/22 (77.3) vs. 8/8	Fisher's exact test <sup>£</sup>	1 [low ROB]	Inconclusive			
	(100.0) vs. 6/6 (100.0) <sup>51</sup>	p=0.55 [1 vs. 2] NS					
		p=0.84 [1 vs. 3] NS					
		p>0.99 [1 vs. 4] NS					
		p=0.37 [2 vs. 3] NS					
		p=0.53 [2 vs. 4] NS					
Elemental n	utrition/Drug <sup>μ</sup> (restricted diet) vs. Dru	g <sup>µ</sup> (unrestricted diet)					
14 mo	25/32 (78.1) vs. NR (NR) <sup>58</sup>	NR	1 [NA]	No evidence			
95% CI=95 p	ercent confidence interval; NA=not app	licable; NI=no intervention; NR=no	ot reported; NS=stat	tistically not significant;			
RCT=random	nised controlled trial; RR=risk ratio (rela	tive risk); SROB=summary risk of	bias				

# Table 17: Proportion of patients with adherence (n/N) – Non-randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
 \*\* Decision was consensus-based
 <sup>f</sup> Calculated
 <sup>β</sup> Sulfasalazine (3g/d) or prednisolone (10mg/d)
 <sup>μ</sup> Infliximab (5 mg/kg)

# 4.4.6 Withdrawal from Steroids

Two of the eight included trials (one  $RCT^{55}$  and one non- $RCT^{56}$ ) reported the proportion of participants who withdrew from taking steroids. Results from both trials showed statistically non-significant differences in the withdrawals from steroids at 12 months post-baseline between the groups of elemental nutrition vs. polymeric nutrition (42.1% vs. 42.8%, RR=0.98, 95% CI: 0.44, 2.19)<sup>55</sup> or no intervention – unrestricted diet (23.8% vs. 22.2%, RR=1.07, 95% CI: 0.33, 3.39)<sup>56</sup> [review conclusion: inconclusive]. See Table 18 and Table 19.

	Arm-specific estimates	Difference	# of RCTs	Treatment	
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across studies]**	effect	
				Conclusion*	
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)					
12 mo	NR <sup>52</sup>	NR	1 [NA]	No evidence	
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)					
24 mo	NR <sup>50</sup>	NR	1 [NA]	No evidence	
Elemental n	utrition (with unrestricted diet) vs. ]	Polymeric nutrition (with u	unrestricted diet)		
12 mo	8/19 (42.1) vs. 6/14 (42.8) <sup>55</sup>	p=NR [NS]	1 [unclear ROB]	Inconclusive	
		RR=0.98 (0.44, 2.19) <sup>£</sup>			
95% CI=95 percent confidence interval; mo=month(s); MP=Mercaptopurine; NA=not applicable; NI=no intervention; NR=not					
reported; NS=statistically not significant; RR=risk ratio (relative risk); SROB=summary risk of bias					

# Table 18: Proportion of patients who withdrew from taking steroids (n/N) – Randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

\*\* Decision was consensus-based

<sup>£</sup> Calculated

	Arm-specific estimates	Difference	# of non-RCTs	Treatment effect	
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across studies]**	Conclusion*	
Elemental nut	rition (unrestricted diet) vs. NI (u	nrestricted diet)	I		
12 mo	5/21 (23.8) vs. 4/18 (22.2) <sup>56</sup>	p=NR	1 [unclear ROB]	Inconclusive	
		RR=1.07 (0.33, 3.39) <sup>£</sup>			
Elemental nut	rition (restricted diet) vs. NI (unro	estricted diet)			
6, 12, 60 mo	NR <sup>30</sup>	NR	1 [NA]	No evidence	
12 mo	NR <sup>57</sup>	NR	1 [NA]	No evidence	
Elemental nut	rition (restricted diet) vs. Element	al nutrition/Drug <sup>β</sup> (restric	ted diet) vs. Drug (restricted	diet) vs. NI	
(restricted die	t)				
12, 24, 48 mo	NR <sup>51</sup>	NR	1 [NA]	No evidence	
Elemental nutrition/Drug <sup>µ</sup> (restricted diet) vs. Drug <sup>µ</sup> (unrestricted diet)					
14 mo	NR <sup>58</sup>	NR	1 [NA]	No evidence	
95% CI=95 percent confidence interval; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported;					
RCT=randomised controlled trial; SROB=summary risk of bias					

# Table 19: Proportion of patients who withdrew from taking steroids (n/N) – Non-randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive \*\* Decision was consensus-based  ${}^{f}$  Calculated  ${}^{\beta}$  Sulfasalazine (3g/d) or prednisolone (10mg/d)  ${}^{\mu}$  Infliximab (5 mg/kg)

# 4.4.7 Steroid Dose Tapering

Only one trial (non-RCT) reported this outcome.<sup>56</sup> At 12 months of follow-up, the difference in the proportion of participants whose steroid dose was tapered in those receiving elemental nutrition vs. no intervention (unrestricted diet) was not statistically significant (47.6% vs. 22.2%, RR=2.14, 95% CI: 0.80, 5.67) [review conclusion: inconclusive]. See Table 20.

	Arm-specific estimates	Difference	# of non-RCTs	Treatment effect	
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across studies]**	Conclusion*	
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)					
12 mo	10/21 (47.6) vs. 4/18 (22.2) <sup>56</sup>	p=NR	1 [unclear ROB]	Inconclusive	
		RR= $2.14 (0.80, 5.67)^{\text{f}}$			
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)					
6, 12, 60 mo	NR <sup>30</sup>	NR	1 [NA]	No evidence	
12 mo	NR <sup>57</sup>	NR	1 [NA]	No evidence	
Elemental nut	rition (restricted diet) vs. Elemental	nutrition/Drug <sup>β</sup> (restric	ted diet) vs. Drug (restricted	diet) vs. NI	
(restricted diet	t)				
12, 24, 48 mo	NR <sup>51</sup>	NR	1 [NA]	No evidence	
Elemental nutrition/Drug <sup>µ</sup> (restricted diet) vs. Drug <sup>µ</sup> (unrestricted diet)					
14 mo	NR <sup>58</sup>	NR	1 [NA]	No evidence	
95% CI=95 percent confidence interval; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported;					
RCT=randomised controlled trial; SROB=summary risk of bias					

Table 20: Proportion of patients whose steroid dose was tapered (n/N) – Non-randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

\*\* Decision was consensus-based

<sup>£</sup> Calculated

<sup> $\beta$ </sup> Sulfasalazine (3g/d) or prednisolone (10mg/d)

<sup>µ</sup>Infliximab (5 mg/kg)

# 4.4.8 Crohn's Disease Activity Index

Two non-RCTs<sup>57, 58</sup> reported incomplete data on 12-14 month post-treatment mean CDAI score (missing study group-specific means and variability parameters) showing significantly lower mean disease activity in favour of the elemental nutrition vs. no intervention (unrestricted diet) group  $(p=0.04)^{57}$  and non-significant difference between the groups of elemental nutrition plus infliximab vs. infliximab alone  $(p>0.05)^{58}$  [review conclusion: inconclusive]. See Table 21.

	Arm-specific estimates	Difference	# of non-RCTs	Treatment effect			
Follow-up	Mean (SD or 95% CI)	(p value or 95% CI)	[SROB across	Conclusion*			
			studies]**				
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)							
12 mo	NR <sup>56</sup>	NR	1 [NA]	No evidence			
Elemental nut	rition (restricted diet) vs. NI (unrestricted diet	)					
6, 12, 60 mo	NR <sup>30</sup>	NR	1 [NA]	No evidence			
12 mo	NR <sup>57</sup>	p=0.04 [SS] in favour	1 [high ROB]	Inconclusive			
		of elemental nutrition					
		group					
Elemental nut	rition (restricted diet) vs. Elemental nutrition/	Drug <sup><math>\beta</math></sup> (restricted diet) vs	. Drug (restricted	diet) vs. NI			
(restricted die	t)						
12, 24, 48 mo	NR <sup>51</sup>	NR	1 [NA]	No evidence			
Elemental nut	rition/Drug <sup>µ</sup> (restricted diet) vs. Drug <sup>µ</sup> (unrest	ricted diet)					
14 mo	NR <sup>58</sup>	p>0.05 [NS]	1 [high ROB]	Inconclusive			
95% CI=95 percent confidence interval; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported;							
NS=statistically not significant; RCT=randomised controlled trial; SD=standard deviation; SROB=summary risk of bias;							
SS=statistically	v significant						

# Table 21: Crohn's Disease Activity Index (score: 0-600) – Non-randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

\*\* Decision was consensus-based

<sup>£</sup> Calculated

 $^{\beta}$  Sulfasalazine (3g/d) or prednisolone (10mg/d)

<sup>µ</sup>Infliximab (5 mg/kg)

# 4.4.9 Health Related Quality of Life

Only one trial  $(RCT)^{52}$  reported any information on health related quality of life. At 12 month of follow-up, the adjusted mean Inflammatory Bowel Disease Questionnaire (IBDQ) score did not differ between the participants receiving elemental nutrition vs. no intervention unrestricted diet (171.9 vs. 176.7, p>0.05). See Table 22.

	Arm-specific estimates	Difference	# of RCTs	Treatment			
Follow-up	Mean (SD or 95% CI)	(p value or 95% CI)	[SROB	effect			
			across	Conclusion*			
			studies]**				
Elemental n	utrition (with unrestricted diet) vs. NI (unrestricted	d diet)					
12 mo	171.9 (126.4, 217.3) vs. 176.7 (142.5, 211.0) <sup>52</sup>	Adjusted mean IBDQ	1 [high ROB]	No difference			
		score difference					
		p>0.05 [NS]					
Elemental n	utrition (with restricted diet) vs. 6-MP (with unrest	tricted diet) vs. NI (unres	tricted diet)				
24 mo	NR <sup>50</sup>	NR	1 [NA]	No evidence			
Elemental n	utrition (with unrestricted diet) vs. Polymeric nutr	ition (with unrestricted d	liet)				
12 mo	NR <sup>55</sup>	NR	1 [NA]	No evidence			
95% CI=95 percent confidence interval; mo=month(s); MP=mercaptopurine; NA=not applicable; NI=no intervention; NR=not							
reported; NS=statistically not significant; RCT=randomised controlled trial; SD=standard deviation; SROB=summary risk of							
bias; IBDQ=	bias; IBDQ= Inflammatory Bowel Disease Questionnaire						

Table 22: Health-related quality of life (mean IBDQ score; score range: 32-224) – Randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

\*\* Decision was consensus-based

 $^{\pounds}$  Calculated

# 4.4.10 Adverse Events and Complications

For two RCTs reporting adverse events,<sup>50, 52</sup> no meaningful comparison was possible, since the effect estimates could not be generated due to zero counts in the nominators [review conclusion: inconclusive]. For example, one trial reported the absence of adverse events.<sup>52</sup> In the other trial,<sup>50</sup> none of the 32 participants in the elemental nutrition group experienced any adverse event or complication. Of the 30 participants in the 6-MP group, two experienced elevated aspartate transaminase (AST), one participant- hair loss, and one participant – abscess (complication). Of the 33 participants in the no intervention group (unrestricted diet), one experienced elevated amylase. None of the participants in this group experienced any complication. See Table 23 and Table 24.

	Arm-specific estimates	Difference	# of RCTs	Treatment		
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across	effect		
			studies]**	Conclusion*		
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)						
12 mo	$0/26 (0.0)$ vs. $0/25 (0.0)^{52}$		1 [low ROB]	Inconclusive		
Elemental n	Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)					
24 mo	Elemental nutrition vs. 6-MP	Elemental nutrition vs. 6-MP	1 [low ROB]	Inconclusive		
	0/32 (0.0) vs. 2/30 (6.6) [elevated	-				
	AST] and 1/30 (3.1) [hair loss] <sup>50</sup>					
	Elemental nutrition vs. NI	Elemental nutrition vs. NI				
	0/32 (0.0) vs. 1/33 (3.0) [elevated					
	amylase] <sup>50</sup>					
Elemental n	Elemental nutrition (with unrestricted diet) vs. Polymeric nutrition (with unrestricted diet)					
12 mo	NR <sup>55</sup>	NR	1 [NA]	No evidence		
95% CI=95 percent confidence interval; AST=aspartate transaminase; mo=month(s); MP=mercaptopurine; NA=not applicable;						
NI=no interv	vention; NR=not reported; NS=statistically	v not significant; RCT=randomised	controlled trial; SRO	B=summary risk		
of bias; SS=	statistically significant					

#### Table 23: Proportion of patients with adverse event(s) (n/N) – Randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

\*\* Decision was consensus-based

<sup>£</sup> Calculated

	Arm-specific estimates	Difference	# of RCTs	Treatment	
Follow-up	n/N (%)	(p value or 95% CI)	[SROB across	effect	
			studies]**	Conclusion*	
Elemental r	nutrition (with unrestricted diet) vs. NI (	(unrestricted diet)			
12 mo	0/26 (0.0) vs. 0/25 (0.0) <sup>52</sup>		1 [low ROB]	Inconclusive	
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)					
24 mo	Elemental nutrition vs. 6-MP	Elemental nutrition vs. 6-MP	1 [low ROB]	Inconclusive	
	0/32 (0.0) vs. 1/30 (3.1) [abscess] <sup>50</sup>				
	Elemental nutrition vs. NI	Elemental nutrition vs. NI			
	0/32 (0.0) vs. 0/33 (3.0) <sup>50</sup>				
Elemental r	nutrition (with unrestricted diet) vs. Poly	meric nutrition (with unrestricted	ed diet)		
12 mo	NR <sup>55</sup>	NR	1 [NA]	No evidence	
95% CI=95 percent confidence interval; mo=month(s); MP=mercaptopurine; NA=not applicable; NI=no intervention; NR=not					
reported; NS	S=statistically not significant; RCT=randor	nised controlled trial; SROB=sumr	nary risk of bias; SS=	statistically=	
significant					

# Table 24: Proportion of patients with complication(s) (n/N) – Randomised controlled trials

\* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive \*\* Decision was consensus-based <sup>£</sup> Calculated

### 4.4.11 Unreported Outcomes of Interest

None of the eight included trials reported changes in anthropometric measures (e.g., weight, BMI, height, linear growth) and pubertal development.

# 4.5 Cost-effectiveness of elemental diet

This review did not identify any study assessing cost-effectiveness of elemental nutrition. One RCT<sup>52, 54</sup> reported monthly costs for the two study groups of elemental nutrition and no intervention (i.e., free diet). This study was not an economic evaluation; therefore no formal assessment of methodological quality of economic assessment was undertaken. In addition there was not sufficient information on the cost data collection and analysis. According to this study report,<sup>54</sup> the adjusted one year monthly cost treatments were not significantly different between the elemental nutrition and free diet groups (US\$ 880.00 vs. US\$ 600.00, p>0.05). See Cost Table in Appendix IV.

# 4.6 Rating the overall quality of evidence (GRADE System)

The overall quality ratings for each gradable outcome (i.e., maintenance of remission, risk of relapse, mucosal healing, need of surgery, withdrawal from steroids, steroid dose tapering, adherence, and adverse events) are presented in the Evidence Profile (EP) Table (see Table 25).

The overall quality of evidence for each gradable outcome was rated for the comparison between elemental nutrition and no intervention, given that two RCTs<sup>50, 52</sup> comparing elemental nutrition to no intervention (unrestricted diet) were judged to be the only potentially combinable evidence.

The overall quality ratings across the gradable outcomes for the above-mentioned comparison were as follows: maintenance of remission (Grade: Very Low), risk of relapse (Grade: High), need of surgery (Grade: Very Low), adherence (Grade: Very Low), and adverse events (Grade: Moderate). Mucosal healing, withdrawal from steroids, and steroid dose tapering were not rated due to the absence of evidence.

# **Table 25: GRADE evidence profile for gradable outcomes reported in RCTs of Crohn's disease** (adapted from Guyatt et al., 2011)<sup>49</sup>

Outcome [follow-up timing]	N of studies reporting outcome (participants)	Pooled effect estimate (95% CI) and conclusion	SROB across studies	Consistency	Directness	Precision	Outcome reporting bias	Quality of the evidence (GRADE)*
Elemental nutrition vs. NI (i.e.,	unrestricted/free di	$et) - 2 RCTs^{50, 52}$			1			
Maintenance of remission [12 mo]	1 (65) <sup>50</sup>	No pooled estimate RR=1.37 (0.86, 2.17) Inconclusive	High SROB	NA	Direct	Imprecise	Likely	Very low
Maintenance of remission [24 mo]	1 (65) <sup>50</sup>	No pooled estimate RR=2.06 (1.00, 4.43) In favour of elemental nutrition	High SROB	NA	Direct	Precise	Likely	Very low
Development of relapse/recurrence [12 mo-24 mo]	2 (116) <sup>50, 52</sup>	Pooled estimate RR=0.57 (0.38, 0.84) In favour of elemental nutrition	Low SROB	Consistent	Direct	Precise	Unlikely	High
Mucosal healing [NA]	0 (0)	NA	NA	NA	NA	NA	NA	NA (no evidence)
Need of surgery [24 mo]	1 (65) <sup>50</sup>	No pooled estimate RR=1.03 (0.06, 15.79) Inconclusive	Low SROB	NA	Direct	Imprecise	Likely	Very low
Withdrawal from steroids [NA]	0 (0)	NA	NA	NA	NA	NA	NA	NA (no evidence)
Steroid dose tapering [NA]	0 (0)	NA	NA	NA	NA	NA	NA	NA (no evidence)
Adherence [12 mo]	1 (51) <sup>52</sup>	No pooled estimate RR=0.96 (0.72, 1.28) Inconclusive	Low SROB	NA	Direct	Imprecise	Likely	Very low
Adverse events [12 mo-24 mo]	2 (116) <sup>50, 52</sup>	No pooled estimate Parameters not estimable <b>Inconclusive</b>	Low SROB	Consistent	Direct	Imprecise	Unlikely	Moderate
GRADE= Grading of Recommendations, Assessment, Development, and Evaluation; RCT=randomised controlled trial; CI=confidence interval; SROB=summary risk of bias; RCT=randomised controlled trial; NA=not applicable; mo(s)=month(s); NI=no intervention								

\*GRADE categories: high, moderate, low, very low, NA (no evidence)

# 4.7 Summary of Findings

Limited evidence from two RCTs in patients with CD in remission<sup>50, 52</sup> has indicated a significant beneficial effect of elemental nutrition vs. no intervention (unrestricted diet) in maintaining remission after 24 months of follow-up (RR=2.06, 95% CI: 1.00, 4.43; very low grade evidence<sup>50</sup>) and preventing the occurrence of relapse at 12-24 months of follow-up (pooled RR=0.57, 95% CI: 0.38, 0.84; high grade evidence<sup>50, 52</sup>). The shorter-term maintenance rate of remission (at 6 and 12 months) between the two randomised groups was not significantly different (12 month RR=1.37, 95% CI: 0.86, 2.17; very low grade evidence; inconclusive result due to wide 95% CIs).<sup>50</sup>

Similarly, three non-RCTs also showed significant benefits of elemental nutrition over no intervention (unrestricted diet) in maintaining remission at 12-48 months<sup>30, 57</sup> and preventing the occurrence of relapse at 12 months.<sup>30, 56, 57</sup> Evidence on the maintenance of remission from two non-RCTs was rendered inconclusive due to wide non-significant 95% CIs (RR=2.14, 95% CI: 0.81, 5.67)<sup>56</sup> and missing data (i.e., effect estimates and/or 95% CIs).<sup>51</sup> In one non-RCT,<sup>56</sup> the use of elemental nutrition was associated with a significantly longer time to relapse compared to no intervention after 12 months of follow-up (MD=1.20, 95% CI: 0.35, 2.04).

According to one non-RCT,<sup>57</sup> the incidence of mucosal healing (endoscopic remission) at 12 months between patients receiving elemental nutrition vs. no intervention (unrestricted diet) was not significantly different (inconclusive results; RR=2.70, 95% CI: 0.62, 11.72).

Based on evidence from two non-RCTs,<sup>30, 56</sup> and one RCT,<sup>55</sup> there was a significantly worse adherence rate in the elemental nutrition groups compared to either no intervention (unrestricted diet)<sup>30, 56</sup> or polymeric nutrition group (RR=0.68, 95% CI: 0.50, 0.92).<sup>55</sup>

In general, evidence comparing the effects of elemental nutrition and active treatment(s) (sulfasalazine/prednisolone, infliximab, elemental nutrition, polymeric nutrition, or combination) across the outcomes of interest yielded statistically non-significant results with wide 95% CIs implying possible moderate to large effect size treatment effects in both directions compatible both with benefit and harm from elemental nutrition (inconclusive results).

Evidence on complications and adverse events was too sparse (e.g., zero events, low counts) to derive effect estimates and 95% CIs and permit any meaningful comparison between the treatments.

There was no reported evidence on changes in anthropometric measures (e.g., body weight, height, BMI, linear growth rate) and pubertal development. See Table 26.

# Table 26: Summary of findings and overall quality ratings of evidence regarding the differences between elemental nutrition and other interventions for each reported outcome

Conclusive evidence suggesting difference	Conclusive evidence	Inconclusive evidence				
	suggesting no					
	difference					
N	laintenance of Remission (	n/N)				
Elemental Nutrition vs. No Intervention <sup>30, 50-52, 56, 57</sup>	,					
At 24 months	None	At 6 and 12 months (NS)				
1 RCT <sup>50</sup>		1 RCT <sup>50</sup>				
[very low grade]		[very low grade]				
In favour of elemental nutrition						
At 12-48 months		At 12 months (NS)				
2 non-RCTs <sup>30, 57</sup>		1 non-RCT <sup>56</sup>				
In favour of elemental nutrition						
		At 48 months (SS=favoured elemental nutrition)				
		1 non-RCT <sup>51</sup>				
Elemental Nutrition vs. Drug <sup>50, 51</sup>						
None	None	At 6, 12, 24 months (NS)				
		1 RCT <sup>50</sup>				
		At 48 months (SS=favoured elemental nutrition)				
		1 non-RCT <sup>51</sup>				
Elemental Nutrition vs. Elemental Nutrition plus L	$Drug^{51}$	I				
None	None	At 48 months (NS)				
		1 non-RCT <sup>51</sup>				
Elemental Nutrition plus Drug vs. Drug <sup>51, 58</sup>	I	I				
None	None	At 14 months (NS)				
		1 non-RCT <sup>58</sup>				
		At 48 months (SS=favoured elemental nutrition				
		plus drug)				
		1 non-RCT <sup>51</sup>				
Elemental Nutrition vs. Polymeric Nutrition <sup>55</sup>		1				
None	None	At 12 months (NS)				
		1 RCT <sup>55</sup>				
Ri	sk of Relapse/Recurrence (	(n/N)				
Elemental Nutrition vs. No Intervention <sup>30, 50-52, 56, 57</sup>						
At 12-24 months	None	At 60 months (NS)				

2 RCTs <sup>50, 52</sup>		1 non-RCT <sup>30</sup>
[high grade] – pooled estimate		
In favour of elemental nutrition		
At 12 months		
3 non-RCTs <sup>30, 56, 57</sup>		
In favour of elemental nutrition		
Elemental Nutrition vs. Drug <sup>50, 51</sup>		
None	None	At 24 months (NS)
		1 RCT <sup>50</sup>
Elemental Nutrition plus Drug vs. Drug <sup>51, 58</sup>		1
None	None	At 14 months (NS)
		1 non-RCT <sup>58</sup>
Elemental Nutrition vs. Polymeric Nutrition <sup>55</sup>		
None	None	At 12 months (NS)
		1 RCT <sup>55</sup>
	 Fime To Relanse (# of mon	ths)
Elemental Nutrition vs. No Intervention <sup>30, 50-52, 56, 57</sup>	7	·····)
At 12 months	None	None
1 non-RCT <sup>56</sup>		
In favour of elemental nutrition		
	Mucosal Healing (n/N)	
Elemental Nutrition vs. No Intervention <sup>30, 50-52, 56, 57</sup>	1	
None	None	At 12 months (NS)
		1 non-RCT <sup>57</sup>
	Need for Surgery (n/N)	1
Elemental Nutrition vs. No Intervention <sup>30, 50-52, 56, 57</sup>	7	
None	None	At 24 months (NS)
		1 RCT <sup>50</sup>
		[very low grade]
		At 12 and 60 months (NS)
		2 non-RCTs <sup>30, 57</sup>
Elemental Nutrition vs. Drug <sup>50, 51</sup>		1
None	None	At 24 months (NS)
		1 RCT <sup>50</sup>
	Adherence (n/N)	1
Elemental Nutrition vs. No Intervention <sup>30, 50-52, 56, 57</sup>	7	
At 12 and 60 months	None	At 12 months (NS)

2 non-RCTs <sup>30, 56</sup>		1 RCT <sup>52</sup>		
In favour of no intervention		[very low grade]		
		At 12 and 48 months (NS)		
		2 non-RCTs <sup>51, 57</sup>		
Elemental Nutrition vs. Drug <sup>50, 51</sup>	I	I		
None	None	At 48 months (NS)		
		1 non-RCT <sup>51</sup>		
Elemental Nutrition vs. Elemental Nutrition plus D	Drug <sup>51</sup>			
None	None	At 48 months (NS)		
		1 non-RCT <sup>51</sup>		
Elemental Nutrition plus Drug vs. Drug <sup>51, 58</sup>				
None	None	At 48 months (NS)		
		1 non-RCT <sup>51</sup>		
Elemental Nutrition vs. Polymeric Nutrition <sup>55</sup>				
At 12 months	None	None		
1 RCT <sup>55</sup>				
In favour of polymeric nutrition				
W	/ithdrawal from Steroids (1	n/N)		
Elemental Nutrition vs. No Intervention <sup>30, 50-52, 56, 57</sup>				
None	None	At 12 months (NS)		
		1 non-RCT <sup>56</sup>		
Elemental Nutrition vs. Polymeric Nutrition <sup>55</sup>				
None	None	At 12 months (NS)		
		1 RCT <sup>55</sup>		
Steroid Dose Tapering (n/N)				
Elemental Nutrition vs. No Intervention <sup>30, 50-52, 56, 57</sup>				
None	None	At 12 months (NS)		
		1 non-RCT <sup>56</sup>		
Health Rel	ated Quality of Life (mean	IBDQ score)		
Elemental Nutrition vs. No Intervention <sup>30, 50-52, 56, 57</sup>				
None	At 12 months (NS)	None		
	1 RCT <sup>52</sup>			
	In no favour of either			
	intervention			
Adverse Events and Complications (n/N)				
Elemental Nutrition vs. No Intervention <sup>30, 50-52, 56, 57</sup>				
None	None	At 12 and 24 months (estimates could not be		
		generated)		

		2 RCTs <sup>50, 52</sup>	
		[moderate grade]	
Elemental Nutrition vs. Drug <sup>50, 51</sup>			
None	None	At 24 months (estimate could not be generated)	
		1 RCT <sup>50</sup>	
NS=statistically not significant; RCT=randomised controlled trial; SS=statistically significant			

# 4.8 Other Analyses

# 4.8.1 Publication bias

The impact of publication bias on the pooled treatment effect estimates (i.e., degree of funnel plot asymmetry) could not be explored due to an insufficient number of data points in the forest/funnel plots.

# 4.8.2 Subgroup effects

The reviewed evidence was too sparse and heterogeneous to allow exploration of whether or not the relative effect of elemental nutrition differed by study-level methodological (i.e., risk of bias, type of data analysis) or patient-related characteristics (i.e., age, sex, or induction therapy).

# **5 DISCUSSION**

CD is a chronic relapsing-remitting condition that causes chronic inflammation of the gastrointestinal tract. The clinical presentation of CD is often characterised by malnutrition, abdominal pain, diarrhoea, and weight loss.<sup>33</sup> Despite the availability of a variety of therapeutic options used in the management of CD (medications, surgical, or nutritional), none of these options lead to complete cure of this condition.<sup>32</sup> The main objective of any given management option is to induce and then maintain remission of disease activity by controlling the extent of inflammation, reducing clinical symptoms, and preventing complications. Although corticosteroids are the most widely used drugs for the treatment of active CD, their use has been shown to be associated with short-term remission, steroid dependency, impairment in growth, and risk of infections.<sup>33</sup>

For the past two decades, nutritional therapy/enteral nutrition has been suggested as an effective treatment option in the management of CD in adults and children in terms of controlling CD activity.<sup>31, 37</sup> For example, one meta-analysis indicated that enteral nutrition was at least as effective as steroids in inducing remission in children and young adults with active CD.<sup>36</sup> In contrast, a more recent review demonstrated that enteral nutrition given to adults was in general beneficial but less effective in inducing remission compared to steroids.<sup>27</sup> There has been little clarity as regards to the role of enteral nutrition for maintaining remission in patients with quiescent CD. The relevant evidence has been scarce, mostly of observational nature, and inconsistent in terms of findings.<sup>33, 37</sup> Owing to its good safety profile, and if proved at least as effective as standard medical treatments, enteral nutrition would potentially replace or minimise the use of steroids, biologics, immunosuppressants. This in turn would lead to improved clinical outcomes, fewer adverse events, in general, and better growth rates and pubertal development in younger patients with CD.<sup>35, 37</sup>

The mechanism of action of elemental nutrition on CD is not known. Several hypothesised mechanisms underlying the proposed benefits of enteral nutrition in CD include reduced gut activity, reduction of antigenic load, nutritional effects, anti-inflammatory effects, or modulation of immune system and gastrointestinal flora.<sup>30-33</sup>

# 5.1 Main findings

This review systematically identified, appraised, and synthesised relevant evidence on the comparative clinical effectiveness of elemental nutrition for maintaining remission in patients with CD. Limited

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evidence from two RCTs<sup>50, 52</sup> and three non-RCTs<sup>30, 56, 57</sup> has suggested that elemental nutrition (given orally or via feeding tube) was more effective for the maintenance of remission (at 12-48 months; very low grade evidence based on RCTs) and prevention of relapse (at 12-24 months; high grade evidence based on RCTs) compared to no treatment (i.e., unrestricted diet). Evidence from one non-RCT also indicated that patients receiving elemental nutrition experienced longer mean time to relapse compared to patients in the no intervention group on unrestricted diet only.<sup>56</sup> The 12-month rates of adherence were lower in the elemental nutrition vs. no intervention (i.e., unrestricted diet)<sup>30, 56</sup> or polymeric nutrition group.<sup>55</sup> This finding may be explained by the inconvenience of nasogastric feeding, poor palatability, and/or higher cost of elemental nutrition compared to unrestricted diet and polymeric nutrition.<sup>31, 61</sup> Limited evidence from one RCT<sup>52</sup> demonstrated no difference in health related quality of life between elemental nutrition and no intervention (unrestricted diet).

In general, comparisons of elemental nutrition to active treatments (sulfasalazine/prednisolone, infliximab, elemental nutrition, polymeric nutrition, or combination) across the outcomes of interest were not statistically significant. These results should not be interpreted to mean that the treatments being compared are equivalent (or that there is an absence of effect of elemental nutrition). The associated 95% CIs tended to be so wide and uninformative as to include potential moderate to large treatment effects compatible with both benefit and harm of elemental nutrition. Therefore, these results are inconclusive.

The data on complications and adverse events was too sparse (e.g., zero events, low counts) to derive effect estimates and 95% CIs or to permit any meaningful comparison between the treatments. It is unclear whether insufficient evidence on adverse events and complications is due to the absence or rarity of these events or it is simply due to underreporting of such events.

For some reported evidence (e.g., cumulative probability of survival for being in remission) adequate interpretation was not possible due to poor reporting or missing data (no summary effect measures, 95% CIs, standard deviations), and therefore was considered inconclusive.

# 5.2 Limitations of evidence

The review findings warrant cautious interpretation given the limitations of the evidence in terms of small trial size, methodological quality, and risk of bias in individual trials (lack of blinding, short duration of follow-up, confounding).

For example, the lack of blinding of participants, study personnel, and/or outcome assessors may have led to systematic differences in care giving, administration of co-interventions, and outcome assessments across the compared treatment groups. Generally, subjective measures such as those based on patient-reported outcomes including clinical symptoms (e.g., abdominal pain, number of soft stools), quality of life, or clinically defined remission/relapse) are more prone to bias than objective outcomes (e.g., endoscopic or biologically defined remission using serum/faecal biomarkers and radiography additional to CDAI, adverse events, and complications).

Some of the results, especially in non-RCTs, may have been biased since some known or unknown prognostic factors may have been distributed unevenly between the treatment groups. As for the known confounders, there was some between-group imbalance in two non-RCTs with regards to induction therapy, location of the lesion, and disease duration.<sup>51, 56</sup> Moreover, in three non-RCTs<sup>30, 57, 58</sup> patients with 'good compliance' were assigned to elemental nutrition and those with 'poor compliance' to the control groups. Given that 'good compliers' may be inherently different from 'poor compliers' in clinical characteristics, this selective assignment could have distorted the group balance in some of these prognostic covariates (unclear risk of bias). Additional concern for confounding effects is justified since in some of the studies the use of concomitant drugs given for prophylaxis (e.g., 5-ASA, sulphasalazine, azathioprine, prednisolone) differed across the treatment groups in frequency/dose.<sup>30, 50, 52, 55, 56, 58</sup>

In general, more or less consistent results for primary outcomes observed between RCTs and non-RCTs give more credence to the validity of findings in this review.

Additional limitations of the relevant evidence are worth mentioning. There was a lack of evidence of effects of elemental nutrition in young adolescents and children with CD in remission. The data reported on health related quality of life, adverse events, and complications were insufficient to allow any adequate conclusion. There was no relevant evidence for changes in anthropometric measures (weight, BMI, height, linear growth) and pubertal development. Given that all of the included studies evaluated elemental nutrition in addition to restricted or unrestricted diet, this review was unable to assess the effectiveness of an exclusive elemental nutrition in the maintenance of remission in patients with CD.

# 5.3 Comparison of current findings to previous systematic reviews

We identified two SRs evaluating comparative effectiveness of elemental nutrition in maintaining remission for patients with CD.<sup>32, 37</sup> The Cochrane review's eligibility criterion for design was set to

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RCTs (included two RCTs).<sup>32</sup> The study eligibility for the other SR was wider and encompassed RCTs, prospective non-randomised controlled trials, and retrospective observational cohort studies (included one RCT, three non-RCTs, and six retrospective cohort studies).<sup>37</sup> All potentially eligible trials included in the two SRs, were also included in the present review. In general, findings of this review are in agreement with those from other two SRs in showing benefits of elemental nutrition compared to no intervention (i.e., unrestricted diet) in maintaining remission amongst patients with CD. In agreement with our review, findings in relation to the comparison between elemental and polymeric nutrition were inconclusive.<sup>32</sup>

# 5.4 Strengths and limitations of current review

One of the strengths of this review is that we used systematic, comprehensive, and independent strategies to minimise bias in searching, identifying, selecting, extracting, and appraising the primary studies. The search strategy was applied to multiple electronic sources, relevant websites, as well as reference lists of potentially eligible publications were searched. Moreover, this review included a higher hierarchy of evidence (i.e., randomised and non-randomised controlled trials).

This review has its own limitations. The presence of clinical heterogeneity (e.g., population characteristics, induction therapy), potential for confounding (especially in non-RCTs), and poor reporting (missing data on outcomes) led to limitations for pooling the results across studies. Since this review included only English language full text publications, the effects of publication bias cannot be ruled out. Given the insufficient number of pooled studies (data points), this effect could not be investigated via funnel plots. Likewise, the paucity of data did not allow exploration of whether there was any variation in treatment effect across the pre-defined subgroups of patients or methodological features of studies.

# 5.5 Applicability of findings and implications for clinical practice and policy making

It is not usually easy to determine the extent to which studies are applicable to a broader context of routine clinical practice in a given geographical place and this is true in this case for extrapolating to the UK for a number of reasons. This process of ascertaining applicability is hindered by poor reporting, selective eligibility criteria and enrolment, non-participation and differences between treatments and outcomes used in research versus those used in routine clinical practice. Specifically, the extent of

applicability of this review's findings to clinical practice in the UK may be limited, since six of the eight included studies were conducted in Japan,<sup>30, 50-52, 57, 58</sup> and only two in the UK.<sup>55, 56</sup> The trials reviewed may have been overly selective in enrolling and assigning patients to treatments, thereby leading to samples that are not representative of patients with CD in remission encountered in daily clinical practice. Patient adherence is important for successful treatment with elemental nutrition. However, if studies have reported the effects of elemental nutrition in only good compliers, this will also limit the applicability of findings to a broader group of patients. Since all included studies investigated adult patients, the conclusions regarding the benefits of elemental nutrition in maintaining remission of CD may not be readily applicable to younger patients (< 18 years old). Most results were based on outcomes ascertained at 12-24 months of follow-up. The conclusions of the review regarding longer-term benefits indeterminate and cannot be extrapolated. Finally, our findings may not be readily applicable to patients receiving exclusive elemental nutrition, since the evidence available to us and which we reviewed presented only those scenarios where elemental nutrition was given in addition to diet. In summary we would counsel caution in attempting to extrapolate the findings of this review to practice in the UK and would recommend that further research is required – please see research recommendations.

### **5.6 Implications for future research**

Large well-powered and long-term randomised trials are needed to either refute or corroborate our findings. Future research needs to address gaps in the reviewed evidence (e.g., studies in young adolescents and children with CD in remission; effects of exclusive elemental nutrition; effects of elemental nutrition in subgroups defined by age, sex, duration/location of CD, and type of induction therapy) and improve reporting practices in relation to trial methodology (e.g., methods of treatment assignment, blinding, power analysis, statistical analysis) as well as completeness of reported data (missing effect estimates, 95% CIs, adverse events, complications) for better interpretability of evidence. More research exploring better tasting elemental nutritional to maximise the adherence rate to elemental nutrition feeding is also warranted.

# **6** CONCLUSIONS

This systematic review assessed comparative clinical effectiveness of elemental nutrition for the maintenance of remission in patients with CD based on evidence from eight prospective controlled studies. Overall, the findings warrant cautious interpretation given the limited amount of evidence (small number of studies), methodological shortcomings (short-term follow-up, small studies), poor reporting (missing data, partial reporting of data), and role of bias which cannot be ruled out (adherence to elemental nutrition, confounding, lack of blinding). Given these caveats, the results from five studies indicated significant benefits of elemental nutrition (given orally or via feeding tube) in maintaining remission and preventing relapse compared to no intervention (i.e., unrestricted diet) at 12 to 48 months of follow-up. A limited amount of evidence showed greater patient adherence rates for unrestricted or polymeric nutrition groups compared to an elemental nutrition group at 12 months follow-up. According to evidence from one trial, there was no difference in health related quality of life between patients receiving an elemental vs. an unrestricted diet after 12 months of follow-up. In general, effect estimates for most outcomes across comparisons between elemental nutrition and active treatments (e.g., prednisolone) were statistically non-significant accompanied by a great degree of uncertainty (very wide 95% CIs) and therefore were rendered inconclusive. There was a lack or insufficient evidence on adverse events and complications and no evidence on cost effectiveness. There was no similar evidence reported for children or younger patients with CD in remission. Future large and long-term randomised trials are warranted to draw more definitive conclusions regarding the effects of elemental nutrition in maintaining remission in CD.

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# **8** APPENDICES

# 8.1 Appendix I: Protocol

### **1.** Title of the project

Elemental nutrition for Crohn's disease

# 2. Name of TAR team and project 'lead'

Produced by: Warwick Evidence Health Sciences Research Institute Medical School University of Warwick Coventry CV4 7AL

Lead Author: Paul Sutcliffe, Associate Professor and Deputy Director for Warwick Evidence<sup>1</sup>
 Co-authors: Alexander Tsertsvadze, Senior Research Fellow<sup>1</sup>
 Rachel Court, Information Specialist<sup>1</sup>
 Ruth Pulikottil-Jacob, Research Fellow<sup>1</sup>
 Tara Gurung, Research Fellow<sup>1</sup>
 Ngianga-Bakwin Kandala, Principal Research Fellow<sup>1</sup>
 Aileen Clarke, Professor of Public Health and Health Services Research and Director for Warwick Evidence<sup>1</sup>

<sup>1</sup>Warwick Evidence, Health Sciences Research Institute University of Warwick

Correspondence to:	Dr Paul Sutcliffe	
	Health Sciences Research Institute,	
	Medical School	
	University of Warwick	
	Coventry CV4 7AL	
Tel:	02476 150189	
Fax:	02476 528375	
Email:	p.a.sutcliffe@warwick.ac.uk	

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### 3. Plain English Summary

Crohn's disease (CD) is a chronic relapsing-remitting condition that causes inflammation of the intestines. Frequent symptoms of CD include malnutrition, abdominal pain, and diarrhoea. None of the currently available therapeutic options (e.g., medical, surgical, nutritional) lead to a complete cure of CD. The management involves induction and maintenance of remission of disease activity through alleviating inflammatory process and correcting malnutrition. In children, a major additional goal is to promote normal growth and pubertal development. Although there is some evidence indicating beneficial effects of elemental diet for induction of remission in patients with active CD, clinical evidence regarding the role of elemental diet in maintaining remission in CD has not been well studied or clarified. This systematic review aims to evaluate recent comparative evidence on clinical effectiveness and costeffectiveness of elemental diet for the maintenance of remission in patients with CD.

# 4. Decision problem

### **Objectives**

The general objective of this systematic review is to identify, appraise, and evaluate the evidence on clinical effectiveness and cost-effectiveness of elemental diet, a type of enteral nutrition (EN), for the maintenance of remission in Crohn's disease (CD).

- To evaluate the clinical effectiveness and cost-effectiveness of elemental nutrition administered alone or in combination with other interventions (e.g., diet, standard drug treatment) compared to other intervention(s) (e.g., placebo, diet, standard drug treatment) for maintaining remission in patients with CD.
- To compare the clinical effectiveness and cost-effectiveness of elemental nutrition with other types of EN (semi-elemental, polymeric nutrition), duration, and dose in regards to maintaining remission and adherence.
- To explore subgroup effects of elemental nutrition on maintenance of remission (i.e., risk of relapse or recurrence). Specifically, to examine if the treatment effect of elemental nutrition varies across groups defined by sex (males, females), age (adults, adolescents, and children), and type of induction therapy (medically-, nutritionally-, surgically-induced).
- To evaluate additional outcomes for patients with CD such as adherence to EN, CD activity index (CDAI), incidence of mucosal healing, quality of life, adverse events, gain in body weight (or body mass index), growth, and pubertal development.

# 4.1 Background

Crohn's disease (CD), a form of inflammatory bowel disease (IBD), is a chronic relapsing-remitting condition which causes chronic inflammation of the intestines. CD can affect any part of the digestive tract, from the mouth to the anus.<sup>1</sup> The most frequent symptoms of CD include malnutrition, abdominal pain, diarrhoea, weight loss, fever, and rectal bleeding. Although currently there are medical (e.g., corticosteroids, biologics, aminosalicylates, immunosuppressants, tumor necrosis factor inhibitors, antibiotics), endoscopic/surgical (indicated for complications such as bowel obstruction, high grade dysplasia, abscess, internal fistulas, and cancer), and nutritional (e.g., enteral feeding, restricted diet, parenteral feeding) therapeutic options available to patients with CD, none of them leads to complete cure of this condition.<sup>1,2</sup> Therefore, the management of the disease usually involves the induction and maintenance of remission of disease activity by controlling the extent of inflammatory process, correcting malnutrition, as well as reducing symptom presentation and occurrence of complications.<sup>2,3</sup> In children, a major additional goal is to facilitate normal growth and pubertal development which are frequently impeded.

The choice of therapeutic options depends largely on the extent of inflammation, the disease severity, and complications. Any therapeutic recommendation needs to consider a balance between individual response in terms of beneficial effects, treatment-related adverse events, and long term complications.<sup>2,3</sup> Corticosteroids are most widely used agents for the management of active CD. However, their use is associated with high risk of relapse, low rates of mucosal healing, steroid dependency, and other adverse events (e.g., growth impairment, infections). There have been safety concerns with long term use of other agents such as tumor necrosis factor (TNF) inhibitors.<sup>1</sup>

Nutritional therapy has played an important but controversial role in the alleviation of malnutrition and control of disease activity in patients with active CD. There is some evidence on clinical benefits and long term safety of EN in inducing remission in patients, especially children and young adults with active CD.<sup>4,5</sup> For example, in Japan, EN is recommended as the first-line treatment in the management of active CD.<sup>1,6</sup> Although EN has been shown to be an effective and safe intervention for induction of remission in patients with active CD, withdrawal of EN and resumption of normal diet would often be followed by reoccurrence of gastrointestinal symptoms and use of corticosteroids.<sup>7</sup> Evidence comparing clinical effectiveness of EN to corticosteroids for the induction of remission has been inconsistent, with one meta-analysis showing no difference between the two,<sup>5</sup> and more recent meta-analysis indicating a superiority of corticosteroids over EN.<sup>8</sup>

Equally important evidence on the efficacy of different types of EN (i.e., elemental, semi-elemental, polymeric) in maintaining remission in CD has been insufficient and less clear.<sup>1,6,7,9</sup> If EN proves to be at least as effective as conventional medications, its use might minimize or replace the use of steroids, biologics, and immunosuppresants.<sup>1,6,7</sup>

Most evidence on the comparative clinical effectiveness of EN in the maintenance of CD remission rests upon retrospective observational cohort studies and prospective non-randomised controlled experimental trials.<sup>1,6,9</sup> The similar evidence from RCTs is insufficient due to difficulties with consent and adherence of patients assigned to EN.<sup>7,10-12</sup> In general, retrospective observational cohort studies pose difficulties in establishing causality due to their methodological limitations.<sup>6</sup> For example, given the retrospective nature of such studies, temporality between the occurrence of exposure and outcome is unclear or indeterminate. Furthermore, since retrospective studies utilize the patient data that had been collected for other purposes than the question of interest, these studies may not be able to adjust the effect estimates of elemental nutrition for many important confounders (e.g., disease activity, smoking, age, adherence, comorbidities, nutritional status) since such data had not been collected.

In order to bring more clarity to this area, this review aimed to evaluate evidence on clinical effectiveness and cost-effectiveness of elemental diet (a type of enteral nutrition) for the maintenance of remission in CD. Given the above-mentioned limitations of retrospective observational cohort studies in establishing causality, this review will focus on higher hierarchy of evidence by including only prospective studies, i.e., randomised and non-randomised controlled clinical trials.

### 4.2 Report methods for synthesis of evidence

### Search strategy

Scoping searches have been undertaken to inform the development of the search strategy and assess the volume and type of literature relating to the assessment question. We used an iterative procedure with input from clinical advisors and previous systematic reviews.<sup>6,7,13</sup> The yield of 324 records from the search developed for MEDLINE, before any limits were applied or any sifting was undertaken, demonstrated that there is limited evidence in this area (see Appendix 1).

A copy of the main database search strategy that is likely to be used in the major databases is provided in the Appendix 1. This draft search strategy, developed for MEDLINE, will be adapted as appropriate for other databases and will include the concepts of CD, remission and elemental nutrition. This strategy will not include limits for study design, language or publication date, as the number of articles to sift identified in the scoping search is not anticipated to be high.

The overall search strategy will comprise the following main elements:

- Searching of electronic bibliographic databases and trial registries
- Supplementary searching (including scrutiny of references of included studies, citation searching, searching relevant websites)
- Contact with clinical advisors in the field

### Databases will include:

MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE (via OVID); CDSR, CENTRAL, DARE, NHS EED, HTA database (via the Cochrane Library); Science Citation Index and Conference Proceedings (via Web of Knowledge); WHO ICTRP; UKCRN Study Portfolio.

Citation searches of included studies will be undertaken using the Web of Science citation search facility. The reference lists of included studies and relevant review articles will also be checked. Clinical advisors in the field will be consulted and websites of relevant organisations checked. Two supplementary database searches using limits will be undertaken. The first, combining CD with the concept of nutrition therapy and limited to systematic reviews or cost-effectiveness, will aim to capture any articles that include the assessment question as part of a broader systematic review or cost study. The second, combining CD with the concept of elemental nutrition and limited to relevant study types, will aim to capture any articles that include our population as part of a controlled clinical trial of both active CD and CD in remission.

All retrieved records will be collected in a specialised database. All duplicate records will be identified and removed.

# Study eligibility criteria

*Inclusion criteria:* <u>Type/language of publication</u> English full text and abstracts (only if companion publications to full text included studies)

# Study design

RCTs and prospective non-randomised controlled clinical trials

# **Population**

Adults, young people, or children with CD in remission (inactive, quiescent CD) at the time of study baseline

# Intervention

- Elemental nutrition via oral passage, nasal passage (naso-gastric tube, naso-jejunal tube, nasoduodenal tube), or direct passage via the abdomen (gastrostomy tube, jejunostomy tube) alone
- Elemental nutrition in combination with other intervention(s) (e.g., standard drug therapy, restricted diet)

# **Comparator**

- Enteral nutrition (elemental, semi-elemental or polymeric nutrition) alone, normal unrestricted diet alone (i.e., no intervention), restricted diet alone, standard drug therapy alone, any other intervention or placebo.
- Enteral nutrition (elemental, semi-elemental or polymeric nutrition) in combination with other intervention(s) (e.g., standard drug therapy, restricted diet, any other intervention or placebo )

• Any combination of standard drug therapy, restricted diet, any other intervention, and/or placebo

# Exclusion criteria:

- a) Induction studies (patients with active CD at baseline) with or without follow up of remitted patients receiving maintenance therapy
- b) Studies of parenteral (intravenous) nutrition
- c) Studies of ulcerative colitis
- d) Reviews, meta-analyses, case-reports, case-series, retrospective observational studies, editorials, comments
- e) Studies employing non-concurrent (e.g., historical) controls
- f) Studies with mixed patient population (< 80% Crohn's disease)
- g) Studies comparing different nutrition/diets of elemental nutrition

# Outcomes - clinical effectiveness

Adult populations

- a) Maintenance of remission (% patients in remission at end of follow-up, cumulative probability of maintaining remission [Kaplan Meier estimate of survival], duration of remission) – primary outcome
- b) Development of relapse/recurrence (proportion of patients developing relapse/recurrence [n/N], time to relapse/recurrence [mean # of months]) primary outcome
- c) Incidence of mucosal healing primary outcome
- d) Need for surgery (n/N)
- e) Withdrawal from steroids (n/N)
- f) Steroid dose tapering (n/N)
- g) CDAI (measured as continuous or categorical outcome)
- h) Quality of life (QOL)
- i) Adverse events (treatment-related)
- j) Complications of CD
- k) Gain in body weight or body mass index
- 1) Adherence

Younger populations (e.g., adolescents, paediatric)

- a) Maintenance of remission (% patients in remission at end of follow-up, cumulative probability of maintaining remission [Kaplan Meier estimate of survival], duration of remission) – primary outcome
- b) Development of relapse/recurrence (proportion of patients developing relapse/recurrence [n/N], time to relapse/recurrence [mean # of months]) primary outcome
- c) Incidence of mucosal healing primary outcome
- d) Need for surgery (n/N)
- e) Withdrawal from steroids (n/N)
- f) Steroid dose tapering (n/N)
- g) CDAI (measured as continuous or categorical outcome)
- h) Quality of life (QOL)
- i) Adverse events (treatment-related)
- j) Complications of CD
- k) Gain in body weight or body mass index
- 1) Adherence
- m) Growth
- n) Pubertal development

Outcomes - cost-effectiveness

- a) Costs (no efficacy measures: cost-minimization analysis)
- b) Costs and efficacy measures clinical and quality-adjusted life years (full economic analysis)
- c) Incremental cost-effectiveness ratios (full economic analysis)
- d) Results from cost-effectiveness acceptability curves
#### Study selection strategy

Two independent reviewers will screen all identified bibliographic records for title/abstract and then for full text using a pre-specified and piloted questionnaire form. The study flow and reasons for exclusion of full text papers will be documented in the PRISMA study flow diagram (Appendix 2).<sup>14</sup>

#### Data extraction strategy

Two reviewers will independently extract relevant data using an *a priori* defined pre-piloted extraction sheet (Appendix 3). The extracted data will be cross-checked and any disagreements will be resolved by discussion or by recourse to a third party reviewer. The extracted data will include study (e.g., author, country, design, sample size, follow-up duration, risk of bias items), participant (e.g., age, sex, inclusion/exclusion criteria, CD activity index, clinical/endoscopy definitions of CD remission, type of induction therapy), intervention/comparator (brand name/manufacturer of EN; type, mode, duration, and dose of administration of EN, any concomitant diet or dietary restriction, and other co-intervention such as medications), and outcome characteristics (e.g., scale of measurement, timing of assessment, definition of CD relapse/recurrence).

For individual studies, the dichotomous and continuous summary clinical effectiveness outcome measures of association will be summarized as risk/odds ratio, mean difference, and measures of variability (p-value, 95% confidence interval). If needed and data allows, we will attempt to calculate missing statistical parameters (e.g., risk ratios, mean differences, standard deviations, standard errors, and 95% confidence intervals) for primary clinical outcomes of interest (e.g., risk of relapse, time to relapse, quality of life, weight gain, CD activity index). All calculated parameters will be entered into the data extraction sheets and will be marked as 'calculated'.

### Individual study quality assessment strategy

Two reviewers will independently assess the methodological and reporting quality of included individual studies. Any disagreements between the two reviewers will be resolved by a third reviewer through a discussion.

RCTs will be assessed using the Cochrane Collaboration Risk of Bias (ROB) tool<sup>15</sup> which covers the following domains of threat to internal validity: selection bias (randomisation sequence generation, treatment allocation concealment), performance bias (blinding of participants/personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data – primary outcome), reporting bias (selective outcome/analysis reporting), and other pre-specified bias (e.g., funding source, adequacy

of statistical methods used, type of analysis, baseline between-group imbalance in important prognostic factors). The risk of bias assessment falls into three categories of high, low, and unclear risk of bias. The assessments will be provided in ROB tables and summary graph (Appendix 4). Prospective non-randomised controlled clinical trials (CCTs) will be assessed using a modified Cochrane ROB tool in which the domain of selection bias will be evaluated in regards to baseline between-group imbalance for important prognostic factors instead of randomisation sequence generation and treatment allocation concealment (Appendix 5). For each study (RCT or non-RCT), the risk of performance, detection, and attrition bias domains for subjective (e.g., patient-administered clinical or quality of life scores) and objective (e.g., presence of remission, relapse/recurrence, time to relapse, weight gain, mucosal healing, growth, adverse events) outcomes will be assessed separately. Afterwards, within-study summary ROB rating across all domains will be derived for subjective and objective outcome groups separately (Appendix 6). At data synthesis stage, across-study average summary ROB will be determined and assigned to each outcome of interest.

The quality of economic analyses of the included studies will be assessed using the Drummond 10-item checklist (Appendix 7).<sup>16</sup>

#### Data analysis and synthesis

Study, treatment, population, and outcome characteristics will be summarised in text, evidence, and summary tables. The study results on the relative effectiveness of EN for each outcome of interest and cost-effectiveness will be compared qualitatively and quantitatively in text and summary tables.

In the clinical effectiveness part of the review, results for any given outcome measures will be presented separately stratified by a) induction therapy (medically-, nutritionally-, surgically-induced remission), b) age (adult vs. paediatric), and c) regimen (elemental, semi-elemental, polymeric nutrition, dose, mode of administration).

The decision to pool individual study results will be based on a degree of similarity with respect to methodological and clinical characteristics of studies under consideration (e.g., design, population, comparator treatment, and outcome). Estimates of post-treatment mean difference for continuous outcomes and RRs for binary outcomes (except for rare events) of individual studies will be pooled using a DerSimonian and Laird random-effects model.<sup>17</sup> Dichotomous outcomes with low event rates (5.0%-10.0%) will be pooled as RR using a Mantel-Haenszel fixed-effects model. Dichotomous outcomes for studies with very low event rates ( $\leq 5.0\%$ ) or zero events in one of the treatment arms were pooled as

odds ratio (OR) using a Peto fixed-effects model.<sup>18</sup> Trials will not be pooled if the mean and/or standard deviation for the continuous outcome of interest cannot not be ascertained.

The degree of statistical heterogeneity across pooled studies will be determined through inspection of the forest plots, Cochran's Q and the I<sup>2</sup> statistics. The heterogeneity will be judged according to predetermined levels of statistical significance (Chi-square p < 0.10 and/or I<sup>2</sup>> 50%). If data allows, study-level clinical and methodological sources of heterogeneity of effect estimates across studies will be explored through *a priori* defined subgroup analysis (i.e., age, sex, induction therapy) and sensitivity analysis (risk of bias item-specific ratings, intention-to-treat vs. per protocol analysis).

Given a sufficient number of data points, publication bias will be assessed through visual inspection of funnel plots with respect to plot asymmetry and use of linear regression tests.<sup>19</sup>

### **Overall quality of evidence (GRADE system)**

The overall quality of evidence for pre-selected gradable outcome (risk of CD relapse/recurrence) across studies will be assessed using the systematic approach developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org).

The GRADE approach<sup>20</sup> indicates level of confidence in the observed treatment effect estimate(s) and is based on assessments across five domains: a) summary ROB across studies per gradable outcome (internal validity across studies; study limitations), b) consistency of results (heterogeneity), c) directness of the evidence (applicability of the results), d) precision of the results (the width of 95% CI around the estimate), and e) publication/reporting bias (detection of asymmetry in the funnel plot; selective outcome reporting). The overall quality of evidence is categorized as high, moderate, low, or very low grade. Initial grade of RCTs will be rated as high and will be downgraded by one point (e.g., from high to moderate) if any of the five criteria is not met. Initial grade for non-RCTs will be rated as low and will be upgraded by one point (e.g., from low to moderate) if any of the three criteria for upgrading a grade is met (e.g., dose-response gradient, large magnitude of effect, and adjustment for confounders).<sup>21</sup> The process of assessment of overall quality of evidence grading will be provided in Appendix 8.

#### 4.3 Results section

The review results will be organised in text and tables (evidence and summary tables). The summary tables will tabulate characteristics, methodological quality, and results for included primary studies.

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Tables for primary studies will present summary data on participants (age, gender, number/range of participants), interventions (enteral diet, comparator), outcomes (e.g., type, summary effect measures, 95% CIs, timing), and settings (e.g., primary care, specialty clinic). Meta-analyses of primary studies will be presented in forest plots accompanied by measures of heterogeneity. If pooling is not feasible, due to the lack of sufficient data or important clinical/statistical heterogeneity across studies, the findings from individual studies will be summarised narratively. Evidence for each outcome of remission maintenance from one or more studies (either un-pooled or pooled) will be summarised and graded accordingly, and presented in a tabular form.

#### 4.4 Discussion section

This section will cover the interpretation and validity of the findings of the review in light of available evidence and the review methodology. We will highlight and discuss strengths and limitations of the review and their likely influence on the effect estimates. The stability of treatment effect measures will be explored and discussed. Future research implications of the review findings will also be discussed. Identified gaps/inconsistencies in the current knowledge (e.g., heterogeneity, lack or insufficiency of evidence) and methodological limitations of the reviewed evidence (e.g., study design, risk of bias in primary studies, short term follow-up, inadequate sample size, outcome measurement methods) will be highlighted and corresponding recommendations for future research directed at mitigation of these limitations will be outlined. Where possible, the recommendations will be of sufficient detail and clarity to form the basis of a future commissioning brief (e.g., PICO and suggested study type).

Unlike most of the previously published reviews, this review will employ a systematic approach by focusing only on higher level hierarchy of evidence (randomised and non-randomised controlled clinical trials) with the purpose of elucidating the role of enteral diet in the maintenance of CD compared to other treatments. Moreover, it will provide an updated evidence base on this topic and will be better equipped in determining comparative clinical and cost-effectiveness of enteral diet for the maintenance of remission in CD.

We anticipate that this review will better inform researchers, clinicians, and policy makers in deriving more robust recommendations for appropriate treatment choices in the maintenance of CD, and serve as an impetus towards improved conduct, methodology, and reporting of future studies in this area.

### 5. Expertise in this TAR team

Warwick Evidence is a technology assessment group located within Warwick Medical School. Warwick Evidence brings together experts in clinical and cost effectiveness reviewing, medical statistics, health economics and modelling. The team planned for the work includes: Dr Paul Sutcliffe, Dr Alexander Tsertsvadze and Dr Tara Gurung, who are experienced systematic reviewers; Mrs Rachel Court, information specialist; Ruth Pulikottil-Jacob, provides modelling and health economic expertise; Professor Aileen Clarke, Dr Ngianga-Bakwin Kandala provide epidemiological and statistical expertise; Dr Ramesh Arasaradnam, University Hospital, Coventry, and Professor Simon Murch, University of Warwick, will provide clinical advice.

### 6. Competing interests of authors and advisors

None of the authors have any competing interests.

### 7. Timetable/milestones

Draft protocol finalised	TBC
Commissioning decision	TBC
Anticipated start date	1 October 2013
Progress report	15 November 2013
Final assessment report	11 January 2014

### 8. Team members' contributions

Research team:	Warwick Evidence
Lead:	Dr Paul Sutcliffe
Title:	Associate Professor
Address:	Warwick Evidence, Populations, Evidence and Technologies, Division of Health
	Sciences, Warwick Medical School, University of Warwick, Coventry CV4 7AL
Tel:	02476 574505
Email:	p.a.sutcliffe@warwick.ac.uk
Contribution:	Co-ordinate review process, protocol development, assessment for eligibility,
	quality assessment of trials, data extraction, data entry, data analysis, and report
	writing
Name:	Dr Alexander Tsertsvadze

Title: Senior Research Fellow

Address:	Warwick Evidence, Populations, Evidence and Technologies, Division of Health				
	Sciences, Warwick Medical School, University of Warwick, Coventry CV4 7AL				
Tel:	02476 574505				
Email:	a_tsertsvadze@hotmail.com				
Contribution:	Co-ordinate review process, protocol development, assessment for eligibility,				
	quality assessment of trials, data extraction, data entry, data analysis, and report				
	writing				
Name:	Ms Rachel Court				
Title:	Information Specialist				
Address:	Warwick Evidence, Populations, Evidence and Technologies, Division of Health				
	Sciences, Warwick Medical School, University of Warwick, Coventry CV4 7AL				
Tel:	02476 522427				
Email:	R.A.Court@warwick.ac.uk				
Contribution:	Protocol development, develop search strategy and undertake the electronic literature				
	searches				
Name:	Ms Ruth Pulikottil-Jacobs				
Title:	Research Fellow Health Economics				
Address:	Warwick Evidence, Populations, Evidence and Technologies, Division of Health				
	Sciences, Warwick Medical School, University of Warwick, Coventry CV4 7AL				
Tel:	02476 151902				
Email:	R.Jacob@warwick.ac.uk				
Contribution:	Health economics modeller, assessment for eligibility and data extraction				
Name:	Dr Tara Gurung				
Title:	Research Fellow				
Address:	Warwick Evidence, Populations, Evidence and Technologies, Division of Health				
	Sciences, Warwick Medical School, University of Warwick, Coventry CV4 7AL				
Tel:	02476 150711				
Email:	t.gurung@warwick.ac.uk				
Contribution:	Protocol development, assessment for eligibility, quality assessment of trials, data				
	extraction, data entry, data analysis, and report writing				

Name:	Dr Ngianga-Bakwin Kandala		
Title:	Principal Research Fellow		
Address:	Warwick Evidence, Populations, Evidence and Technologies, Division of Health		
	Sciences, Warwick Medical School, University of Warwick, Coventry CV4 7AL		
Tel:	02476 575054		
Email:	N-B.Kandala@warwick.ac.uk		
Contribution:	Data entry, data analysis, and statistical modeller		
Name:	Professor Aileen Clarke		
Title:	Director of Warwick Evidence		
Address:	Warwick Evidence, Populations, Evidence and Technologies, Division of Health		
	Sciences, Warwick Medical School, University of Warwick, Coventry CV4 7AL		
Tel:	02476 150189		
Email:	Aileen.Clarke@warwick.ac.uk		
Contribution:	Co-ordinate review process, protocol development, data analysis, synthesis of findings		
	and report writing		

### 9. Clinical Advisors

1) Dr Ramesh Arasaradnam: Gastroenterology, University Hospital, Coventry. His clinical and research interests are in gut physiology, nutrition, inflammatory and cancer biology.

2) Professor Simon Murch: Professor of Paediatrics, Warwick Medical School, Coventry. His research background is in mucosal immunology, and his early work was based on the role of macrophage cytokines in intestinal and lung inflammation. This work contributed to the introduction of anti-TNF therapy in Crohn's disease, and also provided the first demonstration of the role of inflammatory cytokines in lung disease affecting preterm infants.

Contribution of above clinical advisors include: protocol development, help interpret data, provide a methodological, policy and clinical perspective on data and review development of background information and clinical effectiveness and review of report drafts.

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### Appendices

### Appendix 1. Draft search strategy details

1	Crohn Disease/	29507
2	Inflammatory Bowel Diseases/	12777
3	crohn*.tw.	29987
4	Inflammatory bowel disease*.tw.	23863
5	IBD.tw.	10207
6	1 or 2 or 3 or 4 or 5	53451
7	remission*.tw.	83291
8	inactiv*.tw.	227468
9	quiescen*.tw.	20271
10	disease-free survival/	41204
11	relaps*.tw.	111733
12	recurr*.tw.	348455
13	maintenance.tw.	175893
14	7 or 8 or 9 or 10 or 11 or 12 or 13	923305
15	6 and 14	8307
16	((enteral or elemental or chemically defined) and (nutrition* or diet* or feed*)).tw.	13181
17	Enteral Nutrition/	15194
18	Food, Formulated/	5229
19	16 or 17 or 18	24823
20	15 and 19	324

Ovid MEDLINE(R) 1946 to May Week 5 2013, searched on 13 June 2013

### Appendix 2. PRISMA study flow diagram



Appendix 3. Data extraction sheet for included primary study reports

Name of first reviewer:				
Study details				
First author surname	e vear of	publication:		
Country:		<b>I</b>		
Study design:				
Study setting (primar	v care/sr	ecialty clinic/o	other - specify):	
Number of centres	, euro, sp			
Total length of follow	v un.			
Funding (government	/private/	manufacturer/	other - specify).	
Aim of the study	/ pii vale/	manufacturer	other speeny).	
Particinants				
Recruitment dates				
Total N of nationts w	ha racai	ved induction	therenze	
Total N of patients w	no recer	remission off	induction thereasy	
Total N of patients a	iling to	remission at	er induction therapy.	
Total N of patients in	uning to	achieve renns	sion after induction therapy:	
Total N of patients ex	anta alla	before start of	i maintenance therapy (e.g., lost to it	low up):
Total number of path	ents and	cated to main	itenance treatment:	
Evolution criteria:				
Exclusion criteria:			• )	
Characteristics of pa	rticipan	ts (total study	sample)	
Mean (range or SD) ag	ge (years	):		
Women (n [%]):				
Race/ethnicity (n [%])	:			
Diagnostic criteria for	CD:			
Mean Crohn's Disease Activity Index (CDAI) (range or SD):				
CD location:				
Type of induction therapy (n [%]):				
Intervention				
Elemental diet group	:			
Intervention 2 group	:			
Intervention 3 group	:			
Outcomes (study-bas	ed)			
Primary outcomes (li	ist):			
Measure of disease a	ctivity (a	linical, endos	conic):	
Definition of remission	on (clini	cal. endosconi	(c):	
Definition of relanse/	recurre	nce (clinical) e	endosconic).	
Definition of mucosal healing (clinical endosconic):				
Post-baseline timings of primary outcome assessment:				
Number of natients	or prin	ury outcome		
rumber of patients	Total	Elemental	Intervention 2 group	Intervention 3 group
	i Utai	diet group	intervention 2 group	intervention 5 group
Allocated to		uici gi oup		
Anocateu to				
Analyzed				
Analysea (If more them are				
(II more than one				
tollow-up, choose				
and specify the last				

one)					
Losses to follow.					
un/dron out/sample					
attrition					
(If more than one					
follow up choose					
and specify the last					
and specify the last					
Une)					
Interventions				•	
	(e.g	g., formula man	Desc nufacturer, calorie co admini	ontent, type, mode, istration)	dose, and duration of
		Die	et	Co-i	intervention
Elemental diet group					
Intervention 2 group					
Intervention 3 group					
Patient baseline char	acterist	ics		1	
	Eleme	ntal diet grou	p Interven	tion 2 group	Intervention 3
				9.1	group
Age (years)					
Mean (SD)					
Sex –female n/N					
(%)					
Weight (kg)					
Mean (SD)					
<b>BMI</b> $(kg/m^2)$					
Mean (SD)					
Smoking n/N (%)					
Previous bowel					
resection n/N (%)					
Duration of CD					
(months)					
Mean (SD)					
Crohn's Disease					
Activity Index					
(CDAI)					
Mean (SD)					
Crohn's Disease					
Endosconic Index					
of Severity					
(CDEIS)					
(CDLIS) Mean (SD)					
Disease activity					
other than CDAI					
(specify)					
Mucosal ulceration					
n/N (%)					
Other					
complications n/N					
(%)					
(79)					

Efficacy outcomes				
For each timing of ass	essment please provide	e a separate table		
For scores, extract on	ly total scores			
Post-procedural follow	v-up assessment timing	(Specify):		
	Elemental diet group	Intervention 2 group	Intervention 3 group	Between-group difference p value (or 95% CI)*
Patients remaining in remission n/N (%)				
Duration of				
remission (months) Mean (SD) or 95% CI				
<b>Risk of relapse or</b>				
recurrence n/N (%)				
<b>Time to relapse</b> (months) Mean (SD) or 95% CI				
Survival rate (%				
patients in remission				
who have not				
relapsed)				
(Kaplan-Meier				
estimate and 95%				
CI)				
Patients achieving				
mucosal healing				
n/N (%)				
Crohn's Disease				
Activity Index				
(CDAI)				
Mean (SD)				
The Short Form				
Health Survey (SF-				
36)				
Mean (SD)				
95% CI				
The Short Form				
Health Survey (SF-				
12)				
Mean (SD)				
95% CI				
The Euro-Qol				
questionnaire (EQ-				
5D)				
Mean (SD)				
93% CI	1		1	1

Other HQOL (specify) Mean (SD)				
95% CI				
Weight (kg)				
Mean (SD)				
95% CI				
Weight gain (kg)				
Mean change (SD)				
Body mass index				
$(kg/m^2)$				
Mean change (SD)				
95% CI				
Height gain (cm)				
Mean (SD)				
95% CI				
Linear growth rate				
(mean height-for-				
age Z-score)				
Adherence n/N (%)				
Need for surgery				
n/N (%)				
Steroid dose to point $p(N_{1}(0))$				
Withdrawal from				
steroids n/N (%)				
Adverse events due				
to treatment n/N				
(%)				
<b>Complications - Num</b>	ber (%) of patients w	rith an event	L	
[if more than one foll	low-up, choose and sp	ecify the last follow	v up]	
	<b>Elemental diet</b>	<b>Intervention 2</b>	Intervention 3	B Between-group
	group	group	group	difference
				p value
				(or 95% CI)*
Impaired growth $n(N_{1}(0))$				
II/IN (%) Delay in pubartal				
development				
n/N (%)				
Bowel obstruction				
Fistulae				
Abscess				
Colon/bowel				
cancer				
Intestinal infection				
Others (Specify)				
Authors conclusion				
<b>Reviewer's conclusio</b>	n			

\* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

Appendix 4. The risk of bias assessment of included randomised controlled trials (adapted from Higgins et al. 2011)<sup>15</sup>

### Name of first reviewer: Name of second reviewer: First author surname year of publication:

Bias		Source of bias	Support for	Authors'	
domain			judgment	judgment	
Selection	Random seq	uence generation			
bias	Allocation co	oncealment			
	Blinding of	Subjective (e.g., patient-reported)			
Performance	participants	Objective (e.g., radiography,			
bias	and	endoscopy)			
	Personnel				
Detection	Blinding of	Subjective (e.g., patient-reported)			
bias	outcome	Objective (e.g., radiography,			
0103	assessors	endoscopy)			
	Incomplete	Subjective outcomes (e.g., patient-			
Attrition	outcome	reported)			
bias	data	Objective outcomes (e.g.,			
		radiography, endoscopy)			
Reporting	Selective rep	orting of the outcome, subgroups, or			
bias	analysis				
	Funding source, adequacy of statistical methods				
Other bias	used, type of	analysis [ITT/PP], baseline imbalance			
	in important characteristics				
ITT=intention	ITT=intention to treat; PP=per protocol; NA=not applicable; ROB=risk of bias				

\* Statement, description or quote supporting the judgment \*\* Low risk of bias, high risk of bias, or unclear risk of bias

Appendix 5. The risk of bias assessment of included non-randomised controlled trials (adapted from Higgins et al. 2011)<sup>15</sup>

### Name of first reviewer: Name of second reviewer: First author surname year of publication:

Bias	Ť	Source of bias	Support for	Authors'
domain			judgment <sup>*</sup>	judgment <sup>**</sup>
Selection bias	The presence imbalance in characteristic duration of C during induc therapy, pre- and/or smoki	<ul> <li>absence of baseline between-group</li> <li>amportant prognostic</li> <li>as/factors (e.g., age, sex, CDAI,</li> <li>b, location of CD, complications</li> <li>and therapy, type of induction</li> <li>and therapy compliance, co-intervention,</li> <li>ang)</li> </ul>		
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported) Objective (e.g., radiography, endoscopy)		
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported) Objective (e.g., radiography, endoscopy)		
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient- reported) Objective outcomes (e.g., radiography, endoscopy)		
Reporting bias	Selective reporting of the outcome, subgroups, or analysis			
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]			
ITT=intention ROB=risk of	to treat; PP=p bias	er protocol; NA=not applicable; CDAI=	Crohn's disease activity	index;

\* Statement, description or quote supporting the judgment \*\* Low risk of bias, high risk of bias, or unclear risk of bias

### Appendix 6. Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission	· · · · · ·
(e.g., CDAI<150), occurrence of relapse/recurrence (e.g.,	
CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150),	
quality of life measures, clinical scores of severity (e.g.,	
CDAI)	
Objective (list of outcomes): Maintenance of remission	
(includes additional objective parameters besides	
clinical), occurrence of relapse/recurrence (includes	
additional objective parameters besides clinical), time to	
relapse/recurrence (includes additional objective	
parameters besides clinical), mucosal healing (endoscopic	
remission), weight gain, linear growth rate, complications,	
adverse events, adherence	
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Ind	lex; ROB=risk of bias

Item#*	Study #1	Study #2	Study #3	Study #4	Study #5	Study #6	Study #7	Proportion of studies with 'Yes' (%)
Item 1								
Item 2								
Item 3								
Item 4								
Item 5								
Item 6								
Item 7								
Item 8								
Item 9								
Item 10								

Appendix 7. Methodological quality of economic evaluations in included studies (The Drummond Checklist<sup>16</sup>)

\*Responses to items: Yes, No, Can't Tell

Item 1: Was a well-defined question posed in answerable form?

Item 2: Was a comprehensive description of the competing alternatives given?

Item 3: Was the effectiveness of the programmes or services established?

Item 4: Were all the important and relevant costs and consequences for each alternative identified?

**Item 5:** Were costs and consequences measured accurately in appropriate physical units (e.g. number of physician visits, lost work-days, gained life-years)?

Item 6: Were costs and consequences valued credibly?

Item 7: Were costs and consequences adjusted for differential timing?

Item 8: Was an incremental analysis of costs and consequences of alternatives performed?

Item 9: Was allowance made for uncertainty in the estimates of costs and consequences?

Item 10: Did the presentation and discussion of study results include all issues of concern to users?

Appendix 8. GRADE evidence profile for gradable outcomes (adapted from Guyatt et al., 2011<sup>20</sup>)

Outcome [follow-up timing]	N of studies reporting outcome (participants)	Pooled effect estimate [95% CI] and conclusion	SROB across studies	Consistency	Directness	Precision	Outcome reporting bias	Quality of the evidence (GRADE)*
Treatment 1 vs. Treatme	ent 2 (n studies)							
Outcome 1								
Outcome 2								
Outcome 3								
Outcome 4								
Treatment 1 vs. Treatme	ent 3 (n studies)							
Outcome 1								
Outcome 2								
Outcome 3								
Outcome 4								
GRADE= Grading of Rec	ommendations, A	ssessment, Development, a	nd Evaluati	on; CI=confide	nce interval; SR	OB=summary	risk of bias; N	A=not applicable

\*GRADE categories: high, moderate, low, very low, NA (no evidence)

### 8.2 Appendix II: Search strategies

### Ovid MEDLINE 1946 to August 2013 (searched on 29/08/2013)

- 1. Crohn Disease/
- 2. Inflammatory Bowel Diseases/
- 3. crohn\*.tw.
- 4. Inflammatory bowel disease\*.tw.
- 1 or 2 or 3 or 4 5.
- 6. ((Enteral or elemental or chemically defined) and (Nutrition\$ or diet\$ or therap\$ or feed\$ or formula\$)).tw.
- 7. Enteral Nutrition/
- 8. Food, Formulated/
- 9. 6 or 7 or 8
- 10. (remission\* or inactiv\* or quiescen\* or relaps\* or recurr\* or maintenan\*).tw
- 11. disease-free survival/
- 12. 10 or 11
- 13. 5 and 9 and 12
- 14. limit 13 to english language

### EMBASE 1947 to August 2013 (searched on 29/08/2013)

- 1. Crohn disease/
- 2. crohn\*.tw.
- 3. Inflammatory bowel disease\*.tw.
- 4. 1 or 2 or 3
- 5. ((Enteral or elemental or chemically defined) and (nutrition\$ or diet\$ or therap\$ or feed\$ or formula\$)).tw.
- 6. enteric feeding/
- elemental diet/
   5 or 6 or 7
- 9. (remission\* or inactiv\* or quiescen\* or relaps\* or recurr\* or maintenan\*).tw.
- 10. disease free survival/
- 11. 9 or 10
- 12. 4 and 8 and 11
- 13. limit 12 to english language

# Ovid MEDLINE In-Process & Other Non-Indexed Citations August 2013 (searched on

### 29/08/2013

- 1. crohn\*.tw.
- 2. Inflammatory bowel disease\*.tw.
- 3. 1 or 2
- 4. ((Enteral or elemental or chemically defined) and (Nutrition\$ or diet\$ or therap\$ or feed\$ or formula\$)).tw.
- 5. Enteral Nutrition.tw.
- 6. Food, Formulated.tw.
- 7. 4 or 5 or 6
- 8. (remission\* or inactiv\* or quiescen\* or relaps\* or recurr\* or maintenan\*).tw.
- 9. disease-free survival.tw.
- 10. 8 or 9
- 11. 3 and 7 and 10
- 12. limit 11 to english language

### Science Citation Index and Conference Proceedings via the Web of Science (searched on

### 29/08/2013)

Topic= (crohn\* or Inflammatory bowel disease or Crohn Disease) and (Enteral or elemental or chemically defined or Nutrition\* or diet\* or therap\* or feed\* or formula\* or Enteral Nutrition or Food, Formulated) and (remission\* or inactiv\* or quiescen\* or relaps\* or recurr\* or maintenan\* or disease-free survival)

### Cochrane Library, searched on 04/09/13

- #1 MeSH descriptor: [Crohn Disease] this term only
- #2 MeSH descriptor: [Inflammatory Bowel Diseases] this term only
- #3 (crohn\*):ti,ab,kw
- #4 (Inflammatory bowel disease\*):ti,ab,kw
- #5 (#1 or #2 or #3 or #4)
- #6 (#1 or #2)
- #7 ((Enteral or elemental or chemically defined) and (Nutrition\$ or diet\$ or therap\$ or feed\$ or formula\$)):ti,ab,kw
- #8 MeSH descriptor: [Enteral Nutrition] this term only
- #9 MeSH descriptor: [Food, Formulated] this term only
- #10 (#7 or #8 or #9)
- #11 (remission\* or inactiv\* or quiescen\* or relaps\* or recurr\* or maintenan\*):ti,ab,kw
- #12 MeSH descriptor: [Disease-Free Survival] this term only
- #13 (#11 or #12)
- #14 (#5 and #10 and #13)

All Results (61) Cochrane Reviews (4) All Review Protocol Other Reviews (5) Trials (52) Methods Studies (0) Technology Assessments (0) Economic Evaluations (0) Cochrane Groups (0)

### **Trial database**

### WHO ICTRP, searched on 20/09/20138

8 records for 8 trials found for: crohn\* and element\* 3 records for 3 trials found for: inflammatory bowel disease\* and element\* 13 records for 12 trials found for: crohn\* and enteral\* 2 records for 2 trials found for: inflammatory bowel disease\* and enteral\* Total: 25 Total after duplicates removed: 21 Total after initial sifting by RC: 3 Total after check by AT and TG: 0

### **UKCRN Study Portfolio**

Topic: All

AND

Research summary: inflammatory bowel diseases elemental (All terms) OR Research summary: inflammatory bowel disease elemental (All terms) OR Research summary: inflammatory bowel diseases enteral (All terms) OR Research summary: inflammatory bowel disease enteral (All terms) OR Research summary: crohn elemental (All terms) OR Research summary: crohn enteral (All terms) OR Research summary: crohn enteral (All terms) OR Research summary: crohn's elemental (All terms) OR Research summary: crohn's elemental (All terms)

Total: 1 Total after sifting by RC: 0

# 8.3 Appendix III: Full data extraction of included primary study reports

# <u>RCTs</u>

Name of first reviewer:	Alexan	der Tsertsvadze	2			
Name of second review	er: Tara	a Gurung				
Study details						
First author surname y	ear of p	ublication: Hana	ai 2012 <sup>56</sup>			
Country: Japan						
Study design: RCT						
Study setting (primary of	care/spec	cialty clinic/other	- specify): specialty clinic			
Number of centres: one	;					
Total length of follow u	<b>ip</b> : 24 m	0				
Funding (government/pa	rivate/m	anufacturer/other	r - specify): NR			
Aim of the study						
To evaluate the efficacy	of eleme	ental nutrition ver	rsus 6-mercaptopurine as maintenance therapy in	Crohn's disease		
Participants						
Recruitment dates: NR						
Total N of patients who	) receive	d induction the	rapy: NR			
Total N of patients achi	ieving re	emission after ir	duction therapy: 105			
Total N of patients una	ble to ac	hieve remission	after induction therapy. NR			
Total N of patients excl	uded be	fore start of ma	intenance therapy (e.g., in relapse, lost to follo	w up): 10		
Total number of nation	its allocs	ated to maintens	ance treatment <sup>,</sup> 95	( <b>up</b> ). 10		
Inclusion criteria: age >	>18 vear	s who achieved r	emission (CDAI < 150) within 30 days of entry t	o this trial		
Exclusion criteria: nation	nte with	abdominal abso	ess stricture (B1 of Vienna and Montreal classifi	cation) pregnant		
women patients with car	rdiovase	ular disorders an	d history of intolerance to 6 MP	eation), pregnant		
Characteristics of parti	icinante	(total study can				
Mean (range or SD) age	(vears).	mean range 20.8	32.5			
Woman $(n [\% ]) \cdot 25/05 ['$	(years).	incan range 29.8	-32.5			
<b>P</b> $_{000}$ (athricity (n [%]): <b>N</b> $_{000}$	20.3] JD					
Diagnostic criterio for C	NK D. ND					
Diagnostic criteria for C.			SD) 90.0 102.4			
Mean Cronn's Disease A	Activity I	ndex (CDAI) (ra	linge of SD): mean range $89.9-103.4$	\ \		
CD location (n [%]): Ilio	-colic ty	pe (59/95 [62.2]	), fieal type $(27/95 [28.4])$ , Colic type $(8/95 [8.4])$	)		
I ype of induction therap	y (e.g., 1	nedical, surgical	): parenteral nutrition ( $70/95$ [ $73.7$ ]), central vend	bus feeding (25/95		
[26.3]), prednisolone (9/	95 [9.5])	), infliximab (4/9	5 [4.2]), 6-MP (14/95 [14.7])			
Previous surgery (n [%])	: 19/95 [	[20.0]				
Intervention						
Elemental nutrition gro	oup: elei	mental nutrition				
Intervention 2 group: 6	-mercap	topurine (MP)				
Intervention 3 group: n	o interve	ention				
<b>Outcomes</b> (study-based	l)					
Primary outcomes (list)	): remiss	ion maintenance	rate, risk of relapse			
Measure of disease acti	vity (cli	nical, endoscopi	c): CDAI score			
<b>Definition of remission</b>	(clinical	l, endoscopic): (	CDAI < 150			
<b>Definition of relapse/re</b>	currenc	e (clinical, endo	<b>scopic):</b> clinical (CDAI $\geq$ 200 or the need for an a	additional medication		
to suppress worsening sy	mptoms	3)				
Definition of mucosal h	ealing (	, clinical. endosco	opic): NR			
Post-baseline timings of primary outcome assessment: 6 12 18 24 mo						
Number of nationts						
	Total	Elemental	6-MP groun	No intervention		
	10001	nutrition	o titt Prouh	groun		
		groun		group		
Allocated to	95	32	30	33		
traatmant	,,	54		55		
Analyzad (crasify	95	32	30	33		
Analyseu (specify	95 (ITT)	32	00	55		
III and/or per	(111)					
protocol)						
	1					

(If more than one follow-up, choose and specify the last one)						
Losses to follow-	11 5	2		4		
up/drop out/sample		2				
attrition						
(If more than one						
follow-up, choose and						
specify the last one)						
Interventions	I					
		Descr	iption			
	(e.g., formula manufac	cturer, calorie content, ty	pe, mode, dose, and	duration of administration)		
		iet	<b>Co-</b>	intervention		
Elemental nutrition	Elental (Ajinomoto, 10	(b) $at \geq 900 \text{ kcal/day},$	5-aminosalicylic a	cid (n=NR; 5-ASA, 2250–		
group	by oral intake (32 pts)	reeding tube (2 pis) or	5000 mg/day)			
	by oral make (52 pts).		Sulphasalazine			
	Restricted diet: patient	s were allowed an	(n=NR: 3000 mg/dav)			
	intake of 3.5–4.0 kcal/	kg/dav from food as	(n-141, 5000 mg/day)			
	recommended by a qua	lified dietician.	Duration: 24 mo			
	Duration: 24 mo					
6-MP group	Starting dose 20 mg/da	y (weight<45 kg)	5-aminosalicylic a	cid (n=NR; 5-ASA, 2250–		
	starting dose 30 mg/da	y (weight ≥45 kg)	3000 mg/day)			
			<b>G</b> 1 1 1 1			
	Within 8–12 weeks of $T_{CN}$ level $\leq 200$ received	the initial dosing, if $6-$	$suppressuperiod (n-NR \cdot 3000 mg/day)$			
	I GN level $\leq 200 \text{ pmol/8} \times 10^{\circ} \text{ RBC}$ , the dose		(1-1) ( $(1-1)$ ( $(1-1)$ ( $(1-1)$ ) ( $(1-1)$ ( $(1-1)$ )			
	increments up to a max	vinum of 80 mg/day	Duration: 24 mo			
	merements up to a max	annum of 60 mg/day.	Duration. 24 mo			
	When 6-TGN level rea	ched 450 pmol/ $8 \times 10^8$				
	RBC, but the patient ha	ad not responded, a 5				
	mg/day increase could	be made and the				
	patient was monitored	every 2 weeks for				
	efficacy and toxicity or	until white blood cell				
	count (WBC) started to	) decrease.				
No intervention group	-		5-aminosalicylic a	cid (n=NR; 5-ASA, 2250–		
			3000 mg/day)			
			Sulphasalazine			
			Sulphasalazine (n-NR; 2000 mg/day)			
			(11-1414, 5000 112/4	iuy)		
			Duration: 24 mo			
Patient baseline charac	teristics					
	Elemental nutrition	6-MP gi	roup	No intervention group		
	group			20.0 (10.2)		
Age (years)	30.1 (7.7)	32.5 (8.9)		29.8 (10.3)		
$\frac{\text{Mean}(SD)}{\text{Sev. female } n/N(0/2)}$	10/22 (21.2)	7/20 (22.2)		8/22 (24.2)		
$\frac{3c_{A} - 1c_{H}a_{H}c_{H}(N)}{W_{eq}b_{H}c_{H}c_{H}c_{H}c_{H}c_{H}c_{H}c_{H}c$	10/32 (31.2) NR	1/30 (23.3) NR		NR		
Mean (SD)	INIX	INK		INIX		
<b>BMI</b> $(kg/m^2)$	NR	NR		NR		
Mean (SD)						
Smoking n/N (%)	18/32 (56.2)	15/30 (50.0)		18/33 (54.5)		
Previous bowel	NR	NR		NR		
resection n/N (%)						
Duration of CD	73.2 (69.6)	67.2 (80.4)		58.8 (75.6)		
(months)						
Mean (SD)						

Crohn's Disease	103.4 (21.4)	93.2 (27.8)		89.9 (30.1)
Activity Index				
(CDAI)				
Mean (SD)				
Crohn's Disease	NR	NR		NR
Endoscopic Index of				
Severity (CDFIS)				
Mean (SD)				
Disease activity other	ND	ND		ND
than CDAL (specify)	INIX			
Musseel ulcoration	ND	ND		ND
$m(N_{1}(0))$	INK	INK		INK
	ND	ND		ND
Other complications	INK	INK		INK
n/N (%)				
Efficacy outcomes				
For each timing of asses	sment please provide a s	eparate table		
For scores, extract only	total scores			
Post-baseline follow-up	assessment timing (Spec	1ty): 6, 12, 18, 24 mo	1	
	Elemental nutrition	6-MP group	No intervention	Between-group
	group		group	difference
				p value
				(or 95% CI)*
Patients remaining in	27/32 (84.4) at 6 mo	24/30 (80.0) at 6 mo	23/33 (69.6) at 6 m	io <u>(1 vs. 2)</u>
remission n/N (%)	20/32 (62.5) at 12 mo	20/30 (66.7) at 12	15/33 (45.5) at 12 n	no $\overline{RR=1.05}$ (0.83, 1.33)
	14/32 (46.9) at 24 mo	mo	7/33 (21.2) at 24 m	at 6 mo; calculated
		17/30 (56.7) at 24		
		mo		RR=0.93 (0.64, 1.35)
				at 12 mo; calculated
				RR=0.77 (0.46, 1.27)
				at 24 mo; calculated
				(1 vs. 3)
				RR=1.21 (0.92, 1.58)
				at 6 mo: calculated
				,
				RR=1.37 (0.86, 2.17)
				at 12 mo: calculated
				RR=2.06(1.00.4.43)
				at 24 mo: calculated
Duration of	NR	NR	NR	NA
remission (months)				
Mean (SD) or 95% CI				
Risk of relanse or	12/32 (37 5) at 24 mo	7/30 (23 3) at 24 mo	21/33 (63 6) at 24 n	10 (1 vs. 2)
recurrence n/N (%)	12/32 (37.3) at 24 mo	7750 (25.5) at 24 mo	21/33 (03.0) at 24 II	$\frac{(1 + 3 + 2)}{RR = 1.61 (0.73 + 3.53)}$
				at 24 mo: calculated
				(1  vs  3)
				RR=0.58 (0.35, 0.98)
				at 24 mo: calculated
Time to relance	NR	NR	NR	NA
(months)	111	1111	111	
Mean (SD) or 05% CI				
Survival rate (0/	NP	NP	NP	(1 vc ?)
patients in ramission		INK	INK	$\frac{(1 \text{ VS. } 4)}{n=0.83 \text{ [NS] at 6 ma}}$
patients in remission				p=0.03 [1NS] at 0 III0
(Koplan Major				p=0.34 [1NS] at 12
(Kapian-Meler				$\frac{1110}{n=0.41}$
estimate and 95% CI)				p=0.41 [NS] at 18
				mo
				p=0.31 [NS] at 24

				mo
				$\frac{(1 \text{ vs. } 3)}{n - 0.10 \text{ [NS]}}$
				p=0.19 [NS] at 0 mo p=0.17 [NS] at 12
				mo
				p=0.04 [SS] at 18 mo
				p=0.03 [SS] at 24 mo
Patients achieving	NR	NR	NR	NA
mucosal healing n/N				
(%)	ND	ND.		
Crohn's Disease	NR	NK	NK	NA
(CDAI)				
Mean (SD)				
The Short Form	NR	NR	NR	NA
Health Survey (SF-				
36)				
Mean (SD)				
95% Cl The Short Form	ND	ND	ND	ΝΔ
Health Survey (SF-	INK	INK	INIX	INA
12)				
Mean (SD)				
95% CI				
The Euro-Qol	NR	NR	NR	NA
questionnaire (EQ-				
SD) Mean (SD)				
95% CI				
Other HQOL	NR	NR	NR	NA
(specify) Mean (SD)				
95% CI				
Weight (kg)	NR	NR	NR	NA
Mean (SD)				
95% Cl Weight gain (kg)	NR	NR	NR	NΔ
Mean change (SD)				1111
95% CI				
Body mass index	NR	NR	NR	NA
$(kg/m^2)$				
Mean change (SD)				
90% CI Height gain (cm)	NR	NR	NR	NA
Mean (SD)	111	111		11/2
95% CI				
Linear growth rate	NR	NR	NR	NA
(mean height-for-age				
Z-score)	ND	ND	ND	NT A
Adherence n/N (%)	NK 1/32 (3.1)	INK 1/20 (2.1)	NK 1/32 (3 0)	NA 1 vg 2
n/N (%)	1/32 (3.1)	1/30 (3.1)	1/33 (3.0)	<u>1 vs. 4</u> p>0 99 [NS] Fisher's
(/*/				exact test; RR=0.93
				(0.06, 14.32)
				calculated
				<u>1 VS. 3</u> n>0 99 [NS] Fisher's
				exact test: $RR=1.03$
				(0.06, 15.79)

				calculated
Steroid dose tapering	NR	NR	NR	NA
n/N (%)				
Withdrawal from	NR	NR	NR	NA
steroids n/N (%)				
Adverse events due to	0/32 (0.0)	2/30 (6.6) [elevated	1/33 (3.0) [elevated	-
treatment n/N (%)		AST]	amylase]	
		1/30 (3.1) [hair loss]		
<b>Complications - Numb</b>	er (%) of patients with a	an event		
[if more than one follow	v-up, choose and specify	y the last follow up]		
	Elemental nutrition	6-MP group	No intervention	Between-group
	group		group	difference
				p value
				(or 95% CI)*
Impaired growth n/N	NR	NR	NR	NA
(%)				
Delay in pubertal	NR	NR	NR	NA
development				
n/N (%)				
Bowel obstruction	NR	NR	NR	NA
Fistulae	NR	NR	NR	NA
Abscess	0/32 (0.0)	1/30 (3.1)	0/33 (0.0)	-
Colon/bowel cancer	NR	NR	NR	NA
Intestinal infection	NR	NR	NR	NA
Others (Specify)	NR	NR	NR	NA
Authors conclusion				
Elemental nutrition as m	aintenance therapy in Cr	ohn's disease patients w	as as effective as 6-me	ercaptopurine. Elental
should be useful for long	g-term maintenance thera	py in Crohn's disease		

### **Reviewer's conclusion**

At all follow up points (6, 12, and 24 mo), pts on elemental nutrition and 6-MP experienced similar rates of remission maintenance and relapse; at 6 and 12 mo of follow-up, the rates for remission maintenance and relapse were not different between the elemental nutrition and the control (no intervention) groups. However, at 24 mo of follow up, the elemental nutrition group had significantly greater remission maintenance rates and reduced risk of relapse compared to the control (no intervention) group

\* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

AST; Serum Aspartate transaminase, 6-TGN level; 6-Thioguanine nucleotide

### Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Tara Gurung

Study details						
First author surname	e year of	<b>publication</b> : Tak	agi 2006, <sup>52</sup> Takagi 2009, <sup>54</sup> Takagi 2006, <sup>53</sup>			
Country: Japan	·	•				
Study design: RCT						
Study setting (primar	Study setting (primary care/specialty clinic/other - specify): specialty clinic					
Number of centres: t	wo		speens). speening ennie			
Total length of follow	v un· 24	mo				
Funding (government	t/nrivate/	manufacturer/othe	r - specify): no external funding received			
A im of the study	/private/		a - specify). no external funding received			
Alm of the study	. • .	··· ·· · · · · · · · · · · · · · · · ·		1		
To compare relapse ra	ites in pts	with inactive CD	receiving half elemental nutrition (elemental	I nutrition +		
unrestricted diet) vs. n	o interve	ention (unrestricted	d diet)			
Participants						
Recruitment dates: D	December	: 2002-June 2005				
Total N of patients w	ho recei	ved induction the	erapy: 82			
Total N of patients a	chieving	remission after i	nduction therapy: 56			
Total N of patients u	nable to	achieve remission	n after induction therapy: 26			
Total N of patients ex	xcluded	before start of m	aintenance therapy (e.g., in relapse, lost to	follow up): 31		
Total number of pati	ents allo	cated to mainten	ance treatment: 51	1,		
Inclusion criteria <sup>.</sup> CI	) nts if th	ev had just under	gone induction of remission			
Exclusion criteria: N	R	ley mud just under	gone maderion of remission			
Charactaristics of no	n rticinar	te (total etudu car	nnle)			
Maan (rongo or SD) of	rucipan	13 (total study sat				
Mean (range or SD) ag	ge (years	): mean range 28.	9-30.8			
Women (n [%]): 14/5	1 [27.4]					
Race/ethnicity (n [%])	: NR					
Diagnostic criteria for	CD: clir	ically, endoscopic	cally, radiologically and/or histologically (dia	ignostic criteria as		
defined by the Ministr	y of Hea	lth, Labour and W	elfare of Japan)			
Mean Crohn's Disease	e Activit	y Index (CDAI) (ra	ange or SD): mean range 86.4-101.8			
CD location (n [%]): s	mall boy	vel only (15/51 [29	9.4]), colon only (9/51 [17.6]), small bowel a	nd colon (27/51		
[53.0])						
Type of induction ther	apy (e.g.	, medical, surgica	l): elemental enteral nutrition 22/51 [43.1] (1	800–2100 kcal/day)		
for 6–8 weeks: total pa	arenteral	nutrition 25/51 [4	9.01 (1500–2100 kcal/day) for 6–8 weeks: or	al/IV prednisolone		
1/51 [2.0] (40 mg/day	then tar	ered down every	2 weeks by 5–10 mg): 5 mg/kg IV infliximat	3/51 [5.9], and/or		
(5/51 [2.0] (10 mg) au)	, mon tup	lerea ao wir every i		5/51 [5.5], and of		
$\frac{\text{Burgery}(0,01[(1,0]))}{\text{Previous surgery}(n[0])}$	(1)· 22/5	1 [/3 1]				
Intervention	0]). 22/5	1 [+3.1]				
Flow end al model de la model	1	16 1		1		
Elemental nutrition	group: h	alf elemental nutri	ition (i.e., elemental nutrition + unrestricted c	liet)		
Intervention 2 group	: free (ui	restricted) diet [n	o intervention]			
Intervention 3 group	: NA					
Outcomes (study-bas	sed)					
Primary outcomes (la	ist): cum	ulative rate of rela	pse			
Measure of disease a	ctivity (o	linical, endoscop	ic): CDAI			
Definition of remission	on (clini	cal, endoscopic):	CDAI<150			
Definition of relapse/	recurre	nce (clinical, end	<b>(Scopic):</b> CDAI $> 200$ , or the need for the rap	v to induce remission		
Definition of mucosa	l healing	(clinical endosc	onic). NR	,		
Post baseline timings	of nrim	ary outcome ass	$assment \in 12, 18, 24 \text{ mo}$			
Number of notionts	or prin	ary outcome asso	<b>ESSINGIL:</b> 0, 12, 10, 24 mo			
rumber of patients	T-4-1	Flower 4-1	Fuce/manatariated dist (	Intormation 2		
	Total	Elemental	r ree/unrestricted diet group (no	intervention 3		
		nutrition	intervention)	group		
		group				
Allocated to	51	26	25	NA		
treatment						
Analysed (specify	51	26	25	NA		
ITT and/or per	(ITT)					
protocol)	、 <i>- /</i>					
F-0000000						
(If more than one						
follow-up choose						
and another the last						
and specify the last						

one)					
Losses to follow-	11	6(non-	5 (non-adherent: cross-inte	ervention)	NΔ
un/dren out/comple	11	o (non-	5 (non-adherent, cross-inte	n vention)	
up/drop out/sample		adherent;			
attrition		discontinuation			
(If more than one		of elemental			
follow-up, choose		nutrition)			
and specify the last					
one)					
Interventions					
			Description		
		(e.g., formula mar	ufacturer, calorie content, ty	pe, mode, dose,	and duration of
			administration	)	
		Γ	Diet	Co-ii	ntervention
Elemental nutrition	Pts had	to take half the a	mount of their daily	Mesalazine 225	50–3000 mg/dav/p.o.
group	allowa	nce of calories by	elemental nutrition and the	(26/26 [100])	8 9 1
Sroup	remain	ing half by usual i	interstricted meals	(20/20 [100])	
	Ternam	ing han by usual t	in ostricted means.	Azathioprine 5	0 mg/day/n o
	Florital		HARMA Co. Tokyo	(2/26 [7 6])	o mg/day/p.o.
	Lienan)	through a solf inst	artad tuba and/or by oral	(2/20[7.0])	
	intoko	Total anargy cont	cont of 375 keel 100 g. The		
	docago	was 000 1200 kg	ratio = 1/d (240, 220) = 20		
	uosage	$= 000 \pm 1200 \text{ kC}$	$a_1/d (240-320 \text{ g as})$		
	powde	1,900-1200 IIIL as	s solution in water, 3–4		
	sachets	5)			
	<b>T</b> T (	• • • • •			
	Unrest	ricted diet			
	- ·				
	Duratio	on: NR			
Free/unrestricted	Unrest	ricted diet; pts too	k all nutrients via their	Mesalazine 225	50–3000 mg/day/p.o.
diet group (no	usual u	in-restricted meals	. The energy requirements	(25/25 [100])	
intervention)	of indi	vidual patients we	re 35–40 kcal/kg ideal		
	body w	veight/day.		Azathioprine 5	0 mg/day/p.o. (4/25
				[16.0])	
Intervention 3 group	NA			NA	
Patient baseline char	acterist	ics	1		
	Elem	ental nutrition	Free/unrestricted o	liet group	Intervention 3
	20.0.(1	group	(no intervent	ion)	group
Age (years)	30.8 (1	1.1)	28.9 (8.1)		NA
Mean (SD)		2.4	0/25 (22.0)		
Sex – temale n/N	6/26 (2	(3.1)	8/25 (32.0)		NA
(%)					
Weight (kg)	NK		NK		NA
$\frac{1}{2}$	00.1./2	1)			NT A
<b>BIVII</b> (kg/m <sup>2</sup> )	20.1 (3	.1)	20.0 (3.6)		NA
Mean (SD)					
Smoking n/N (%)	NR		NK		NA
Previous bowel	11/26 (	(42.3)	11/25 (44.0)		NA
resection n/N (%)					
Duration of CD	49.2 (5	0.4)	67.2 (78.0)		NA
(months)					
Mean (SD)					
Crohn's Disease	101.8 (	(34.1)	86.4 (31.3)		NA
Activity Index					
(CDAI)					
Mean (SD)					
Crohn's Disease	NR		NR		NA
Endoscopic Index					
of Severity					
(CDEIS)					
Mean (SD)					

Disease activity other than CDAI (specify)	NR	NR		NA
Mucosal ulceration	Perianal lesions 12/26 (46.1)	Perianal lesions 10/25 (40.0)		NA
Other complications n/N (%)	NR	NR		NA
Efficacy outcomes	· · · · ·			
For each timing of ass For scores extract on	sessment please provide a ly total scores	separate table		
Post-baseline follow-u	ip assessment timing (Spec	cify): 12 mo		
	Elemental nutrition group	Free/unrestricted diet group (no intervention)	Intervention 3 group	Between-group difference p value (or 95% CI)*
Patients remaining in remission n/N (%)	NR	NR	NA	NA
Duration of remission (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Risk of relapse or recurrence n/N (%)	9/26 (34.6)	16/25 (64.0)	NA	HR (adjusted)=0.40 (0.16, 0.98) study reported; in favour of elemental nutrition group RR=0.54 (0.29, 0.99) calculated; in favour of elemental nutrition group
Time to relapse (months) Mean (SD) or 95%	NR	NR	NA	NA
Survival rate (% patients in remission who have not relapsed) (Kaplan-Meier estimate and 95% CI)	NR	NR	NA	NA
Patients achieving mucosal healing n/N (%)	NR	NR	NA	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NA	NA
The Short Form Health Survey (SF- 36) Mean (SD) 95% CI	NR	NR	NA	NA
The Short Form Health Survey (SF- 12)	NR	NR	NA	NA

95% C1     NR     NR     NA       Other HQOL (Inflammatory)     Adjusted mean IBDQ sore at 13 mo     NA     Adjusted mean IBDQ sore at 13 mo       Bowlen (SD)     171.9 (126.4, 217.3)     176.7 (142.5, 211.0)     NA       Weight (Eg)     NR     NR     NA       Weight (Eg)     NR     NR     NA       Mean (SD)     95% C1     NR     NA       95% C1     NR     NR     NA       Weight (Eg)     NR     NR     NA       95% C1     NR     NR     NA       Weight (Eg)     NR     NR     NA       95% C1     NR     NR     NA       Na     NA     NA	Mean (SD)				
Ine Euro-Voi guestionnaire (E)- SD)     NR     NR     NR     NA     NA       Wein (SD)     95% CT     Adjusted mean IBDQ score at 13 mo     Adjusted mean IBDQ score at 13 mo     NA     Adjusted mean IBDQ score (BDQ score at 13 mo       Other HQOL     Adjusted mean IBDQ score at 13 mo     NR     NR     NA     Adjusted mean IBDQ score (BDQ score at 13 mo       Weight (g)     NR     NR     NR     NA     NA       Weight (g)     NR     NR     NA     NA       Weight (g)     NR     NR     NA     NA       Mean (SD)     95% CT     NR     NR     NA       95% CT     NR     NR     NA     NA       Mean change (SD)     95% CT     NR     NR     NA       95% CT     NR     NR     NA     NA       Mean change (SD)     95% CT     NR     NA     NA       95% CT     NR     NR     NA     NA       Mean change (SD)     95% CT     NR     NA     NA       Mean change (SD)     95% CT     NR     NA     NA       Mean change (SD)     95% CT     NA     NA     NA       Mean change (SD)     95% CT     NA     NA     NA       Mean change (SD)     95% CT     NA	95% CI	ND	ND	NT A	NT A
questionnaire (RQ- 50)       Adjusted mean IBDQ       Adjusted mean IBDQ       Adjusted mean IBDQ         gest C1       Adjusted mean IBDQ       score at 13 mo       score at 13 mo         Bowel Discuse       geore at 13 mo       score at 13 mo       p>0.05 (NS)         Bowel Discuse       171.9 (126.4, 217.3)       176.7 (142.5, 211.0)       p>0.05 (NS)         S% C1       NR       NR       NA       NA         Weight (kg)       NR       NR       NA       p>-NR (NS) study reported         S% C1       NR       NR       NA       p-NR (NS) study reported         S% C1       NR       NR       NA       p-NR (NS) study reported         S% C1       NR       NR       NA       NA         Mean change (SD)       NR       NR       NA       NA         S% C1       NR       NR       NA       NA         Linear growth rate (Mgm')       NR       NR       NA       NA         S% C1       NR       NR       NA       NA       NA         Linear growth rate (mean linght-for- age Z-score)       NR       NA       NA       NA         Adterence n/N (%)       20/26 (07.0)       20/25 (0.0)       NA       NA       NA	The Euro-Qol	NK	NK	NA	NA
Adjusted mean IBDQ     Adjusted mean IBDQ     Adjusted mean IBDQ     Adjusted mean IBDQ       95% (Cl     score at 13 mo     score at 13 mo     BBQ score       Questionnaire)     171.9 (126.4, 217.3)     176.7 (142.5, 211.0)     mpice       95% (Cl     NR     NR     NA     NA       Weight (kg)     NR     NR     NA     NA       95% (Cl     NR     NR     NA     NA       Mean (SD)     95%     NR     NR     NA       95% (Cl     NR     NR     NA     NA       Height gain (cm)     NR     NR     NA     NA       Mean (SD)     95% (Cl     NR     NR     NA       Mean (SD)     95% (Cl     NR     NR     NA       Mean (SD)     95% (Cl     NR     NR     NA       Mean (SD)     95% (Cl     NR     NA     NA       Imeas field gain (cm)     NR     NR     NA     NA       Imeas field gain (cm)     NR     NR     NA	questionnaire (EQ-				
95% CI     Adjusted mean IBDQ score at 13 mo     NA     Adjusted mean IBDQ score at 13 mo       Bowel Disease Questionnaire     171.9 (126.4, 217.3)     176.7 (142.5, 211.0)     P=005 (NS)       Weight (kg) Mean (SD)     NR     NR     NA     NA       Weight (kg) Mean (SD)     NR     NR     NA     NA       Weight gain (kg) Mean change (SD)     NR     NR     NA     NA       S% C1     NR     NR     NA     NA       Body mass index (kg/m <sup>3</sup> )     NR     NR     NA     NA       S% C1     NR     NR     NA     NA       JS% C1     NR     NR     NA     NA       Body mass index (kg/m <sup>3</sup> )     NR     NR     NA     NA       S% C1     NR     NR     NA     NA       JS% C1     NR     NR     NA     NA       Body mass index (kg/m <sup>3</sup> )     NR     NR     NA     NA       S% C1     NR     NR     NA     NA       JS% C1     NR     NR     NA     NA       Systep (C1     NR <td>Mean (SD)</td> <td></td> <td></td> <td></td> <td></td>	Mean (SD)				
Other HQOL (Inflammatory Bowel Disease Questionnaire)         Adjusted mean IBDQ score at 13 mo score at 13 mo         Adjusted mean BDQ score difference at 13 mo p=0.05 (NS)         Adjusted mean BDQ score difference at 13 mo p=0.05 (NS)           95% C1         NR         NR         NA         NA           Weight (kg) Mean (SD)         NR         NR         NA         NA           95% C1         NR         NR         NA         NA           Weight (kg) Mean change (SD)         NR         NR         NA         NA           95% C1         NR         NR         NR         NA         NA           Weight (kg) Mean change (SD)         NR         NR         NA         NA         NA           95% C1         NR         NR         NR         NA         NA           Mean change (SD)         95% C1         NR         NR         NA           Mean (SD)         20/26 (77.0)         20/25 (80.0)         NA         Re-0.96 (0.72, 1.28) calculated           Adherence n/N (%)         20/26 (77.0)         20/25 (80.0)         NA         RA           Net ord oxe tapering n/N (%)         NR         NR         NA         NA           Vitidrawal from steroid nw (%)         NR         NR         NA         NA	95% CI				
(Inflammatory Bowel Disease Questionnaire)     score at 13 mo     score at 13 mo     IBD Question difference at 13 mo       Questionnaire)     171.9 (126.4, 217.3)     176.7 (142.5, 211.0)     P-0.05 (NS)       Mean (SD)     NR     NR     NA       95% (C1     NR     NR     NA       Weight gain (kg)     NR     NR     NA       Mean change (SD)     95% (C1     NR     NR       Body mass index (kg/m²)     NR     NR     NA       S% (C1     NR     NR     NA       Body mass index (kg/m²)     NR     NR     NA       S% (C1     NR     NR     NA       Jinear growth rate (mean height-for- age Z-score)     NR     NR       Adherence n/N (%)     20/26 (77.0)     20/25 (80.0)     NA       NR     NR     NA     NA       viertoid s/N (%)     NR     NR     NA       off (0.72, 1.28) calculated     NA     NA       Vithdrawal from steroids n/N (%)     NR     NA     NA       Olde (0.0)     025 (0.0)     NA     NA       Mittorawal from steroids n/N (%)     NR     NA     NA       Olde (0.0)     025 (0.0)     NA     NA       Merence n/N (%)     NR     NA     NA       Orgoup	Other HQOL	Adjusted mean IBDQ	Adjusted mean IBDQ	NA	Adjusted mean
Bowel Disease Questionnaire)171.9 (126.4, 217.3)176.7 (142.5, 211.0)difference at 13 mo p>-0.05 (NS)95% C1NRNRNANAMean (SD) 95% C1NRNRNANAMeight (kg) Mean change (SD) 95% C1NRNRNAp=-NR (NS) study reportedBody mass index (kg/m') Mean change (SD) 95% C1NRNRNANABody mass index (kg/m') Mean change (SD) 95% C1NRNRNRNAHeight gain (cm) Mean change (SD) 95% C1NRNRNANAMean change (SD) 95% C1NRNRNANAMean change (SD) 95% C1NRNRNANAMean (SD) 95% C1NRNRNANAMean (SD) 95% C1NRNRNANAMean (SD) 95% C120/26 (77.0)20/25 (80.0)NARR=0.96 (0.72, 1.28) calculatedNeed for surgery n/N (%)NRNRNANASteroid dose tapering n/N (%)NRNRNANAOrdification N (%) (%)0/26 (0.0)0/25 (0.0)NANAComplications - Number (%) of patients with an event if more than one follow-up, choose and specify the last follow up]Intervention 3 group (no intervention)Between-group difference p value (or 95% CD)*Impaired growth n/N (%)0/260/25NANADelay in pubertal development n/N (%)0/260/25NANADelay in pubert	(Inflammatory	score at 13 mo	score at 13 mo		IBDQ score
Questionnaire) Mean (SD)         171.9 (126.4, 217.3)         176.7 (142.5, 211.0)         p>0.05 (NS)           95% C1         NR         NR         NA         NA           Weight (kg) Mean (SD)         NR         NR         NA         NA           95% C1         NR         NR         NA         P=NR (NS) study reported           95% C1         NR         NR         NA         P=NR (NS) study reported           95% C1         NR         NR         NA         NA           Body mass index (kg/m <sup>3</sup> )         NR         NR         NA         NA           Weight gain (cm) Mean change (SD)         NR         NR         NA         NA           95% C1         NR         NR         NR         NA         NA           Linear growth rate (mean height-for- age Z-score)         NR         NR         NA         RE=0.96 (0.72, 1.28) calculated           Atherence nN (%)         20/26 (77.0)         20/25 (80.0)         NA         RE=0.96 (0.72, 1.28) calculated           Steroid dose tapering nN (%)         NR         NR         NA         NA           Steroid dose tapering nN (%)         NR         NR         NA         NA           Complications - Number (%) of patients with an event group (no intervention)	Bowel Disease				difference at 13 mo
Mean (SD)     95% CI     NR     NR     NA       Weight (kg)     NR     NR     NA     NA       Weight gain (kg)     NR     NR     NR     NA       Weight gain (kg)     NR     NR     NR     NA       Body mass index     (kg/m <sup>2</sup> )     NR     NR     NA       Sy% CI     NR     NR     NA     NA       Height gain (cm)     NR     NR     NA     NA       Sy% CI     NR     NR     NA     NA       JS% CI     NR     NR     NA     NA       Mean change (SD)     95% CI     NR     NR     NA       JS% CI     NR     NR     NA     NA       Mean change (SD)     95% CI     NR     NR     NA       JInear growth rate     NR     NR     NA     NA       Gaberone nN (%)     20/26 (77.0)     20/25 (80.0)     NA     RR=0.96 (0.72, 1.28) calculated       Steroid dos     NR     NR     NA     NA     NA       tapering n/N (%)     NR     NR     NA     NA       Steroid dos     NR     NR     NA     NA       tapering n/N (%)     NR     NR     NA     NA       (%)     0/26 (0.0)     0/25	Questionnaire)	171.9 (126.4, 217.3)	176.7 (142.5, 211.0)		p>0.05 (NS)
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean (SD)				
Weight (kg) Mean (SD) 95% C1     NR     NR     NA     NA       Weight gain (kg) Mean change (SD) 95% C1     NR     NR     NA     p=NR (NS) study reported       Body mass index (kg/m <sup>3</sup> )     NR     NR     NA     NA       Height gain (mass index (kg/m <sup>3</sup> )     NR     NR     NA     NA       95% C1     NR     NR     NA     NA       Height gain (mass index (kg/m <sup>3</sup> )     NR     NR     NA     NA       Mean (SD) 95% C1     NR     NR     NA     NA       Linear growth rate (mean height-for- age Z-score)     NR     NR     NA     NA       Adherence n/N (%)     20/26 (77.0)     20/25 (80.0)     NA     NA     NA       Steroid dose targery n/N (%)     NR     NR     NA     NA     NA       Vithdrawal from steroids n/N (%)     NR     NR     NA     NA       Adverse events due to treatment n/N (%)     0/26 (0.0)     0/25 (0.0)     NA     NA       (%)     0/26     0/25     NA     NA     NA       Impaired growth n/N (%)     0/26     0/25     NA     NA       Delay in pubertal development n/N (%)     0/26     0/25     NA     NA       Bowet obstruction networks     0/26     0/25     NA     NA	95% CI				NY 4
Mean (SD)       95% CI       P=NR (NS) study         Weight gain (kg)       NR       NR       NA       p=NR (NS) study         Body mass index       (kg/m <sup>3</sup> )       NR       NR       NA       NA         Weight gain (kg)       NR       NR       NA       NA       NA         Js% CI       NR       NR       NA       NA       NA         Height gain (cm)       NR       NR       NA       NA         Mean (SD)       95% CI       NR       NR       NA       NA         Linear growth rate (mean height-for-age Z-score)       NR       NA       NA       RR=0.96 (0.72, 1.28) calculated         Adherence nV (%)       20/26 (77.0)       20/25 (80.0)       NA       RR=0.96 (0.72, 1.28) calculated         Need for surgery n/N (%)       NR       NR       NA       NA         Steroid dose       NR       NR       NA       NA         Steroid dose       NR       NR       NA       Adverse events due (or 95% CI)*         Gomplications - Number (%) of patients with an event       Intervention 3       Between-group difference p value (or 95% CI)*         Impaired growth n/N (%)       0/26       0/25       NA       NA         Delay in pubertal divelopment n/N (%	Weight (kg)	NR	NR	NA	NA
$\begin{array}{c c c c c c c c } 32\% C1 & & & & & & & & & & & & & & & & & & $	Mean (SD)				
Vregni gain (gg) Mean change (SD) 95% C1NRNRNAp=NR (NS) sludy reported reported reported reported reported reported reported NRBody mass index (kg/m²) Mean change (SD) 95% C1NRNRNANAHeight gain (em) Mean change (SD) 95% C1NRNRNANAHeight for age Z-score) age Z-score) Adherence n/N (%)NRNRNANAAdherence n/N (%) Steroid dos toriod ose toriod set odsNRNRNANANRNRNRNANASteroid dos (%)NRNRNANAAdverse events due to treatment n/N (%)0/26 (0.0)0/25 (0.0)NANAComplications - Number (%) of patients with an event group (no intervention)Intervention 3 group (no intervention)Between-group difference p value (or 95% C1)*Impaired growth n/N (%)0/260/25NANADelay in pubertal development n/N (%)0/260/25NANABowel obstruction intervention0/260/25NANABowel obstruction intervention0/260/25NANABowel obstruction intervention0/260/25NANAComplexition (N (%)0/260/25NANABowel obstruction intervention0/260/25NANAComplexition (N (%)0/260/25NANAComplexition (N (%)0/260	95% Cl Weight goin (leg)	ND	ND	NA	n-ND (NC) study
Near Intange (SD)     Provide       Body mass index (kg/m <sup>2</sup> )     NR     NR     NA     NA       Wean change (SD)     S% C1     NR     NR     NA     NA       Height gain (cm) Mean (star)     NR     NR     NA     NA       J5% C1     NR     NR     NA     NA       Linear growth rate (mean height-for- age Z-score)     NR     NR     NA     NA       Adherence n/N (%)     20/26 (77.0)     20/25 (80.0)     NA     RE=0.96 (0.72, 1.28) calculated       Need for surgery n/N (%)     NR     NR     NA     NA       Steroid dose tareing n/N (%)     NR     NR     NA     NA       Withdrawal from steroids n/N (%)     NR     NR     NA     NA       Ox26 (0.0)     0/26 (0.0)     0/25 (0.0)     NA     NA       (%)     NR     NR     NA     NA       (%)     0/26 (0.0)     0/25 (0.0)     NA     NA       Complications - Number (%) of patients with an event group     Intervention 3 group     Between-group difference p value (or 95% CI)*       Impaired growth n/N (%)     0/26     0/25     NA     NA       Delay in pubertal development n/N (%)     0/26     0/25     NA     NA       Bowel obstruction     0/26     0/25     NA </td <td>Mean change (SD)</td> <td>INK</td> <td>INK</td> <td>NA</td> <td>p=INK (INS) study</td>	Mean change (SD)	INK	INK	NA	p=INK (INS) study
Body mass index (kg/m²) Mean change (SD) 95% CINRNRNANAHeight gain (em) Mean (SD) 95% CINRNRNANAHeight gain (em) Mean (SD) 95% CINRNRNANAHeight for- age Z-score)NRNRNANAAdherence n/N (%)20/26 (77.0)20/25 (80.0)NARR=0.96 (0.72, 1.28) calculatedAdherence n/N (%)20/26 (77.0)20/25 (80.0)NANASteroid dose tareing n/N (%)NRNRNANAWithdrawal from steroid n/N (%)NRNRNANAWithdrawal from (%)NRNRNANAComplications - Number (%) of patients with an event group (no intervention)Intervention 3 groupBetween-group difference group (no intervention)Between-group difference p value (or 95% CI)*Impaired growth n/N (%)0/260/25NANADelay in pubertal development n/N (%)0/260/25NANABowel obstruction or 0/260/25NANANAElemental nufrition group0/260/25NANABowel obstruction concer0/260/25NANAIntestinal infection 0/260/25NANAColon/bowel concer0/260/25NANAAdverses0/260/25NANACombrowel concer0/260/25NANACondonbowel conc	95% CI				reported
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Body mass index	NR	NR	NA	NA
$\begin{array}{c c c c c c } \hline Mean change (SD) \\ 95\% C1 \\ \hline Height gain (cm) \\ Mean (SD) \\ 95\% C1 \\ \hline Inear growth rate (mean height-for-age Z-score) \\ \hline Adherence n/N (%) \\ 20/26 (77.0) \\ 20/25 (80.0) \\ Adherence n/N (%) \\ 20/26 (77.0) \\ 20/25 (80.0) \\ NA \\ RR=0.96 (0.72, 1.28) calculated \\ NR \\ NR \\ NR \\ NA \\ NA \\ RR=0.96 (0.72, 1.28) calculated \\ NR \\ n/N (\%) \\ NR \\ NR \\ NR \\ NR \\ NA \\ Adverse events due (or 90\% NR \\ NR \\ NR \\ NR \\ NR \\ NA \\ Adverse events due (or 90\% NR \\ O'25 (0.0) \\ NA \\ Adverse events due (or 90\% NR \\ O'25 (0.0) \\ O'25 (0.0) \\ NA \\ Adverse events due (or 90\% NR \\ O'26 (0.0) \\ O'25 (0.0) \\ O'25 (0.0) \\ O'25 (0.0) \\ O'25 \\ NA \\ N$	$(kg/m^2)$				
$\begin{array}{c c c c c c } 95\% \ CI & & & & & & & & & & & & & & & & & & $	Mean change (SD)				
Height gain (cm) Mean (SD) 95% C1NRNRNANAMean (SD) 95% C1NRNRNANALinear growth rate (man height-for- age Z-score)NRNRNANAAdherence n/N (%)20/26 (77.0)20/25 (80.0)NARR=0.96 (0.72, 1.28) calculatedNeed for surgery n/N (%)NRNRNANASteroid dose targing n/N (%)NRNRNANASteroid dose targing n/N (%)NRNRNANAAdverse events due (%)0/26 (0.0)0/25 (0.0)NANAComplications - Number (%) of patients with an event group (no intervention)Intervention 3 groupBetween-group difference p value (or 95% C1)*Impaired growth n/N (%)0/260/25NANADelay in pubertal development n/N (%)0/260/25NANABowel obstruction0/260/25NANAImpaired growth n/N (%)0/260/25NANABowel obstruction0/260/25NANAImpaired growth n/N (%)0/260/25NANAImpaired growth n/N (%)0/260/25NANAImpaired growth n/N (%)0/260/25NANAImpaired growth n/N (%)0/260/25NANAImpaired growth n/N (%)0/260/25NANAImpaired growth n/N (%)0/260/25NANA <td>95% CI</td> <td></td> <td></td> <td></td> <td></td>	95% CI				
Mean (SD) 95% CIImage (SD) 95% CINRNRNANALinear growth rate (mean height-for- age Z-score)NRNRNANAAdherence n/N (%)20/26 (77.0)20/25 (80.0)NARR=0.96 (0.72, 1.28) calculatedAdherence n/N (%)20/26 (77.0)20/25 (80.0)NARR=0.96 (0.72, 1.28) calculatedNeed for surgery n/N (%)NRNRNANASteroid dose tapering n/N (%)NRNRNANAAdverse events due to treatment n/N (%)0/26 (0.0)0/25 (0.0)NANAComplications - Number (%) of patients with an event group no intervention)Free/unrestricted diet group difference p value (or 95% CI)*Between-group difference p value (or 95% CI)*Impaired growth n/N (%)0/260/25NANADelay in pubertal n/N (%)0/260/25NANABowel obstruction 0/260/25NANANAFistulae0/260/25NANAFistulae0/260/25NANAOlon/bowel cancer0/260/25NANAIntestinal infection cancer0/260/25NANAAdverse events/bue group0/260/25NANAAdverse events/bue group0/260/25NANAImpaired growth n/N (%)0/260/25NANADelay in pubertal n/N (%)0/260/25NANA <td>Height gain (cm)</td> <td>NR</td> <td>NR</td> <td>NA</td> <td>NA</td>	Height gain (cm)	NR	NR	NA	NA
95% CIImage of the sign of t	Mean (SD)				
Linear growth rate (mean height-for- age Z-score)NRNRNANAAdherence n/N (%)20/26 (77.0)20/25 (80.0)NARR=0.96 (0.72, 1.28) calculatedAdherence n/N (%)20/26 (77.0)20/25 (80.0)NARR=0.96 (0.72, 1.28) calculatedNeed for surgery n/N (%)NRNRNANAsteroid dose tapering n/N (%)NRNRNANAWithdrawal from steroids n/N (%)NRNRNANAAdverse events due to freatment n/N0/26 (0.0)0/25 (0.0)NANAComplications - Number (%) of patients with an event (%)Elemental nutrition group (no intervention)Intervention 3 group groupBetween-group difference p value (or 95% CI)*Impaired growth n/N (%)0/260/25NANADelay in pubertal development n/N (%)0/260/25NANABowel obstruction 0/260/25NANANAFistulae colon/bowel 0/260/25NANANAColon/bowel colon/bowel 0/260/25NANANAColon/bowel cancer0/260/25NANANAColon/bowel cancer0/260/25NANANAColon/bowel cancer0/260/25NANANAColon/bowel cancer0/260/25NANANAColon/bowel cancer0/260/25NANANAColon/bowel <b< td=""><td>95% CI</td><td></td><td></td><td></td><td></td></b<>	95% CI				
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to treatment n/N (%)Image: mean of the section of th	Adverse events due	0/26 (0.0)	0/25 (0.0)	NA	NA
(%)Image: constraint of the section of th	to treatment n/N				
Complications - Number (%) of patients with an event [if more than one follow-up, choose and specify the last follow up]         Elemental nutrition group       Free/unrestricted diet group (no intervention)       Intervention 3 group       Between-group difference p value (or 95% CI)*         Impaired growth n/N (%)       0/26       0/25       NA       NA         Delay in pubertal development n/N (%)       0/26       0/25       NA       NA         Bowel obstruction       0/26       0/25       NA       NA         Fistulae       0/26       0/25       NA       NA         Abscess       0/26       0/25       NA       NA         Intervention       0/26       0/25       NA       NA         Abscess       0/26       0/25       NA       NA         Abscess       0/26       0/25       NA       NA         Colon/bowel       0/26       0/25       NA       NA         Authors conclusion       0/26       0/25       NA       NA	(%)				
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n/N (%)              Bowel obstruction         0/26         0/25         NA         NA           Fistulae         0/26         0/25         NA         NA           Abscess         0/26         0/25         NA         NA           Colon/bowel         0/26         0/25         NA         NA           Intestinal infection         0/26         0/25         NA         NA           Others (Specify)         0/26         0/25         NA         NA	development				
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Abscess         0/20         0/25         NA         NA           Colon/bowel         0/26         0/25         NA         NA           cancer         Intestinal infection         0/26         0/25         NA         NA           Others (Specify)         0/26         0/25         NA         NA           Authors conclusion         V         V         V         V	r istulae	0/26	0/25	INA NA	NA
Colon/bower0/200/25NANAcancer0/260/25NANAIntestinal infection0/260/25NANAOthers (Specify)0/260/25NANA	ADSCESS	0/26	0/25	INA NA	INA NA
CancerCancerIntestinal infection0/260/25NANAOthers (Specify)0/260/25NANAAuthors conclusion	Cololl/Dowel	0/20	0/23	INA	INA
Others (Specify)     0/26     0/25     NA     NA       Authors conclusion     0/25     NA     NA	Intestinal infection	0/26	0/25	NΔ	ΝΔ
Authors conclusion	Others (Specify)	0/26	0/25	NA	NA
	Authors conclusion	0,20	0/20	11/1	1111

At 24 mo, pts receiving elemental nutrition experienced significantly reduced risk of relapse compared to those on free diet. No differences were detected in quality of life or cost of treatment between the two groups

### **Reviewer's conclusion**

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At 24 mo, pts receiving elemental nutrition experienced significantly reduced risk of relapse compared to those on free diet. No differences were detected in quality of life or cost of treatment between the two groups; no adverse events; adherence was similar between the treatment groups; trial terminated at 24 mo for ethical reasons

\* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

Cost table (mean per patient monthly m yen)	Cost	table	(mean	per	patient	monthly	in	yen) <sup>5</sup>
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	Elemental nutrition group	Free diet group	Between-group difference n value
			(or 95% CI)
Crude costs	109,160	68,970	NR
	(95% CI: 63,240 - 155,090)	(95% CI: 22,140–115,800)	
Age-/sex-adjusted costs	111,540	66,490	NR
	(95% CI: 66,850–156,240)	(95% CI: 20,900–112,080)	
Multivariate costs*	105,860	72,400	p>0.05 (NS)
	(95% CI: 57,380 - 154,340)	(95% CI: 22,810–122,000)	
	About \$880.00 US	About \$600.00 US	

Adjusted for age, sex, duration of disease, site, perianal lesions, previous gut operation, frequency of relapse, administration of azathioprine, inductive therapy (+surgery), and mean CDAI at baseline

Study details         The study or summe year of publication: Verma 2001 <sup>35</sup> Country: UK         Study setting: (primary care/specially clinic/other - specify): specialty clinic           Number of centres: one         Total length of follow up: 24 no           Funding (government/private/manufacture/other - specify): NR         Among the study           To compare safety and efficacy of elemental and polymeric nutrition in terms of the maintenance of remission, relapse, and inclerance         Participants           Recruitment dates:         Total length of holerance         Participants           Total N of patients unable to achieve remission after induction therapy: NR         Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR         Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR         Total N of patients achieving to with/dxw storid dependency or maintaining clinical remission after is to with/dxw storid dependency or maintaining clinical remission after isolocated to maintenance treatment: 33           Industries of patients allocated to maintenance treatment: 33         Industries of patients andiversite total that/dxw storid dependency or maintaining clinical remission after isological eriteria: returnet small-bowel obstruction due to Crohn strictures, significant sepsis including perianal discuse, previous intofarace to central feeding or unwilling to give formal written consent Characteristics fol (all Si30, Si): 2.7), range: 17.76	Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Tara Gurung								
Irist author surname year of publication: Verma 2001 <sup>35</sup> Country: UK           Study design: RCT           Study setting (primary care/specialty clinic/other - specify): specialty clinic           Number of care/specialty and fileacy of elemental and polymeric autrition in terms of the maintenance of remission, relapse, and intolerance.           Participants           Recruitment drawn manual to achieve remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy: NR           Total N of patients achieving remission after induction therapy is a relative charactive characteris on the anistenance treating (edge) in relative characteristic achieving or after 30           Otal N of patients achieving intervice characteristic achieving and intervice characteristic achieving or after 3	Study details								
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Study design: RCT         Study setting (primary care/specialty clinic/other - specify): specialty clinic         Number of curters: one         Total length of follow up: 24 mo         Funding (government/private/manufacturer/other - specify): NR         Aim of the study         To compare safety and efficacy of elemental and polymeric nutrition in terms of the maintenance of remission, relapse, and intolerance         Participants         Recruitment dates:         Total N of patients who received induction therapy: NR         Total N of patients anable to achieve remission after induction therapy; NR         Total N of patients anable defore start of maintenance therapy (e.g. in relapse, lost to follow up); 4         Total N of patients excluded before start of maintenance therapy (e.g. in relapse, lost to follow up); 4         Total N or patients excluded before start of maintenance therapy (e.g. in relapse, lost to follow up); 4         Total N or patients excluded before start of maintenance treatment: 33         Inclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (Tohe): 23/33 (70.7)         Race/thmicity (n 1%b): SR         Diagnostic criteria for CD: standard elimical, radiological, endoscopic and histological criteria         Mean C	Country: UK	year or r		2001					
Study setting (primary care/specialty clinic/other - specify): specialty clinic         Number of centres: one         Total length of follow up: 24 mo         Funding (government/private/manufacture/other - specify): NR         Alim of the study         To compare safety and efficacy of elemental and polymeric nutrition in terms of the maintenance of remission, relapse, and intolerance:         Participants         Recruitment dates:         Total N of patients who received induction therapy: NR         Total N of patients achieving remission after induction therapy: NR         Total N of patients usable to achiever emission after induction therapy: NR         Total N of patients excluded before start of maintenance tentrary (e.g., in relapse, lost to follow up): 4         Total number of patients allocated to maintenance treatment: 33         Inclusion criteria: rescurent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous insolerance to enteral feeding or unwilling to give formal written consent.         Characteristics of participants (total study sample)         Mean (range or SD) arge (vars): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 [70.7]         Reacvetinicity (n [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean Crohn's Disease Activity (Index (CDA) (range or SD): mean range 90.4-106.4         CD location (n [%]): sma	Study design: RCT	Study design: RCT							
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Formula of centres out:         24 mo           Funding (government/private/manufacturer/other - specify): NR	Number of centres: one								
Total function of the study         Temperature         Temperature           Aim of the study         To compare safety and efficacy of elemental and polymeric nutrition in terms of the maintenance of remission, relapse, and intolerance         Participants           Recruitment dates:         Total N of patients who received induction therapy: NR         Total N of patients schleving remission after induction therapy: NR           Total N of patients schleving remission after induction therapy: NR         Total N of patients schleded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4           Total N of patients schleving remission after induction therapy: NR         Total N of patients schleded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4           Total N of patients schleving remission after induction therapy: NR         Total N of patients schleded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4           Total N of patients schled before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total N of patients schledus downmote dual previously steroid dependency for maintaining clinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence during or after 30           do withdrawal         Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal discuse, previous intolerance to enteral feeding or unwilling to give formal written consent           Characteristics of participants (total study sample)         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17	Total length of follow up: 24 mo								
To compare safety and efficacy of elemental and polymeric nutrition in terms of the maintenance of remission, relapse, and intolerance         Participants         Recruitment dates:         Total N of patients who received induction therapy: NR         Total N of patients achieving remission after induction therapy: NR         Total N of patients achieving remission after induction therapy: NR         Total N of patients achieving remission after induction therapy: NR         Total N of patients achieving remission after induction therapy: NR         Total N of patients achieving remission after induction therapy: NR         Total number of patients allocated to maintenance therapy (e.g., in relapse, lost to follow up): 4         Total number of patients allocated to maintenance therapy (e.g., in relapse, lost to follow up): 4         Indusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolal-patient bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolal-patient feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (range or SD) age (vgest): 40.8 (SD: 2.7), range or SD): mean range 90.4-106.4         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean (range or [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic, mean dose 7.0 (0.5) mg/d)         P	Funding (government/private/manufacturer/other - specify): NR								
All of the study       To compare safety and efficacy of elemental and polymeric nutrition in terms of the maintenance of remission, relapse, and intolerance.         Participants       Participants         Recruitment dates:       Total N of patients who received induction therapy: NR         Total N of patients who received induction therapy: NR       Total N of patients unable to achieve remission after induction therapy: NR         Total N of patients sculed before start of maintenance therapy (e.g., in relapse, lost to follow up): 4       Total normation of patients allocated to maintenance therapy (e.g., in relapse, lost of follow up): 4         Total N of patients excluded before start of maintenance treatment: 33       Inclusion criteria: returnets in within active CD and documented previously steroid dependency for maintaining clinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence during or after 30 d of withdrawal         Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)       Mean (ning or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 (70.7]       Race(chnicity] (ndex (CDAI) (range or SD): mean range 90.4-106.4         CD location (n [%]): small bowel (11/33 (33.3), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d) <td colspan="8">r unung (government/private/manufacturer/other - specify): NK</td>	r unung (government/private/manufacturer/other - specify): NK								
To compare safety and efficacy of elemental and polymeric nutrition in terms of the maintenance of remission, relapse, and intolerance.         Participants         Recruitment dates:         Total N of patients who received induction therapy: NR         Total N of patients achieving remission after induction therapy: NR         Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total norm of patients allocated to maintenance transment. 33         Inclusion eriteria: pts with inactive CD and documented previously steroid dependency for maintaining clinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence during or after 30 do withdrawal         Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolerance to entral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%): 23/33 [70.7]         Race/ethnicity (n [%)): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean Crohn's Disease Activity Index (CDAI) (range or SD); mean range 90.4-106.4         CD location (n [%]): SNR         Intervention         Elemental nutrition (EO28)         Intervention 2 group: polymeric nutrition (EO28)         In	Aim of the study To compare sofety and officercy of elemental and polymorie putrition in terms of the unintercore of an initial								
relapse, and intolerance Participants Recruitment dates: Total N of patients who received induction therapy: NR Total N of patients achieving remission after induction therapy: NR Total N of patients anable to achieve remission after induction therapy: NR Total N of patients anable to achieve remission after induction therapy: NR Total N of patients achieving remission after induction therapy: NR Total N of patients achieving remission after induction therapy: NR Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4 Total N of patients excluded before start of maintenance therapy (e.g., in relapse. Instituting etinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence during or after 30 d of withdrawal Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent Characteristics of participants (total study sample) Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76 Women (n [%]): 23/33 [70.7] ReacetInticity   ndws (CDAI) (range or SD): mean range 90.4-106.4 CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6:0]) Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d) Previous surgery (n [%]): NR Intervention group: clemental nutrition (EO28) Intervention 3 group: NA Outcomes (files): remission maintenance rate, time to relapse Measure of disease activity (clinical, endoscopic): clinical (CDAI) ≥200 or increased by 100 points from baseline) Definition of remission (clinical, endoscopic): clinical (CDAI) ≥00 or increased by 100 points from baseline) Definition of remission (clinical, endoscopic): clinical (CDAI) ≥00 or increased by 100 points from baseline) Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI) ≥00 or increased by 10	To compare safety and efficacy of elemental and polymeric nutrition in terms of the maintenance of remission,								
Participants         Recruitment dates:         Total N of patients who received induction therapy: NR         Total N of patients wable to achieve remission after induction therapy: NR         Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total N of patients unable to achieve remission after induction therapy: NR         Total N of patients unable to achieve remission after induction therapy (e.g., in relapse, lost to follow up): 4         Total N of patients unable to achieve remission after induction therapy (e.g., in the pass, including periand disease, previous unsuccessful attempts to withdraw steroid that prompted recurrence during or after 30 d of withdrawal         Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including periand disease, previous invession and total study sample)         More (ref.) [%]: NR         Total Corb standard clinical, radiological, endoscopic; man	relapse, and intolerance								
Recruitment dates: Total N of patients who received induction therapy: NR Total N of patients achieving remission after induction therapy: NR Total N of patients exclude before start of maintenance therapy (e.g., in relapse, lost to follow up): 4 Total N of patients exclude before start of maintenance therapy (e.g., in relapse, lost to follow up): 4 Total N of patients exclude before start of maintenance therapy (e.g., in relapse, lost to follow up): 4 Total N of patients exclude before start of maintenance therapy (e.g., in relapse, lost to follow up): 4 Total norms of patients allocated to maintenance threaty (e.g., in relapse, lost to follow up): 4 Total N of patients (rotal allocated to maintenance threaty (e.g., in relapse, lost to follow up): 4 Total N of patients (rotal study sample) Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76 Women (n [%]): 23/33 [70.7] Race/ethnicity (n [%]): NR Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria Mean Crohn's Disease Activity Index (CDA1) (range or SD): mean range 90.4-106.4 CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0]) Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d) Previous surgery (n [%]): NR Intervention 2 group: colymeric nutrition (EO28) Intervention 2 group: polymeric nutrition (Fortisip) Intervention 2 group: polymeric nutrition (Fortisip) Intervention 2 group: NA Outcomes (study-based) Primary outcomes (fixt): remission maintenance rate, time to relapse Measure of disease activity (clinical, endoscopic): clinical (CDA1) Definition of remission (clinical, endoscopic): clinical (CDA1) Definition of remission (clinical, endoscopic): NR Post-baseline timings of primary outcome assessment: 12 mo Number of patients Primary outcomes Alexalistical, endoscopic): NR Post-baseline timings of primary outcome assessment: 12 mo Number of patients Pri	Participants								
Total N of patients who received induction therapy: NR         Total N of patients achieving remission after induction therapy: NR         Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total number of patients allocated to maintenance therapy (e.g., in relapse, lost to follow up): 4         Total number of patients allocated to maintenance treatment: 33         Inclusion criteria: pts with inactive CD and documented previously steroid dependency for maintaining clinical remission and two previous intolerance to enteral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 [70.7]         Race/ethnicity (n [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 [70.7]         Race/ethnicity (n [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean Crange or (js) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): SNR         Intervention         Primary outcome (is [%]): NR         Intervention         Primary outcome (is [%]): NR         Intervention 2 group: polymeric nutrition (Fortis	Recruitment dates:	Recruitment dates:							
Total N of patients achieving remission after induction therapy: NR         Total N of patients unable to achieve remission after induction therapy: NR         Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total N of patients ablocated to maintenance treatment: 33         Inclusion criteria: pts with inactive CD and documented previously steroid dependency for maintaining clinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence during or after 30 d of withdrawal perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 [70.7]         Race/ethnicity on [%]): SmR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean Crohn's Disease Activity Index (CDAI) (range or SD): mean range 90.4-106.4         CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention 2 group: polymeric nutrition (Fortisp)         Intervention 3 group: polymeric nutrition (Fortisp)         Intervention 3 group: polymeric nutrition (CDAI)         Definition of remission (clin	Total N of patients who	o receiv	ed induction tl	herapy: NR					
Total N of patients unable to achieve remission after induction therapy: NR         Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total number of patients allocated to maintenance treatment: 33         Inclusion criteria: pis with inactive CD and documented previously steroid dependency for maintaining clinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence during or affer 30 d of withdrawal         Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including periand disease, previous intolerance to enteral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/3 [70.7]         Race/ethnicity (n [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean Crohn's Disease Activity Index (CDAI) (range or SD): mean range 90.4-106.4         CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention 2 group; polymeric nutrition (EO28)         Intervention 3 group; NA         Outcomes (study-based)         Primary outcomes (i/s): remission maintenan	Total N of patients ach	ieving r	emission after	induction therapy: NR					
Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4         Total number of patients allocated to maintenance treatment: 33         Inclusion criteria: pts with inactive CD and documented previously steroid dependency for maintaining clinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence during or after 30 d of withdrawal         Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 [70.7]         Race/ethnicity (n [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean (range or SD) age (years): 40.8 (SD: 2.7), conger SD): mean range 90.4-106.4         CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention         Elemental nutrition (Fortisp)         Intervention 2 group: polymeric nutrition (Fortisp)         Intervention 3 group: polymeric nutrition (BC28)         Intervention 3 group: polymeric nutrition (adsence of diarrhoea and	Total N of patients una	able to a	chieve remissi	on after induction therapy: NR					
Total number of patients allocated to maintenance treatment: 33         Inclusion criteria: pis with inactive CD and documented previously steroid dependency for maintaining clinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence during or after 30 d of withdrawal         Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 [70.7]         Race/ethnicity (n [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 [70.7]         Race/ethnicity (n [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean Crohn's Disease Activity Index (CDAI) (range or SD); mean range 90.4-106.4         CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention 3 group: NA         Outcomes (study-hased)         Primary outcomes (isn):	Total N of patients exc	luded b	efore start of <b>n</b>	naintenance therapy (e.g., in relapse, l	ost to follow up): 4				
Inclusion criteria: pts with inactive CD and documented previously steroid dependency for maintaining clinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence during or after 30 of withdrawal         Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 [70.7]         Race/ethnicity (n [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean Crohn's Disease Activity Index (CDA1) (range or SD): mean range 90.4-106.4         CD location (n [%]): small bowel (11/33 [33.3), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention         Elemental nutrition group: elemental nutrition (EO28)         Intervention 2 group: polymeric nutrition (Fortisip)         Intervention 3 group: NA         Outcomes (listy): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDA1)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDA1 ≥00 or increased by 100 points from base	Total number of patien	nts alloc	ated to mainte	enance treatment: 33	_				
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d of withdrawal Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perinal disease, previous intolerance to enteral feeding or unwilling to give formal written consent Characteristics of participants (total study sample) Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76 Women (n [%)): 23/33 [70.7] Racc/ethnicity (n [%)): NR Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria Mean Crohn's Disease Activity Index (CDA1) (range or SD): mean range 90.4-106.4 CD location (n [%)): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0]) Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d) Previous surgery (n [%]): NR Intervention 2 group: polymeric nutrition (EO28) Intervention 2 group: polymeric nutrition (Fortisip) Intervention 3 group: polymeric nutrition (Fortisip) Intervention 3 group: NA Outcomes ( <i>study</i> -based Values activity (clinical, endoscopic): clinical (CDA1) Definition of remission (clinical, endoscopic): clinical (CDA1) Definition of relapse/recurrence (clinical, endoscopic): clinical (CDA1) Definition of mecasal healing (clinical, endoscopic): clinical (CDA1)≥00 or increased by 100 points from baseline) Definition of mecasal healing (clinical, endoscopic): NR Post-baseline timings of primary outcome assessment: 12 mo Number of patients N	remission and two previ	ous unsu	accessful attem	pts to withdraw steroid that prompted red	currence during or after 30				
Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 [70.7]         Race/ethnicity (n [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean Crohn's Disease Activity Index (CDAI) (range or SD): mean range 90.4-106.4         CD location (n [%]): Small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention         Elemental nutrition group: elemental nutrition (EO28)         Intervention 3 group: NA         Outcomes (study-based)         Primary outcomes (liss): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (CDAI)         Definition of relapses/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)	d of withdrawal			1 1	e				
perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent         Characteristics of participants (total study sample)         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n %): 23/33 [70.7]         Race/ethnicity (n [%]): NR         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean (rohn's Disease Activity Index (CDAI) (range or SD): mean range 90.4-106.4         CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention         Elemental nutrition group: elemental nutrition (EO28)         Intervention 3 group: NA         Outcomes (isduy-based)         Primary outcomes (lisf): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Intervention 3 group         Intervention 3 33         19	Exclusion criteria: recu	irrent sm	all-bowel obst	ruction due to Crohn strictures, signification	nt sepsis including				
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	perianal disease previou	us intole	rance to enteral	feeding or unwilling to give formal writ	ten consent				
Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): 23/33 [70.7]         Race/ethnicity (n [%]): NR         Diagnostic critteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76         Women (n [%]): SIR         Diagnostic critteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean (role %): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic         (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention         Elemental nutrition group: elemental nutrition (EO28)         Intervention 3 group: NA         Outcomes (list): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of nuccosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Intervention 3 group         Allocated to       33         19       14         Analysed (specify       33	Characteristics of part	ticinants	(total study s	amnle)					
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Notice of the term of ter	Woman $(n [\%]) \cdot 23/33$	(years).	40.0 (SD. 2.7)	, Talige. 17-70					
Nate endineration (1 % 0).* NK         Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria         Mean Crohn's Disease Activity Index (CDAI) (range or SD): mean range 90.4-106.4         CD location (n [%)): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic         (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention         Elemental nutrition group: clemental nutrition (EO28)         Intervention 3 group: NA         Outcomes (study-based)         Primary outcomes (list): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (CDAI)         Definition of readises/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Postbaseline timings of primary outcome assessment: 12 mo         Number of patients         Intervention 3 group         Allocated to       33         19       14         Analysed (specify       33         19       14 (ITT)         NA         Intervention a qroup	Women (ii $[70]$ ). 23/33 [	[/U./] ND							
Diagnostic criteria for CD: standard crimical, radiological, endoscopic and instological criteria         Mean Crohn's Disease Activity Index (CDAI) (range or SD): mean range 90.4-106.4         CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic         (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention         Elemental nutrition group: elemental nutrition (EO28)         Intervention 2 group: polymeric nutrition (Fortisip)         Intervention 3 group: NA         Outcomes (study-based)         Primary outcomes (list): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI)         Definition of nelapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mecosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Allocated to       33       19         12       14       NA         Irreatment       19       14         Analysed (specify       33       19 (ITT)       14 (IPP)	Race/ethnicity (II [%]):	INK ID. stand	land altated as	distant and security and histolesissts					
Mean Croin 's Disease Activity Index (CDAI) (range or SD): mean range 90.4-106.4         CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention         Elemental nutrition group: elemental nutrition (EO28)         Intervention 3 group: NA         Outcomes (study-based)         Primary outcomes ( <i>list</i> ): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (ADAI)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of nucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Vammer of patients         Analysed (specify 33       19 (ITT)         14 (ITT)       NA         Irreatment       27         13 (PP)       14 (PP)         (If more than one       (PP)         (If more than one       (PP)         (If more than one       (PP)	Diagnostic criteria for C	D: stand	lard clinical, ra	diological, endoscopic and histological c	riteria				
CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic         (2/33 [6.0])         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention         Elemental nutrition group: elemental nutrition (EO28)         Intervention 2 group: polymeric nutrition (Fortisip)         Intervention 3 group: NA         Outcomes ( <i>list</i> ): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Allocated to         33         Allocated to         Allocated to         19         Allocated to         27         14 (PP)         (If more than one         (PP)         14 (PP)	Mean Cronn's Disease A	Activity	Index (CDAI)	(range or SD): mean range $90.4-106.4$					
(2/3) (5.0))         Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)         Intervention         Elemental nutrition group: clemental nutrition (EO28)         Intervention 3 group: polymeric nutrition (Fortisip)         Intervention 3 group: intervention 3 group: polymeric nutrition (Fortisip)         Intervention 3 group: NA         Outcomes (study-based)         Primary outcomes (list): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (CDAI)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         It for al anutrition group         Intervention 3 group         Allocated to       33         19       14         Analysed (specify       33         27       13 (PP)         14 (PP)       (If more than one (PP)         (If more than one (PP)       14 (PP)	CD location (n $[\%]$ ): sm	all bowe	el (11/33 [33.3]	), colon $(10/33 [30.3])$ , mixed cites $(10/3)$	33 [30.3]), anastomotic				
Type of induction therapy (e.g., medical, surgical): medical (predinisolone; mean dose 7.0 (0.5) mg/d)         Previous surgery (n [%]): NR         Intervention         Elemental nutrition group: elemental nutrition (EO28)         Intervention 3 group: NA         Outcomes (study-based)         Primary outcomes (lish): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)	$(2/33 \ [6.0])$	1	1. 1 .		0 (0 5) (1)				
Previous surgery (n [%]): NR         Intervention         Elemental nutrition group: elemental nutrition (EO28)         Intervention 2 group: polymeric nutrition (Fortisip)         Intervention 3 group: NA         Outcomes (study-based)         Primary outcomes ( <i>list</i> ): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Intervention 3 group         Allocated to       33       19 (ITT)       NA         Analysed (specify       33       19 (ITT)         Allocated to       33       19 (ITT)       NA         Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2"         Outcome secolspa	Type of induction therap	py (e.g.,	medical, surgic	cal): medical (prednisolone; mean dose 7	.0 (0.5)  mg/d				
Intervention         Elemental nutrition group: elemental nutrition (EO28)         Intervention 2 group: polymeric nutrition (Fortisip)         Intervention 2 group: polymeric nutrition (Fortisip)         Intervention 2 group: polymeric nutrition (Fortisip)         Intervention 3 group: NA         Outcomes (Study-based)         Primary outcomes (list): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Intervention 3 group         Intervention 3 group         Allocated to 133       19       14       NA         Allocated to 133       19 (ITT)       14 (ITT)       NA         Intervention 3 group       Intervention 3 group </td <td>Previous surgery (n [%]</td> <td>): NR</td> <td></td> <td></td> <td></td>	Previous surgery (n [%]	): NR							
Elemental nutrition group: elemental nutrition (EO28)         Intervention 2 group: polymeric nutrition (Fortisip)         Intervention 3 group: NA         Outcomes (study-based)         Primary outcomes (list): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (absence of diarnhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)	Intervention								
Intervention 2 group: polymeric nutrition (Fortisip)         Intervention 3 group: NA         Outcomes (study-based)         Primary outcomes (list): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Intervention 3 group         Allocated to         Allocated to         Analysed (specify       33       19 (ITT)       14 (ITT)         NA         Mater the more than one (PP)         Intervention 3 (PP)	Elemental nutrition gr	oup: ele	mental nutritio	n (EO28)					
Intervention 3 group: NA         Outcomes (study-based)         Primary outcomes (list): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)       Definition of remission (clinical, endoscopic): clinical (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)       Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo       Intervention 3 group       Intervention 3 group         Allocated to       33       19       14       NA         Itra and/or per       (ITT)       14 (ITT)       NA         ITT and/or per       27       13 (PP)       14 (PP)       NA	Intervention 2 group: 1	polymeri	c nutrition (For	rtisip)					
Outcomes (study-based)         Primary outcomes (list): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         V         Allocated to       33       19       14         Analysed (specify)       33       19 (ITT)       14 (ITT)       NA         ITT and/or per       (ITT)       27       13 (PP)       14 (PP)       NA         (If more than one       (PP)       14 (PP)       Intervention and patients       Intervention and patients	Intervention 3 group: 1	NA							
Primary outcomes ( <i>list</i> ): remission maintenance rate, time to relapse         Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)	Outcomes (study-based	d)							
Measure of disease activity (clinical, endoscopic): clinical (CDAI)         Definition of remission (clinical, endoscopic): clinical (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Intervention 3 group         Allocated to         33       19       14         TT and/or per (ITT)       14 (ITT)       NA         If more than one (PP)       14 (PP)         (If more than one (PP)	Primary outcomes (list	t): remiss	sion maintenan	ce rate, time to relapse					
Definition of remission (clinical, endoscopic): clinical (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)         Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo       Intervention 3 group         Number of patients       Total       Elemental nutrition group       Intervention 3 group         Allocated to       33       19       14       NA         ITT and/or per protocol)       27       13 (PP)       14 (PP)       NA         (If more than one follow-un choose and       27       13 (PP)       14 (PP)       Intervention and point in the follow-un choose and	Measure of disease act	ivity (cli	inical, endosco	<b>pic</b> ): clinical (CDAI)					
the 2 weeks preceding the study, and ESR<20 mm/h)	Definition of remission	(clinica	d. endoscopic)	clinical (absence of diarrhoea and abdo	minal pain. CDAI<150 in				
Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)         Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Image: Total for the provide mark of the prime system of the pri	the 2 weeks preceding the	he study.	and ESR< $20$ r	nm/h)					
Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients         Image: Contract of the point of the	Definition of relapse/re	ecurrenc	re (clinical, en	<b>doscopic</b> ): clinical (CDAI >200 or incre	ased by 100 points from				
Definition of mucosal healing (clinical, endoscopic): NR         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients       Total       Elemental nutrition       Polymeric nutrition group       Intervention 3 group         Allocated to       33       19       14       NA         treatment       -       -       -         Analysed (specify protocol)       33       19 (ITT)       14 (ITT)       NA         ITT and/or per protocol)       -       -       -       -         27       13 (PP)       14 (PP)       -       -       -         (If more than one follow-un choose and follow-un choose	haseline)		ee (ennieur, en		used by 100 points nom				
Definition of indecisal nearing (clinical, endoscopic): NK         Post-baseline timings of primary outcome assessment: 12 mo         Number of patients       Total       Elemental nutrition group       Intervention 3 group         Allocated to       33       19       14       NA         treatment       33       19 (ITT)       14 (ITT)       NA         ITT and/or per protocol)       27       13 (PP)       14 (PP)       Intervention       Intervention         If more than one       (PP)       14 (PP)       Intervention       Intervention       Intervention	Definition of mucocal b	haaling (	clinical and a	sconic): NP					
Number of patients         Total       Elemental nutrition       Polymeric nutrition group       Intervention 3 group         Allocated to treatment       33       19       14       NA         Analysed (specify protocol)       33       19 (ITT)       14 (ITT)       NA         27       13 (PP)       14 (PP)       Intervention 3 group         (If more than one follow-up, choose and       (PP)       14 (PP)       Intervention 3 group	Post baseline timings of	of nrima	ry outcome as	scopic). NK					
Number of patients       Total       Elemental nutrition group       Polymeric nutrition group       Intervention 3 group         Allocated to treatment       33       19       14       NA         Analysed (specify ITT and/or per protocol)       33       19 (ITT)       14 (ITT)       NA         (If more than one follow-up, choose and       27       13 (PP)       14 (PP)       It (PP)       It (PP)	T ost-baseline timings of	л ріша	Ty outcome as	sessment. 12 mo					
Iotal     Elemental nutrition group     Forymeric nutrition group     Intervention 3 group       Allocated to     33     19     14       treatment	rumber of patients	Total	Flowertal	Dolumonio nutviti ou succes	Intervention 2 more				
nutrition groupnutrition groupAllocated to treatment331914Analysed (specify protocol)3319 (ITT)14 (ITT)ITT and/or per protocol)(ITT)14 (ITT)NA2713 (PP)14 (PP)14 (PP)(If more than one follow-up, choose and(PP)14 (PP)14 (PP)		Total	Liemental	Forymeric nutrition group	intervention 3 group				
Allocated to treatment331914NAAnalysed (specify protocol)3319 (ITT)14 (ITT)NAITT and/or per protocol)(ITT)14 (PP)Itt (PP)Itt (PP)(If more than one follow-up, choose and(PP)Itt (PP)Itt (PP)Itt (PP)			nutrition						
Allocated to331914NAtreatment114NAAnalysed (specify protocol)3319 (ITT)14 (ITT)NAITT and/or per protocol)(ITT)14 (PP)ItIt(If more than one follow-up, choose and(PP)14 (PP)ItIt			group						
treatmentImage: constraint of the systemAnalysed (specify3319 (ITT)14 (ITT)NAITT and/or per protocol)(ITT)14 (ITT)ITTprotocol)Image: constraint of the system14 (PP)Image: constraint of the system(If more than one follow-up, choose and(PP)Image: constraint of the systemImage: constraint of the system	Allocated to	33	19	14	NA				
Analysed (specify ITT and/or per protocol)33 (ITT)19 (ITT)14 (ITT)NA2713 (PP)14 (PP)(If more than one follow-up, choose and(PP)14 (PP)	treatment								
ITT and/or per protocol)     (ITT)       27     13 (PP)       (If more than one follow-up, choose and     (PP)	Analysed (specify	33	19 (ITT)	14 (ITT)	NA				
protocol)2713 (PP)14 (PP)(If more than one follow-up, choose and(PP)14 (PP)	ITT and/or per	(ITT)							
(If more than one follow-up, choose and2713 (PP)14 (PP)	protocol)								
(If more than one (PP) follow-up, choose and	·	27	13 (PP)	14 (PP)					
follow-up choose and	(If more than one	(PP)							
	follow-up, choose and	、 - <i>)</i>							

specify the last one)							
Losses to follow-	6	6	0		NA		
up/drop out/sample							
attrition							
(If more than one							
follow-up choose and							
specify the last one)							
Interventions	I						
	T T		Docor	intion			
	Description (a.g. formula manufacturar caloria contant turns made does and duration of						
	(e.g., formula manufacturer, calorie content, type, mode, dose, and duration of						
	auministration)						
		Die	et	intervention			
Elemental nutrition	Orally	Drally taken (EO28, Scientific Hospital Steroids/prednisol			blone $(n=19; 6.5 (0.8) mg)$		
group	Supplie	es Ltd, Liverpoo	bool, UK); sachetsAzathioprine (n=6; dose: NR)				
	contain	ning powdered f	eed mixed with tap	5ASA (n=3; dose	e: NR)		
	water (	(20 g/100 ml); e	nergy content 76				
	Kcal pe	er 20g/100 ml; t	the mean daily intake	Duration: 12 mo			
	730 (ra	unge 600–1017)	Kcal				
	Unrest	ricted normal di	et				
	Duratio	on: 12 mo					
Polymeric nutrition	Orally	taken (Fortisip,	Nutricia, UK);	Steroids/prednise	olone (n=14; 7.1 (0.9) mg)		
group	ready-t	o-drink cartons	(200 ml); energy	Azathioprine (n=	8; dose: NR)		
	content	t 150 Kcal per 1	00 ml; the mean	5ASA (n=2; dose	e: NR)		
	daily ir	ntake 730 (range	e 600–1017) Kcal				
				Duration: 12 mo			
	Unrest	ricted normal di	iet				
	Duratio	on: 12 mo					
Intervention 3 group	NA			NA			
Intervention 3 group Patient baseline chara	NA cteristic	8		NA			
Intervention 3 group Patient baseline chara	NA cteristics Elem	s ental nutrition	Polymeric n	NA utrition group	Intervention 3 group		
Intervention 3 group Patient baseline chara	NA cteristics Elem	s ental nutrition group	Polymeric n	NA utrition group	Intervention 3 group		
Intervention 3 group Patient baseline chara Age (years)	NA cteristic Elema 41.7 (5.	s ental nutrition group .4)	<b>Polymeric n</b> 44.1 (3.2)	NA utrition group	Intervention 3 group NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD)	NA cteristic Elem 41.7 (5.	s ental nutrition group .4)	<b>Polymeric n</b> 44.1 (3.2)	NA utrition group	Intervention 3 group NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex –female n/N (%)	NA cteristic: Elema 41.7 (5. 13/19 (	s ental nutrition group (4) 68.4)	Polymeric n           44.1 (3.2)           9/14 (64.3)	NA utrition group	Intervention 3 group         NA         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex –female n/N (%) Weight (kg)	NA cteristics Elema 41.7 (5. 13/19 (d 62.4 (3.	s ental nutrition group .4) .68.4) .4)	Polymeric n           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)	NA utrition group	Intervention 3 group         NA         NA         NA         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD)	NA           cteristic:           Elema           41.7 (5.)           13/19 (0           62.4 (3.)	s ental nutrition group .4) 68.4) .4)	Polymeric n           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)	NA utrition group	Intervention 3 group       NA       NA       NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex –female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> )	NA cteristic Elema 41.7 (5. 13/19 ( 62.4 (3. 21.8 (1.	s ental nutrition group .4) 68.4) .4) .2)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)	NA utrition group	Intervention 3 group       NA       NA       NA       NA       NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex –female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD)	NA           cteristic:           Elema           41.7 (5.)           13/19 (0           62.4 (3.)           21.8 (1.)	s ental nutrition group .4) 68.4) .4) .2)	Polymeric n           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)	NA utrition group	Intervention 3 group       NA       NA       NA       NA       NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%)	NA cteristic: Elema 41.7 (5. 13/19 ( 62.4 (3. 21.8 (1. NR	s ental nutrition group (4) (68.4) (4) (2)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel	NA cteristic: Elema 41.7 (5) 13/19 (0 62.4 (3) 21.8 (1) NR NR	s ental nutrition group (4) (68.4) (4) (2)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           NR	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%)	NA           cteristic:           Elema           41.7 (5.           13/19 (0           62.4 (3.           21.8 (1.           NR           NR	s ental nutrition group .4) .68.4) .4) .2)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           NR	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD	NA           cteristic:           Elema           41.7 (5.)           13/19 (0           62.4 (3.)           21.8 (1.)           NR           NR           154.4 (3.)	s ental nutrition group .4) .68.4) .4) .2) 37.2)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           NR           123.6 (26.4)	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months)	NA           cteristic:           Elema           41.7 (5.)           13/19 (0           62.4 (3.)           21.8 (1.)           NR           NR           154.4 (2)	s ental nutrition group .4) 68.4) .4) .2) 37.2)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           NR           123.6 (26.4)	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex –female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD)	NA cteristic: Elema 41.7 (5. 13/19 (f 62.4 (3. 21.8 (1. NR NR NR 154.4 (f	s ental nutrition group .4) 68.4) .4) 2) 37.2)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           NR           123.6 (26.4)	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex –female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease	NA           cteristic:           Elema           41.7 (5.)           13/19 (0           62.4 (3.)           21.8 (1.)           NR           NR           154.4 (3.)           106.4 (1.)	s ental nutrition group (4) (68.4) (4) (2) (37.2) (14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           NR           123.6 (26.4)           90.4 (17.8)	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease Activity Index	NA           cteristic:           Elema           41.7 (5.)           13/19 (0           62.4 (3.)           21.8 (1.)           NR           NR           154.4 (3.)           106.4 (1.)	s ental nutrition group (4) (68.4) (4) (2) (37.2) (14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           NR           123.6 (26.4)           90.4 (17.8)	NA utrition group	Intervention 3 groupNANANANANANANANANANANANA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease Activity Index (CDAI)	NA           cteristic:           Elema           41.7 (5.           13/19 ((           62.4 (3.           21.8 (1.           NR           NR           154.4 (1)           106.4 (1)	s ental nutrition group (4) (68.4) (4) (2) (37.2) (14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           NR           123.6 (26.4)           90.4 (17.8)	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease Activity Index (CDAI) Mean (SD)	NA           cteristic:           Elema           41.7 (5.           13/19 (0           62.4 (3.           21.8 (1.           NR           NR           154.4 (1)           106.4 (1)	s ental nutrition group (4) (68.4) (4) (2) (37.2) (14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           123.6 (26.4)           90.4 (17.8)	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease Activity Index (CDAI) Mean (SD) Crohn's Disease	NA           cteristic:           Elema           41.7 (5.           13/19 (0           62.4 (3.           21.8 (1.           NR           154.4 (1)           106.4 (1)           NR	s ental nutrition group (4) (68.4) (4) (2) (37.2) (14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           123.6 (26.4)           90.4 (17.8)           NR	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease Activity Index (CDAI) Mean (SD) Crohn's Disease Endoscopic Index of	NA           cteristic:           Elema           41.7 (5.           13/19 (0           62.4 (3.           21.8 (1.           NR           154.4 (1)           106.4 (1)           NR	s ental nutrition group (4) (68.4) (4) (2) (37.2) (14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           123.6 (26.4)           90.4 (17.8)           NR	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease Activity Index (CDAI) Mean (SD) Crohn's Disease Endoscopic Index of Severity (CDEIS)	NA           cteristic:           Elema           41.7 (5.           13/19 (0           62.4 (3.           21.8 (1.           NR           154.4 (3.           106.4 (           NR	s ental nutrition group .4) 68.4) .4) .2) 37.2) 14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           123.6 (26.4)           90.4 (17.8)           NR	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease Activity Index (CDAI) Mean (SD) Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)	NA           cteristic:           Elema           41.7 (5.)           13/19 (0           62.4 (3.)           21.8 (1.)           NR           154.4 (1)           106.4 (1)           NR	s ental nutrition group (4) (68.4) (4) (2) (37.2) (14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           123.6 (26.4)           90.4 (17.8)           NR	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease Activity Index (CDAI) Mean (SD) Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD) Disease activity	NA           cteristic:           Elema           41.7 (5.)           13/19 (0           62.4 (3.)           21.8 (1.)           NR           154.4 (3.)           106.4 (1.)           NR           NR           NR           NR           NR           NR           NR           NR	s ental nutrition group (4) (68.4) (4) (2) (37.2) (14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           123.6 (26.4)           90.4 (17.8)           NR           NR	NA utrition group	Intervention 3 group         NA         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease Activity Index (CDAI) Mean (SD) Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD) Disease activity other than CDAI	NA           cteristic:           Elema           41.7 (5.)           13/19 ((           62.4 (3.)           21.8 (1.)           NR           154.4 (3.)           106.4 (           NR           NR           NR           NR           NR	s ental nutrition group (4) (68.4) (4) (2) (37.2) (14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           123.6 (26.4)           90.4 (17.8)           NR           NR	NA utrition group	Intervention 3 group         NA		
Intervention 3 group Patient baseline chara Age (years) Mean (SD) Sex -female n/N (%) Weight (kg) Mean (SD) BMI (kg/m <sup>2</sup> ) Mean (SD) Smoking n/N (%) Previous bowel resection n/N (%) Duration of CD (months) Mean (SD) Crohn's Disease Activity Index (CDAI) Mean (SD) Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD) Disease activity other than CDAI (specify)	NA           cteristic:           Elema           41.7 (5.           13/19 ((           62.4 (3.           21.8 (1.           NR           154.4 (3.           106.4 (           NR           NR           NR           NR           NR           NR	s ental nutrition group (4) (68.4) (4) (2) (37.2) (14.9)	Polymeric m           44.1 (3.2)           9/14 (64.3)           71.4 (7.7)           24.4 (1.6)           NR           123.6 (26.4)           90.4 (17.8)           NR           NR	NA utrition group	Intervention 3 group         NA		
n/N (%)							
--------------------------	---------------------------	-----------------	----------------	----------------------			
Other complications	NR	NR		NA			
n/N (%)							
Efficacy outcomes							
For each timing of asse	ssment please provide a s	separate table					
For scores, extract only	total scores	$rac{1}{2}$					
Post-baseline follow-up	Flemental	Polymeric	Intervention 3	Rotwoon_groun			
	nutrition group	nutrition group	group	difference			
	nutrition group	nutrition group	group	p value			
				(or 95% CI)*			
Patients remaining	8/19 (42.1)	6/14 (42.8)	NA	p=NR (NS) study			
in remission n/N (%)				reported			
				RR=0.98 (0.44, 2.19)			
				calculated			
Duration of	NR	NR	NA	NA			
remission (months)							
Rick of release or	8/19 (42 1)	5/14 (35 7)	NA	n-NR (NS) study			
recurrence n/N (%)	0/19 (42.1)	5/14 (55.7)		reported			
				RR=1.18 (0.48. 2.83)			
				calculated			
Time to relapse	NR	NR	NA	NA			
(months)							
Mean (SD) or 95% CI		ND.		<b>X X A</b>			
Survival rate (%	NR	NR	NA	NA			
patients in remission							
relansed)							
(Kaplan-Meier							
estimate and 95% CI)							
Patients achieving	NR	NR	NA	NA			
mucosal healing n/N							
(%)							
Crohn's Disease	NR	NR	NA	NA			
Activity Index							
(CDAI) Mean (SD)							
The Short Form	NR	NR	NA	NA			
Health Survey (SF-							
36)							
Mean (SD)							
95% CI							
The Short Form	NR	NR	NA	NA			
Health Survey (SF-							
$\frac{12}{Mean}$ (SD)							
95% CI							
The Euro-Qol	NR	NR	NA	NA			
questionnaire (EQ-							
5D)							
Mean (SD)							
95% Cl	ND	ND	NA	ΝΔ			
(specify) Mean (SD)			INA				
95% CI							
Weight (kg)	NR	NR	NA	NA			
Mean (SD)							
95% CI							

Weight gain (kg)	NR	NR	NA	NA
Mean change (SD)				
95% CI	ND	ND	N A	NI A
Body mass index $(kg/m^2)$	INK	INK	NA	NA
( <b>kg/III</b> ) Mean change (SD)				
95% CI				
Height gain (cm)	NR	NR	NA	NA
Mean (SD)				
95% CI				
Linear growth rate	NR	NR	NA	NA
(mean height-for-age				
Z-score)				
Adherence n/N (%)	13/19 (68.4)	14/14 (100.0)		RR=0.68 (0.50, 0.92)
				calculated; in favour of
				polymeric nutrition
NT	ND	ND	NT A	group
n/N (%)	NK	NK	NA	NA
Steroid dose	NR	NR	NA	NA
tapering n/N (%)			1 11 1	
Withdrawal from	8/19 (42.1)	6/14 (42.8)		p=NR (NS) study
steroids n/N (%)	× ,	~ /		reported
				RR=0.98 (0.44, 2.19)
				calculated
Adverse events due	NR	NR	NA	NA
to treatment n/N (%)				
Complications - Numb	er (%) of patients with	1 an event ify the last follow up]		
	Flemental nutrition	Polymeric	Intervention	3 Retween-groun
	group	nutrition group	group	difference
	81	BP	8- • • F	p value
				(or 95% CI)*
<b>Impaired growth</b> n/N (%)	ND		NA NA	
	INIX	NR	NA	NA
Delay in pubertal	NR	NR NR	NA NA	NA NA
Delay in pubertal development	NR	NR NR	NA NA	NA NA
<b>Delay in pubertal</b> development n/N (%)	NR	NR NR	NA NA	NA NA
Delay in pubertal development n/N (%) Bowel obstruction	NR	NR NR NR	NA NA NA	NA NA NA
Delay in pubertal development n/N (%) Bowel obstruction Fistulae	NR NR NR	NR NR NR NR	NA NA NA NA	NA NA NA NA
Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess	NR NR NR NR NR	NR NR NR NR NR NR NR	NA NA NA NA NA	NA NA NA NA NA
Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer	NR NR NR NR NR NR	NR NR NR NR NR NR NR	NA NA NA NA NA	NA NA NA NA NA NA
Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection	NR NR NR NR NR NR NR NR NR	NR NR NR NR NR NR NR NR NR	NA NA NA NA NA NA NA	NA NA NA NA NA NA NA NA
Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify)	NR	NR	NA NA NA NA NA NA NA NA NA	NA NA NA NA NA NA NA NA NA NA
Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclusion	NR	NR	NA NA NA NA NA NA NA NA	NA
Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclusion The two formulas are si	NR NR NR NR NR NR NR MR milar in maintaining rer	NR	NA NA NA NA NA NA NA relapse, or withdra	NA         wal from steroids use
Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclusion The two formulas are si Reviewer's conclusion	NR NR NR NR NR NR NR milar in maintaining rer	NR NR NR NR NR NR NR NR NR nssion rate and risk of	NA NA NA NA NA NA NA relapse, or withdra	NA NA NA NA NA NA NA NA wal from steroids use

The two formulas are similar in maintaining remission rate, risk of relapse, or withdrawal from steroids use \* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

## Non-RCTs

Name of first r	Name of first reviewer: Alexander Tsertsvadze					
Name of second	l reviewer	: Tara Gurur	ng			
Study details			51			
First author su	rname yea	r of publicat	ion: Hirakawa 1993 <sup>51</sup>			
Country: Japan						
Study design: n	on random	ised controlle	d trial			
Study setting (p	orimary car	e/specialty cli	nic/other - specify): pri	mary care		
Number of cen	tres: one					
Total length of	follow up:	48 mo				
Funding (gover	mment/priv	ate/manufactu	rer/other - specify): NI	R		
Aim of the stud	ly					
To compare the	effects of e	elemental nutr	ition alone, combinatio	n of elemental nutrition and drug	gs, drugs alone, and no	
intervention on	maintenanc	e of remission	n in CD pts		-	
Participants			_			
Recruitment da	ates: NR					
Total N of pati	ents who r	eceived induc	ction therapy: 84			
Total N of pati	ents achiev	ing remission	n after induction thera	apv: 67		
Total N of patie	ents unabl	e to achieve r	emission after inducti	on therapy: NR		
Total N of patie	ents exclud	led before sta	rt of maintenance the	rapy (e.g., in relapse, lost to fo	llow up): NR	
Total number of	of patients	allocated to a	maintenance treatmen	it: 61		
Inclusion criter	ia: pts with	n CD in remis	sion			
Exclusion crite	ria: pts wit	h active CD				
Characteristics	of partici	pants (total s	tudy sample)			
Mean (range or	SD) age (v	ears): mean 2	1.9-27.0			
Women (n [%])	$\cdot 14/53$ [26	4]				
Race/ethnicity (	n [%])· NR	•••]				
Diagnostic crite	ria for CD.	Criteria of th	e Jananese Society Gas	troenterology		
Mean Crohn's I	)isease Act	ivity Index (C	'DAI) (range or SD) <sup>,</sup> m	ean $61.6-69.3$		
CD location (n l	[%]). small	howel (5/53 [	(1011) (range of $5D$ ). In $(6/5)$	3 [11 3] small and large howels	(42/53 [79 2])	
Type of induction	n therapy (	le g medical	surgical): elemental n	(25/53 [47 1]), small and large bowers	nutrition and drugs	
(23/53 [43 4])	lruge along	(5.9., 11001001, (5.753, 10.41))	surgical). cicilicital in	(25/55 [47.1]), elemental	nutrition and drugs	
(25/55 [45.4]), C	$(n [0/1)) \cdot N$	(J/JJ [J.+])				
Intervention	y (II [ /0]). I					
Flomontal nutr	ition anou	n. alamantal r	utrition			
Intervention 2	mount alor	<b>p</b> . elementar i poptol putritic	nulluon n danga (sulfacelozin	a 2 g/d or produiselone 10 mg/d)		
Intervention 2	group. elei	a (aulfocolog	ine 2 g/d or predniselen	a 10 mg/d		
Intervention 5	group: aru group: Mo	gs (suffasataz	the sg/d or predifisoion	e rollg/d)		
Intervention 4	group: No	Intervention				
Outcomes (stud	iy-based)	1.0.				
Primary outcom	mes (list): c	cumulative co	ntinuous remission rate			
Measure of dis	ease activit	ty (clinical, ei	ndoscopic): CDAI and	International Organization for th	he Study of Inflammatory	
Bowel Disease (	(IOIBD) sc	ores				
Definition of re	emission (c	linical, endos	copic): IOIBD score (v	value: NR) and normal values of	ESR and CRP	
Definition of re	lapse/recu	rrence (clinic	cal, endoscopic): recur	rence of subjective/objective syn	nptoms (increase of the	
IOIBD score by	$\geq 2$ , enhance	ed ESR, and	positive CRP)			
Definition of m	ucosal hea	ling (clinical	, endoscopic): NR			
Post-baseline ti	mings of p	orimary outco	ome assessment: 12, 24	4, 36, and 48 mo		
Number of pati	ients	l				
	Total	Elemental	Elemental	Drugs group	No intervention group	
		nutrition	nutrition + drugs			
		group	group			
Allocated to	61	25	22	8	6	
treatment						
Analysed	(n=53)	22	17	8	6	
(specify ITT	Per					
and/or per	protocol					
protocol)	-					
- ^						
(If means than						

one follow-up,					
choose and					
specify the					
Tast one)	0	2	5	0	0
follow-	0	3	5	0	0
un/dron					
out/sample					
attrition					
(If more than					
one follow-up,					
choose and					
specify the					
last one)					
Interventions	1				
	1	<b>C</b> 1		Description	
	(e.g.,	, formula man	ufacturer, calorie conte	ent, type, mode, dose, and duration	on of administration)
Elementel	> 20 1-201/1	DI La IDW/d the	et	Co-Interve	ention
nutrition	>50 Kcal/i	kg ID W/U UII Jamantal anta	ral hyperalimentation	-	
group	Actual con	nsumption: 3 <sup>4</sup>	5.2 (SD-4.8) $k_{cal}/k_{ca}$		
group	IBW/d	iisumption. 5.	(5D - 4.0) Keal/Kg		
	Brand: NH	R			
	Duration of	of EN: NR			
	Restricted	l diet addition	ally		
Elemental	>30 kcal/l	kg IBW/d thro	ough nasoenteral tube	NR	
nutrition +	as home e	elemental ente	ral hyperalimentation		
drugs group	Actual con	nsumption: 3	1.8 (SD=4.4) kcal/kg		
	IBW/d				
	Brand: NE				
	Duration	of EN: NR			
	Sulfasalaz	$z_{ine} \frac{3g}{d} (n=1)$	0)		
	prednisolo	one $10 \text{mg/d}$ (i	n=7)		
	Duration:	NR	,		
	Restricted	l diet addition	ally		
David and	C-1feeeler	-in - 2 - / 1 (n - 1	0)	ND	
Drugs group	Sullasalaz	$2 \ln \theta \cdot 3g/d (n=)$	(0)	NK	
	Duration	NR	I=7)		
	Duration.				
	Restricted	l diet			
No	Restricted	l diet		-	
intervention					
group					
Patient baselin	e character	ristics		_	
	Elementa	al nutrition	Elemental	Drugs group	No intervention group
	gr	oup	nutrition + drugs		
Age (vears)	27.0(7.4)		26.6 (2.4)	219(26)	257(50)
Mean (SD)	21.0(1.4)		20.0 (2.7)	21.9 (2.0)	23.7 (3.0)
Sex –female	3/22 (13.6	<u>5)</u>	6/17 (35.3)	3/8 (37.5)	2/6 (33.3)
n/N (%)		/			
Weight (kg)	NR		NR	NR	NR
Mean (SD)					
<b>BMI</b> $(kg/m^2)$	NR		NR	NR	NR
Mean (SD)					
Smoking n/N	NR		NR	NR	NR

Previous howel resection n/N (%)NRNRNRNRDuration of ( $(S_0)$ )NRNRNRNRDuration of CO (months) Mean (SD)NRNRNRNRDisease Activity Index (CDA1)61.6 (29.2)56.0 (26.6)68.5 (30.2)69.3 (52.1)Disease Activity Index (CDA1)01.6 (29.2)56.0 (26.6)68.5 (30.2)69.3 (52.1)Disease Endoscopic Index of Mean (SD)NRNRNRNRDisease Endoscopic Index of Mean (SD)0.3 (0.5)0.3 (0.5)0.3 (0.5)Disease Endoscopic Index of Mean (SD)0.2 (0.5)0.3 (0.5)0.3 (0.5)0.3 (0.5)Disease Endoscopic Index of Mean (SD)NRNRNRNRMeane MeaneNRNRNAMucesta Meane Meane Meane Meane Meane MeaneNRNANAMeane Meane Meane Meane <th>(%)</th> <th></th> <th></th> <th></th> <th></th> <th></th>	(%)					
	Previous	NR	NR	NR		NR
$ \begin{array}{ c c c c c } resction n/N &   &   &   &   &   &   &   &   &   & $	bowel					
$ \begin{array}{ c c c } (\%) &   &   &   &   &   &   &   &   &   & $	resection n/N					
Duration of CD (months) Mean (SD)         NR         NR         NR         NR           CT (mont 's) Disease Activity Index (CDA1)         61.6 (29.2)         56.0 (26.6)         68.5 (30.2)         69.3 (52.1)           Mean (SD)         .         .         .         .         .           Crohn 's Disease Endoscopic Index of Severity (CDEIS)         NR         NR         NR         NR           Mean (SD)         .         .         .         .         .           Disease Endoscopic Index of Severity (CDEIS)         0.2 (0.5)         0.3 (0.5)         0.3 (0.5)         0.3 (0.5)           Mean (SD)         .         .         .         .         .           Mean (SD)         .         .         .         .         .           Mean (SD)         .         .         .         .         .         .           Mean (SD)         .         .         .         .         .         .         .           Mucosal utceration nN (%)         .	(%)					
$ \begin{array}{ c c c } \mbox{Cronh's} &   &   &   &   &   &   &   &   &   & $	Duration of	NR	NR	NR		NR
$\begin{array}{ c c c c } \hline Mem (SD) & & & & &$	CD (months)					
Crohn's         61.6 (29.2)         56.0 (26.6)         68.5 (30.2)         69.3 (52.1)           Disease Activity Index (CDA1) Mean (SD)         NR         NR         NR         NR           Disease Endoscopic Index of Severity (CDEBS)         NR         NR         NR         NR           Disease Endoscopic Index of Severity (CDEBS)         0.2 (0.5)         0.3 (0.5)         0.3 (0.5)         0.3 (0.5)           Mucosal utceration n/N (%)         NR         NR         NR         NR           Other complications n/N (%)         NR         NR         NR         NR           Efficacy outcomes         Fistula         Fistula 9/17 (53.0)         Fistula 3/8 (37.5)         Fistula 1/6 (16.6)           Efficacy outcomes         Efficacy outcomes         Efficacy outcomes         Fistula separate table         For score, scarter only total scores           Post-baseline follow-up assessment please provide a separate table group         Dragg group         NR         NR         NA           Patients (%)         NR         NR         NR         NR         NA         NA           Patients for score, scarter only total scores         Scarter off your passessment please provide a separate table         Dispersion passes         NA         NA           Patients (nolify) or 95% C1         NR         <	Mean (SD)					
Disease Activity Index (CDA1) Mean (SD)     Intercently and the second bisease Endoscopic Index of Severity (CDE1S) Mean (SD)     NR     NR     NR       Disease Endoscopic Index of Severity (CDE1S)     NR     NR     NR     NR       Disease Mean (SD)     0.2 (0.5)     0.3 (0.5)     0.3 (0.5)     0.3 (0.5)       Disease Endoscopic Index of Severity (CDE1S)     0.2 (0.5)     0.3 (0.5)     0.3 (0.5)     0.3 (0.5)       Disease Mean (SD)     0.2 (0.5)     0.3 (0.5)     0.3 (0.5)     0.3 (0.5)       Disease Endoscopic Index of Severity (DE1S)     NR     NR     NR       Mucosal Uccration and (Sd)     NR     NR     NR       Disease expression (IOBD)     Fistula 9/17 (53.0)     Fistula 38 (37.5)     Ifisula 16 (16.6)       Efficacy outcomest For score, surfact only total scores protile a separate table For score, surfact only total scores group     NR     NR       Efficacy outcomest For score, surfact only total scores group     Elemental nutrition + drugs group     NR     NR       Patients (%)     NR     NR     NR     NR     NA       Patients for score, surfact only total scores group     NR     NR     NA       Patients (months)     NR     NR     NR     NA       Remaining in remission n/N (%)     NR     NR     NR     NA       Risk of realpse or (por 95% CI)<	Crohn's	61.6 (29.2)	56.0 (26.6)	68.5 (30.2)		69.3 (52.1)
Activity Index (CDA1) Mean (SD)       NR       NR       NR       NR       NR         Disease Endoscopic Index of Severity (CDEIS)       NR       NR       NR       NR       NR         Disease Endoscopic Index of Severity (CDEIS)       0.2 (0.5)       0.3 (0.5)       0.3 (0.5)       0.3 (0.5)         Man (SD)       Disease activity other than CDA1       0.3 (0.5)       0.3 (0.5)       0.3 (0.5)       0.3 (0.5)         Mucosal ulceration n/N (%)       Fistula       Fistula 9/17 (S3.0)       Sig (37.5)       Pistula 1/6 (16.6)       Pistula 1/6 (16.6)         Efficacy outcomest For each timing of assessment please provide a separate table For score, schurat only total scores Post-bascline follow-up assessment please provide a separate table for score, schurat only total scores Post-bascline follow-up assessment please provide a separate table for score, schurat only total scores Post-bascline follow-up assessment please provide a separate table for score, schurat only total scores Post-bascline follow-up assessment please provide a separate table for score, schurat only total scores Post-bascline follow-up assessment please provide a separate table for score, schurat only total scores Post-bascline follow-up assessment please provide a separate table for score, schuration of reminsion n/N       NR       NR       NR       NA         Patients reminsion from ths) Mean (SD) or 95% CI       NR       NR       NR       NR       NA         Time to relapse or 95% CI       NR       NR       NR	Disease	0110 (2)12)		0010 (0012)		0,10 (0,211)
Index (CDA1) Mean (SD)NRNRNRNRDisease Endoscopic Index of Severity (CDE18) Mean (SD)NRNRNRNRDisease Endoscopic Index of Severity (CDE18) Mean (SD)0.2 (0.5)0.3 (0.5)0.3 (0.5)0.3 (0.5)Disease than CDA1 (IOBD)0.2 (0.5)0.3 (0.5)0.3 (0.5)0.3 (0.5)0.3 (0.5)Disease than CDA1 (IOBD)0.3 (0.5)0.3 (0.5)0.3 (0.5)0.3 (0.5)0.3 (0.5)Other than CDA1 (IOBD)Fistula 8/22 (36.4)Fistula 9/17 (53.0)Fistula 38 (37.5)NRNREfficacy outcome transming of assessment impig (Specify): 12, 24, and 48 moFistula 16 (16.6)Fistula 16 (16.6)Fistula 16 (16.6)Patients remaining in remaining in rema	Activity					
All and SD)       NR       NR       NR       NR       NR         Disease Endoscopic Index of Severity (COEEIS)       NR       NR       NR       NR       NR         Disease activity other than CDA1 (OIBD)       0.2 (0.5)       0.3 (0.5)       0.3 (0.5)       0.3 (0.5)       0.3 (0.5)         Mucosal ulceration N(%)       NR       NR       NR       NR       NR <b>Other</b> complications N(%)       Fistula 9/27 (3.0)       Si3 (37.5)       1/6 (16.6)       1/6 (16.6) <b>For</b> scores, extract only total scores For scores, extract only total scores Post-baseline follow-up assessment timing (Specify): 12, 24, and 48 mo <b>Brugg group N Between-group</b> difference <b>p</b> value (or 95% CI)* <b>Patients</b> remaision n/N (%)       NR       NR       NR       NR       NA         (%)       NR       NR       NR       NA       NA         (%)       NR       NR       NR       NA       NA         States of thing of assessment please provide a separate table For scores, extract only total scores post-baseline follow-up assessment timing (Specify): 12, 24, and 48 mo       NA       NA         Patients remission n/N (%)       NR       NR       NR       NA         (%)       NR       NR       NR       NA       A	Index					
Network Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)NRNRNRMark Mean (SD)NRNRNRNRDisease severity (CDEIS) Mean (SD)0.3 (0.5)0.3 (0.5)0.3 (0.5)0.3 (0.5)Disease severity (CDEIS) Mucosal ulceration n/N (%)0.2 (0.5)0.3 (0.5)0.3 (0.5)0.3 (0.5)Mucosal ulceration n/N (%)NRNRNRNRMucosal ulceration n/N (%)NRNRNRNRDisease termining of assessment please provide a separate table For scores, extract only total scores groupFistula Scores, extract only total scores groupFistula total scores groupNRPatients remaining in memision n/N (%)NRNRNRNRPatients remaining in remaining in <b< td=""><td>(CDAI)</td><td></td><td></td><td></td><td></td><td></td></b<>	(CDAI)					
InstitutionNRNRNRNRDisease Endoscopic Index of SeverityNRNRNRNRDisease Severity other than CDA10.2 (0.5)0.3 (0.5)0.3 (0.5)0.3 (0.5)Disease Disease activity other than CDA10.2 (0.5)0.3 (0.5)0.3 (0.5)0.3 (0.5)Mucosal underation n/N (%)NRNRNRNRMucosal underation n/N (%)NRNRNRNREfficacy outcomesFistula groupFistula 9/17 (53.0)3/8 (37.5)Fistula 1/6 (16.6)For each fining of assessment please provide a separate table for scores, certact only total scoresFor group nutrition + drugs groupNo intervention groupBetween-group 0 regregroup nutrition + drugs groupPatients remaining in remaining in	Mean (SD)					
$\begin{array}{c c c c c c c } \mbox{Critical bisease} & n. & n$	Crohn's	NR	NR	NR		NR
$ \begin{array}{ c c c c } \hline Diverse Severity (CDEIS) & & & & & & & & & & & & & & & & & & &$	Diconco					
$ \begin{array}{ c c c c c c } Index of Severity (CDE1S) & & & & & & & & & & & & & & & & & & &$	Endoscopic					
Back of (CDEIS) Mean (SD)       Severity (CDEIS)       N       0.3 (0.5)       0.3 (0.5)       0.3 (0.5)         Disease activity other than CDA1 (DIBD)       0.2 (0.5)       0.3 (0.5)       0.3 (0.5)       0.3 (0.5)       0.3 (0.5)         Mucosal ulceration nVN (%)       NR       NR       NR       NR       NR         Efficacy outcomest For scores, extract only total scores Post-baseline follow-up assessment please provide a separate table For scores, extract only total scores Post-baseline follow-up assessment intring (Specify): 12, 24, and 48 mo       NR       NR       NR         Patients remaining in remission n/N (%)       NR       NR       NR       NR       NA         Duration of post-baseline follow-up assessment remission (months) Mean (SD) or 95% CI       NR       NR       NR       NR       NR       NA         Risk of relapse or recurrence nVN (%)       NR       NR       NR       NR       NR       NR       NA         Risk of relapse (months) Mean (SD) or 95% CI       NR       NR       NR       NR       NR       NA         Response (months) Mean (SD) or 95% CI       NR       NR       NR       NR       NR       NA         Risk of relapse (months) Mean (SD) or 95% CI       NR       NR       NR       NR       NR       NA         Survival rate (	Index of					
$ \begin{array}{ c c c c c c } \hline Mean (SD) & 0.3 (0.5$	Soverity					
$ \begin{array}{ c c c c c c } \hline \textbf{NR} \\ \textbf{Mean (SD)} \\ \hline \textbf{Disease} \\ \textbf{activity other} \\ \textbf{activity other} \\ \textbf{Macosal} \\ \textbf{NR} \\ \textbf{Mucosal} \\ \textbf{NR} \\ $	(CDFIS)					
Instance (DZ)     0.2 (0.5)     0.3 (0.5)     0.3 (0.5)     0.3 (0.5)       Disease activity other than CDAI (IO1BD)     0.3 (0.5)     0.3 (0.5)     0.3 (0.5)     0.3 (0.5)       Mucosal ulceration on (N (%)     NR     NR     NR     NR       Other onplications     8/22 (36.4)     9/17 (53.0)     3/8 (37.5)     Ifstula 1/6 (16.6)       Efficacy outcomes     8/22 (36.4)     9/17 (53.0)     3/8 (37.5)     Ifstula 1/6 (16.6)       Efficacy outcomes     Estula 8/22 (36.4)     Fistula 9/17 (53.0)     Drugs group     No     Between-group difference p value (or 95% CI)*       Post-baseline follow-up assessment timing (Specify): 12, 24, and 48 mo     NR     NR     NR       Patients remaining in remission (months) Mean (SD) or 95% CI     NR     NR     NR     NR       NR     NR     NR     NR     NA       relapse or recurrence nN (%)     NR     NR     NR     NA       relapse (months) Mean (SD) or 95% CI     NR     NR     NR     NR     NA       relapse (months)     NR     NR     NR     NA     NA       relapse (months)     NR     NR     NR     NA     NA       Survival rate     12 mo: 63% (NR)     66% (NR)     63% (NR)     50% (NR)     At 48 mo	Mean (SD)					
$ \begin{array}{ c c c c c c } \hline Particular & Particula$	Disease	0.2 (0.5)	03(05)	03(05)		03(05)
$ \begin{array}{ c c c c c } \hline \begin{tabular}{ c c c c c c } \hline \begin{tabular}{ c c c c c c c } \hline \begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	octivity other	0.2 (0.3)	0.5 (0.5)	0.5 (0.5)		0.5 (0.5)
$ \begin{array}{ c c c c c c } \hline line (D) &   &   &   &   &   &   &   &   &   & $	than CDAI					
$\begin{array}{ c c c c c } \hline Mucosal ulceration n/N(\%) & NR & N$	(IOIRD)					
NRNRNRNRNROther complications n/N (%)FistulaFistula PistulaFistula PistulaFistula PistulaFistula PistulaOther complications n/N (%)8/22 (36.4)9/17 (53.0)3/8 (37.5)1/6 (16.6)M/N (%)Efficacy outcomesImage: state of the state	(IOIDD) Mucosal	NP	NP	NP		NP
$ \begin{array}{ c c c c c c } \hline line \\ \hline$	ulceration					
Init(%)       Fistula       Fistula       Fistula       Sistula	n/N (%)					
	Othor	Fistulo	Fistulo	Fistulo		Fistulo
To (10.0)       If (0.0)       If (0.0	Other	Fistula	Tistula	Pistula		1 Istula
Introduction: Intervention of assessment please provide a separate table         For each timing of assessment please provide a separate table         For scores, extract only total scores         Post-baseline follow-up assessment timing (Specify): 12, 24, and 48 mo       Drugs group       No       Between-group         group       nutrition + drugs       prugs group       No       Between-group       difference         Patients       Remaining in       remaining in       Remember       NR       NR       NR       NR         (%)       NR       NR       NR       NR       NR       NR       NA         (%)       NR       NR       NR       NR       NR       NA         (%)       NR       NR       NR       NR       NA         (months)       NR       NR       NR       NA         Relapse or       recurrence       NR       NR       NR       NA         relapse (months)       NR       NR       NR       NA       A         frequence       NR       NR       NR       NA       A         remission (months)       NR       NR       NR       NA       A         frelapse (months)       NR	complications	8/22(36.4)	0/17(530)	3/8(375)		1/6(166)
Initially during of assessment please provide a separate table         For each timing of assessment timing (Specify): 12, 24, and 48 mo       Drugs group       No       Between-group         Patients       Elemental nutrition       Elemental nutrition + drugs group       Drugs group       No       Between-group         Patients       Remaining in remaining in remission n/N (%)       NR       NR       NR       NR       NR         Duration of remaission (months)       NR       NR       NR       NR       NR       NR         fields of recurrence n/N (%)       NR       NR       NR       NR       NR       NA         Time to relapse (months)       NR       NR       NR       NR       NR       NA         Time to recurrence n/N (%)       NR       NR       NR       NR       NA         Survival rate (% patients in 24 mo: 63% (NR)       75% (NR)       63% (NR)       50% (NR)       At 48 mo p<0.05 (1 vs. 3)	complications	8/22 (36.4)	9/17 (53.0)	3/8 (37.5)		1/6 (16.6)
For scores, extract only total scoresPost-baseline follow-up assessment timitor (Specify): 12, 24, and 48 moDrugs groupNo intervention groupBetween-group difference p value (or 95% CI)*Patients remaining in remission n/N (%)NRNRNRNRNADuration of remission (months) Mean (SD) or 95% CINRNRNRNRNRRisk of relapse (months) Mean (SD) or 95% CINRNRNRNRNRRisk of relapse (months) Mean (SD) or 95% CINRNRNRNRNRStrivival rate (%)12 mo: 94% (NR) 24 mo: 63% (NR)75% (NR) 66% (NR)63% (NR)50% (NR) 33% (NR)At 48 mo p<0.05 (1 vs. 3)	complications n/N (%)	8/22 (36.4)	9/17 (53.0)	3/8 (37.5)		1/6 (16.6)
Post-baseline follow-up assessment timing (Specify): 12, 24, and 48 mo       Drugs group       No       Between-group         group       nutrition + drugs group       Drugs group       No       intervention group       Between-group         Patients       NR       NR       NR       NR       NR       NA         remission n/N (%)       NR       NR       NR       NR       NA         Duration of (months)       NR       NR       NR       NR       NA         Risk of recurrence (n/N (%)       NR       NR       NR       NR       NA         Time to relapse (months)       NR       NR       NR       NR       NA         Survival rate (% patients in 24 mo: 63% (NR)       12 mo: 94% (NR)       75% (NR)       63% (NR)       50% (NR)       At 48 mo	complications n/N (%) Efficacy outcom	8/22 (36.4) nes	9/17 (53.0)	3/8 (37.5)		1/6 (16.6)
Elemental nutrition groupElemental nutrition nutrition + drugs groupDrugs group nutrition + drugs groupNo intervention groupBetween-group u difference p value (or 95% CI)*Patients remaining in remission n/N (%)NRNRNRNRNRDuration of (months) Mean (SD) or 95% CINRNRNRNRNRRisk of recurrence (N(%)NRNRNRNRNRTime to relapse (months) Mean (SD) or 95% CINRNRNRNRTime to posh (M)NRNRNRNRRisk of relapse or recurrence (months)NRNRNRNRTime to posh (CI)NRNRNRNRNRSurvival rate (% patients in (24 mo: 63% (NR)75% (NR) 66% (NR)63% (NR)50% (NR)At 48 mo p<0.05 (1 vs. 3)	complications n/N (%) Efficacy outcom For each timing For scores, extr	8/22 (36.4) nes of assessment please pro- act only total scores	9/17 (53.0) ovide a separate table	3/8 (37.5)		1/6 (16.6)
International numberInternational groupInternational groupIntervention politifierence 	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline fo	8/22 (36.4) nes of assessment please pro- act only total scores llow-up assessment timi	9/17 (53.0) ovide a separate table	3/8 (37.5)		1/6 (16.6)
Patients remaining in remission n/N (%)NRNRNRNRDuration of (%)NRNRNRNRNADuration of (%)NRNRNRNRNARemission (months) Mean (SD) or 95% CINRNRNRNRNARisk of relapse or recurrence (months)NRNRNRNRNATime to relapse (months) Mean (SD) or 95% CINRNRNRNRNASurvival rate (%) turned t	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline fo	8/22 (36.4) nes of assessment please pract only total scores llow-up assessment timit Elemental nutrition	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental	3/8 (37.5) d 48 mo	No	1/6 (16.6)
Patients remaining in remission n/N (%)NRNRNRNRDuration of (months) Mean (SD) or 95% CINRNRNRNRNRRisk of n/N (%)NRNRNRNRNRRisk of n/N (%)NRNRNRNRNRTime to relapse (months) Mean (SD) or 95% CINRNRNRNRTime to relapse (months) Mean (SD) or 95% CINRNRNRNRSurvival rate (% patients in 24 mo: 63% (NR)75% (NR)63% (NR)50% (NR)At 48 mo p<0.05 (1 vs. 3)	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline fo	8/22 (36.4) nes of assessment please products act only total scores llow-up assessment timin Elemental nutrition group	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs	3/8 (37.5) d 48 mo Drugs group	No	1/6 (16.6) Between-group difference
Patients remaining in remission n/N (%)NRNRNRNRDuration of remission (months) Mean (SD) or 95% CINRNRNRNRRisk of n/N (%)NRNRNRNRRisk of n/N (%)NRNRNRNRTime to relapse (months) Mean (SD) or 95% CINRNRNRTime to relapse (months) NRNRNRNRSurvival rate (% patients in 24 mo: 63% (NR)75% (NR)63% (NR)50% (NR)At 48 mo p<-0.05 (1 vs. 3)	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline for	8/22 (36.4) nes of assessment please pract only total scores llow-up assessment timit Elemental nutrition group	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group	3/8 (37.5) d 48 mo Drugs group	No interventio group	1/6 (16.6) Between-group difference p value
remaining in remission n/N (%)Image: Second se	complications n/N (%) Efficacy outcon For each timing For scores, extr Post-baseline fo	8/22 (36.4) nes of assessment please product only total scores llow-up assessment timin Elemental nutrition group	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group	3/8 (37.5) d 48 mo Drugs group	No interventio group	1/6 (16.6) Between-group difference p value (or 95% CD)*
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(%)Image: constraint of constrain	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline fo Patients remaining in	8/22 (36.4) nes of assessment please product only total scores llow-up assessment timin Elemental nutrition group NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR	3/8 (37.5) d 48 mo Drugs group	No interventio group NR	1/6 (16.6)           Between-group           on         difference           p value         (or 95% CI)*           NA
Duration of remission (months) Mean (SD) or 95% CINRNRNRNARisk of relapse or recurrence n/N (%)NRNRNRNRNATime to relapse (months) Mean (SD) or 95% CINRNRNRNRNATime to relapse (months) Mean (SD) or 95% CINRNRNRNRNATime to relapse (months) Mean (SD) or 95% CINRNRNRNRNASurvival rate (% patients in 24 mo: 63% (NR)75% (NR) 66% (NR)63% (NR)50% (NR) 33% (NR)At 48 mo p<0.05 (1 vs. 3)	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N	8/22 (36.4) nes of assessment please pre- act only total scores llow-up assessment timin Elemental nutrition group NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR	3/8 (37.5) d 48 mo Drugs group	No interventio group NR	1/6 (16.6) Between-group difference p value (or 95% CI)* NA
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Mean (SD) or 95% CI         Mean (SD) or 95% CI         Mean (SD) or 95% CI         NR         NR         NR         NA           Risk of relapse or recurrence n/N (%)         NR         NR         NR         NA           Time to n/N (%)         NR         NR         NR         NA           Time to relapse (months)         NR         NR         NR         NA           Survival rate (% patients in         12 mo: 94% (NR)         75% (NR)         63% (NR)         50% (NR)         At 48 mo 33% (NR)	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N (%) Duration of remission	8/22 (36.4) nes of assessment please pract only total scores llow-up assessment timit Elemental nutrition group NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR	3/8 (37.5) d 48 mo Drugs group NR	No interventio group NR	1/6 (16.6)           Between-group difference p value (or 95% CI)*           NA
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Risk of relapse or recurrence n/N (%)NRNRNRNATime to relapse (months) Mean (SD) or 95% CINRNRNRNRNASurvival rate (% patients in 24 mo: 63% (NR)75% (NR) 66% (NR)63% (NR) 42% (NR)50% (NR) 33% (NR)At 48 mo p<0.05 (1 vs. 3)	complications n/N (%) Efficacy outcon For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or	8/22 (36.4) nes of assessment please pract only total scores llow-up assessment timin Elemental nutrition group NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR	3/8 (37.5) d 48 mo Drugs group NR	No interventio group NR	1/6 (16.6)         Between-group difference p value (or 95% CI)*         NA         NA
relapse or recurrence n/N (%)relapseImage: second s	complications n/N (%) Efficacy outcon For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI	8/22 (36.4) nes of assessment please pract only total scores llow-up assessment timit Elemental nutrition group NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR	3/8 (37.5) d 48 mo Drugs group NR	No interventio group NR	1/6 (16.6)         Between-group difference p value (or 95% CI)*         NA         NA
recurrence n/N (%)         NR         NR         NR         NA           Time to relapse (months)         NR         NR         NR         NA           Mean (SD) or 95% CI         12 mo: 94% (NR)         75% (NR)         63% (NR)         50% (NR)         At 48 mo p<0.05 (1 vs. 3)	complications n/N (%) Efficacy outcon For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of	8/22 (36.4) nes of assessment please pract only total scores llow-up assessment timin Elemental nutrition group NR NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR NR	3/8 (37.5) d 48 mo Drugs group NR NR	No interventio group NR NR	1/6 (16.6)         Draw         Between-group         difference         p value         (or 95% CI)*         NA         NA         NA         NA
n/N (%)         NR         NR         NR         NA           relapse (months)         NR         NR         NR         NA           Mean (SD) or 95% CI         Participation         Participation         Participation         Participation           Survival rate         12 mo: 94% (NR)         75% (NR)         63% (NR)         50% (NR)         At 48 mo p<0.05 (1 vs. 3)	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or	8/22 (36.4)  nes of assessment please pract only total scores Ilow-up assessment timin Elemental nutrition group NR NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR NR	3/8 (37.5) d 48 mo Drugs group NR NR	No interventio group NR NR	1/6 (16.6)         Between-group difference p value (or 95% CI)*         NA         NA         NA         NA
Time to relapse (months)         NR         NR         NR         NR         NA           Mean (SD) or 95% CI         -	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence	8/22 (36.4) nes of assessment please pract only total scores llow-up assessment timit Elemental nutrition group NR NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR NR	3/8 (37.5) d 48 mo Drugs group NR NR NR	No interventio group NR NR	1/6 (16.6)         Between-group difference p value (or 95% CI)*         NA         NA         NA         NA
relapse (months) Mean (SD) or 95% CI         Image: Constraint of the second secon	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline for Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	8/22 (36.4) nes of assessment please pract only total scores llow-up assessment timit Elemental nutrition group NR NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR NR	3/8 (37.5) d 48 mo Drugs group NR NR NR	NR NR NR	1/6 (16.6)         Dr       Between-group difference p value (or 95% CI)*         NA         NA         NA         NA         NA
(months) Mean (SD) or 95% CI         Image: Constraint of the second	complications n/N (%) Efficacy outcom For each timing For scores, extr Post-baseline for Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%) Time to	8/22 (36.4) nes of assessment please pract only total scores llow-up assessment timit Elemental nutrition group NR NR NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR NR	3/8 (37.5) d 48 mo Drugs group NR NR NR NR	NR NR NR	1/6 (16.6)         Dr       Between-group difference p value (or 95% CI)*         NA         NA         NA         NA         NA         NA         NA
Mean (SD) or 95% CI         Mean (SD) or 95% (NR)	complications n/N (%) Efficacy outcon For each timing For scores, extr Post-baseline for Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%) Time to relapse	8/22 (36.4) nes of assessment please pract only total scores llow-up assessment timin Elemental nutrition group NR NR NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR NR NR	3/8 (37.5) d 48 mo Drugs group NR NR NR NR	NR NR NR NR	1/6 (16.6)         Dr       Between-group difference p value (or 95% CI)*         NA
95% CI         50% (NR)         50% (NR)           Survival rate         12 mo: 94% (NR)         75% (NR)         63% (NR)         50% (NR)         At 48 mo           (% patients in         24 mo: 63% (NR)         66% (NR)         42% (NR)         33% (NR)         p<0.05 (1 vs. 3)	complications n/N (%) Efficacy outcon For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%) Time to relapse (months)	8/22 (36.4)  nes of assessment please pract only total scores Ilow-up assessment timin Elemental nutrition group NR NR NR NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR NR NR	3/8 (37.5) d 48 mo Drugs group NR NR NR NR NR	NR NR NR NR	1/6 (16.6)         Dr       Between-group difference p value (or 95% CI)*         NA
Survival rate         12 mo: 94% (NR)         75% (NR)         63% (NR)         50% (NR)         At 48 mo           (% patients in         24 mo: 63% (NR)         66% (NR)         42% (NR)         33% (NR)         p<0.05 (1 vs. 3)	complications n/N (%) Efficacy outcon For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%) Time to relapse (months) Mean (SD) or	8/22 (36.4)  nes of assessment please pract only total scores Ilow-up assessment timit Elemental nutrition group NR NR NR NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR NR NR	3/8 (37.5) d 48 mo Drugs group NR NR NR NR NR	NR NR NR NR	1/6 (16.6)         Dn       Between-group difference p value (or 95% CI)*         NA         NA         NA         NA         NA         NA         NA         NA
(% patients in       24 mo: $63\%$ (NR) $66\%$ (NR) $42\%$ (NR) $33\%$ (NR) $p<0.05$ (1 vs. 3)	complications n/N (%) Efficacy outcon For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%) Time to relapse (months) Mean (SD) or 95% CI	8/22 (36.4)  nes of assessment please pract only total scores Ilow-up assessment timit Elemental nutrition group NR NR NR NR NR	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR NR NR	3/8 (37.5) d 48 mo Drugs group NR NR NR NR NR	NR NR NR NR	1/6 (16.6)         Draw       Between-group difference p value (or 95% CI)*         NA         NA         NA         NA         NA         NA         NA         NA         NA         NA
	complications n/N (%) Efficacy outcon For each timing For scores, extr Post-baseline fo Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%) Time to relapse (months) Mean (SD) or 95% CI Survival rate	8/22 (36.4)  nes of assessment please pract only total scores Ilow-up assessment timin Elemental nutrition group NR NR NR 12 mo: 94% (NR)	9/17 (53.0) ovide a separate table ng (Specify): 12, 24, an Elemental nutrition + drugs group NR NR NR NR 75% (NR)	3/8 (37.5) d 48 mo Drugs group NR NR NR NR	NR NR NR NR S0% (NR)	1/6 (16.6)         Draw       Between-group difference p value (or 95% CI)*         NA         NA         NA         NA         NA         NA         NA         NA         NA         At 48 mo

remission who have not relapsed)	48 mo: 63% (NR)	66% (NR)	0% (NR)	0% (NR)	SS p<0.01 (1 vs. 4) SS 0.05 (2 4)
(Kaplan- Meier estimate and					p<0.05 (2 vs. 4) SS
95% CI)					$p \ge 0.05 (2 \text{ vs. } 3)$ NS $p \ge 0.05 (1 \text{ vs. } 2)$
Patients achieving mucosal healing n/N	NR	NR	NR	NR	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NR	NR	NA
The Short Form Health Survey (SF- 36) Mean (SD) 95% CI	NR	NR	NR	NR	NA
The Short Form Health Survey (SF- 12) Mean (SD) 95% CI	NR	NR	NR	NR	NA
The Euro- Qol questionnaire (EQ-5D) Mean (SD) 95% CI	NR	NR	NR	NR	NA
Other HQOL (specify) Mean (SD) 95% CI	NR	NR	NR	NR	NA
Weight (kg) Mean (SD) 95% CI	NR	NR	NR	NR	NA
Weight gain (kg) Mean change (SD) 95% CI	NR	NR	NR	NR	NA
Body mass index (kg/m <sup>2</sup> ) Mean change (SD) 95% CI	NR	NR	NR	NR	NA
Height gain (cm) Mean (SD) 95% CI	NR	NR	NR	NR	NA

Linear	NR	NR	NR	NR	NA
growth rate					
(mean					
height-for-					
age Z-score)					
Adherence n/N (%)	22/25 (88.0)	1//22 (77.3)	8/8 (100.0)	6/6 (100.0)	Fisher's exact test p=0.55 [1 vs. 2] NS p=0.84 [1 vs. 3] NS p>0.99 [1 vs. 4] NS
					p=0.37 [2 vs. 3] NS p=0.53 [2 vs. 4] NS calculated
Need for surgery n/N (%)	NR	NR	NR	NR	NA
Steroid dose	NR	NR	NR	NR	NA
tapering n/N (%)					1121
Withdrawal from steroids	NR	NR	NR	NR	NA
Adverse	NR	NR	NR	NR	NA
events due to				1.11	
treatment					
$\Delta T (\alpha ( ) )$					
n/N (%)	N	4			
n/N (%) Complications	- Number (%) of patien	nts with an event	w upl		
n/N (%) Complications [if more than o	- Number (%) of patien ne follow-up, choose an Elemental nutrition	nts with an event ad specify the last follo Flemental	w up]	No	Retween-group
n/N (%) Complications [if more than o	- Number (%) of patien ne follow-up, choose ar Elemental nutrition group	nts with an event ad specify the last follo Elemental nutrition + drugs	w up] Drugs group	No intervention	Between-group difference
n/N (%) Complications [if more than o	- Number (%) of patien ne follow-up, choose an Elemental nutrition group	nts with an event ad specify the last follo Elemental nutrition + drugs group	w up] Drugs group	No intervention group	Between-group difference p value
n/N (%) Complications [if more than o	- Number (%) of patien ne follow-up, choose an Elemental nutrition group	nts with an event nd specify the last follo Elemental nutrition + drugs group	ow up] Drugs group	No intervention group	Between-group difference p value (or 95% CI)*
n/N (%) Complications [if more than of Impaired growth n/N (%)	- Number (%) of patien ne follow-up, choose an Elemental nutrition group	nts with an event ad specify the last follo Elemental nutrition + drugs group NR	w up] Drugs group NR	No intervention group NR	Between-group difference p value (or 95% CI)* NA
n/N (%) Complications [if more than o Impaired growth n/N (%) Delay in	- Number (%) of patien ne follow-up, choose an Elemental nutrition group NR	nts with an event nd specify the last follo Elemental nutrition + drugs group NR	w up] Drugs group NR	No intervention group NR	Between-group difference p value (or 95% CI)* NA
n/N (%) Complications [if more than of Impaired growth n/N (%) Delay in pubertal	- Number (%) of patien ne follow-up, choose an Elemental nutrition group NR	nts with an event ad specify the last follo Elemental nutrition + drugs group NR	w up] Drugs group NR NR	No intervention group NR NR	Between-group difference p value (or 95% CI)* NA
n/N (%) Complications [if more than of Impaired growth n/N (%) Delay in pubertal development	- Number (%) of patien ne follow-up, choose an Elemental nutrition group NR	nts with an event ad specify the last follo Elemental nutrition + drugs group NR	w up] Drugs group NR NR	No intervention group NR NR	Between-group difference p value (or 95% CI)* NA
n/N (%) Complications [if more than of Impaired growth n/N (%) Delay in pubertal development n/N (%)	- Number (%) of patien ne follow-up, choose an Elemental nutrition group NR	nts with an event ad specify the last follo Elemental nutrition + drugs group NR	w up] Drugs group NR NR	No intervention group NR NR	Between-group difference p value (or 95% CI)* NA NA
n/N (%) Complications [if more than of Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel	- Number (%) of patien ne follow-up, choose an Elemental nutrition group NR NR	nts with an event nd specify the last follo Elemental nutrition + drugs group NR NR	w up] Drugs group NR NR NR	No intervention group NR NR	Between-group difference p value (or 95% CI)* NA NA
n/N (%) Complications [if more than of Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction	- Number (%) of patien ne follow-up, choose an Elemental nutrition group NR NR	nts with an event ad specify the last follo Elemental nutrition + drugs group NR NR	w up] Drugs group NR NR NR	No intervention group NR NR NR	Between-group difference p value (or 95% CI)* NA NA
n/N (%) Complications [if more than of Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae	<ul> <li>Number (%) of patients</li> <li>ne follow-up, choose and Elemental nutrition group</li> <li>NR</li> <li>NR</li> <li>NR</li> <li>NR</li> <li>NR</li> </ul>	nts with an event ad specify the last follo Elemental nutrition + drugs group NR NR NR	w up] Drugs group NR NR NR NR	No intervention group NR NR NR NR	Between-group difference p value (or 95% CI)* NA NA NA
n/N (%) Complications [if more than of Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess	<ul> <li>Number (%) of patien</li> <li>ne follow-up, choose an</li> <li>Elemental nutrition group</li> <li>NR</li> <li>NR</li> <li>NR</li> <li>NR</li> <li>NR</li> <li>NR</li> <li>NR</li> </ul>	nts with an event ad specify the last follo Elemental nutrition + drugs group NR NR NR NR	w up] Drugs group NR NR NR NR NR NR	No intervention group NR NR NR NR NR NR	Between-group difference p value (or 95% CI)* NA NA NA NA
n/N (%) Complications [if more than of growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel concer	<ul> <li>Number (%) of patien</li> <li>ne follow-up, choose an</li> <li>Elemental nutrition group</li> <li>NR</li> </ul>	nts with an event nd specify the last follo Elemental nutrition + drugs group NR NR NR NR NR NR NR NR NR	w up] Drugs group NR NR NR NR NR NR NR NR NR NR	No intervention group NR NR NR NR NR NR NR NR NR NR	Between-group         difference         p value         (or 95% CI)*         NA
n/N (%) Complications [if more than of Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer	Number (%) of patien ne follow-up, choose an Elemental nutrition group NR	nts with an event nd specify the last follo Elemental nutrition + drugs group NR NR NR NR NR NR NR NR	w up] Drugs group NR	No intervention group NR NR NR NR NR NR NR NR NR	Between-group         difference         p value         (or 95% CI)*         NA
n/N (%) Complications [if more than of growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection	<ul> <li>Number (%) of patien ne follow-up, choose an Elemental nutrition group</li> <li>NR</li> </ul>	nts with an event ad specify the last follo Elemental nutrition + drugs group NR NR NR NR NR NR NR NR NR NR	w up] Drugs group NR NR NR NR NR NR NR NR NR NR NR	No intervention group NR NR NR NR NR NR NR NR NR NR	Between-group         difference         p value         (or 95% CI)*         NA
n/N (%) Complications [if more than of Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others	Number (%) of patien ne follow-up, choose an Elemental nutrition group NR	nts with an event ad specify the last follo Elemental nutrition + drugs group NR NR NR NR NR NR NR NR NR NR NR NR	w up] Drugs group NR	No intervention group NR NR NR NR NR NR NR NR NR NR NR NR	Between-group         difference         p value         (or 95% CI)*         NA
n/N (%) Complications [if more than of growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify)	Number (%) of patien ne follow-up, choose an Elemental nutrition group NR	nts with an event nd specify the last follo Elemental nutrition + drugs group NR	w up] Drugs group NR	No         intervention         group         NR         NR	Between-group         difference         p value         (or 95% CI)*         NA
n/N (%) Complications [if more than of growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conche	- Number (%) of patien ne follow-up, choose an Elemental nutrition group NR NR NR NR NR NR NR NR NR NR NR NR NR	nts with an event nd specify the last follo Elemental nutrition + drugs group NR NR NR NR NR NR NR NR NR NR	W up] Drugs group NR	No         intervention         group         NR	Between-group         difference         p value         (or 95% CI)*         NA
n/N (%) Complications [if more than of Jelay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclu At 1, 2, and 4 y	Number (%) of patien ne follow-up, choose an Elemental nutrition group  NR  NR  NR  NR  NR  NR  NR  NR  NR  N	nts with an event nd specify the last follo Elemental nutrition + drugs group NR NR NR NR NR NR NR NR NR NR	w up] Drugs group NR On (with/without dr	No intervention group NR NR NR NR NR NR NR NR NR NR NR NR NR	Between-group         difference         p value         (or 95% CI)*         NA         Significantly greater
n/N (%) Complications [if more than of growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conche At 1, 2, and 4 y rates of remission	Number (%) of patien ne follow-up, choose an Elemental nutrition group NR ST	nts with an event nd specify the last follo Elemental nutrition + drugs group NR NR NR NR NR NR NR NR NR NR	w up] Drugs group NR	No         intervention         group         NR         one (but not elements)	Between-group         difference         p value         (or 95% CI)*         NA
n/N (%) Complications [if more than of Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclu At 1, 2, and 4 yr rates of remission drug) was more	Number (%) of patien ne follow-up, choose an Elemental nutrition group NR	nts with an event nd specify the last follo Elemental nutrition + drugs group NR NR NR NR NR NR NR NR NR NR	w up]         Drugs group         NR         on (with/without dremental nutrition al	No         intervention         group         NR         one (but not element	Between-group         difference         p value         (or 95% CI)*         NA

Long term administration of elemental nutrition with or without drugs in pts with CD resulted in improved rates of maintenance of remission compared with no intervention; there was no significant difference in rates of remission maintenance between the two elemental nutrition or two drug groups

Name of first reviewer: alexander Tsertsvadze						
Name of second revie	wer: Ta	ra Gurung				
Study details			57			
First author surname	e year of	publication: Verm	a 2000 <sup>56</sup>			
Country: UK						
Study design: non-ran	domised	controlled trial				
Study setting (primary	y care/sp	ecialty clinic/other -	- specify): specialty clinic			
Number of centres: or	ne					
Total length of follow	<b>up</b> : 24 1	no				
Funding (government	/private/1	manufacturer/other	- specify): NR			
Aim of the study	•					
To evaluate clinical eff	fectivene	ess of adding an eler	nental nutrition taken orally to normal food for	maintaining remission in		
patients with quiescent	t CD ove	r 12 months	, , , , , , , , , , , , , , , , , , ,	6		
Participants						
Recruitment dates: N	R					
Total N of nationts w	ho receiv	vad induction there	anv: 16			
Total N of patients w	hioving	remission often ind	uption thereas: 20			
Total N of patients at	a bla ta	remission after me	attan induction thereas 7			
Total N of patients un	naule lo	achieve renussion	atice muucuon merapy: / ntonongo thorony (o g in rolongo lost to falle	www)• 7		
Total number of re-	onto alla	optod to mointer	ntenance incrapy (e.g., in relapse, lost to long	w up): /		
I otal number of path	ents allo	cateu to maintenai	ice treatment: 37	AI <150 who had have		
<b>Inclusion criteria</b> : pts	with qui	lescent disease delli	ted by the absence of bower symptoms and CD.	AI<150 who had been		
Traduction with either elem	nental nu	in mon or prednisol	one as an induction therapy within preceding 12	, monuns		
Exclusion criteria: Cl	DAI>150	, sepsis, bowel stric	cures leading to recurrent attacks of small bowe	obstruction or previous		
intolerance to enteral f	eeding		• 、			
Characteristics of par	rticipant	ts (total study sam)	ple)			
Mean (range or SD) ag	ge (years)	): mean 39.2 – 42.0	yrs			
Women (n [%]): 27 [6	9.2]					
Race/ethnicity (n [%])	: NR					
Diagnostic criteria for	CD: stan	dard clinical, endos	copic, radiological, and when possible, histolog	gical criteria		
Mean Crohn's Disease	e Activity	r Index (CDAI) (ran	ge or SD): mean 94.6 – 112.8			
CD location (n [%]): st	mall bow	vel (17[43.6]), large	bowel (n=10[25.6]), mixed (n=9[23.0]), anasto	matic (n=3[7.6])		
Type of induction there	apy (e.g.	, medical, surgical):	medical (prednisolone, azathioprine, 5-ASA)			
Previous surgery (n [%	5]): 12 [1	00]				
Intervention						
Elemental nutrition g	group: el	emental nutrition "	EO28 Extra" (with normal unrestricted diet)			
Intervention 2 group	no inter	vention (i.e., norma	l unrestricted diet)			
Intervention 3 group	: NA		,			
Outcomes (study-bas	ed)					
Primary outcomes (li	st): main	tenance of clinical i	remission at 12 mo withdrawal from steroids a	nd duration of remission at		
24 mo	<i>51)</i> . IIIaIII		emission at 12 mo, whildrawar nom storords, a	a curution of remission at		
Measure of disease a	etivity (e	linical endosconic	). CDAI			
Definition of remission	n (elinio	al endosconic).	DAI<150			
Definition of relance/	recurrer	nce (clinical andog	<b>conic</b> ): increase in CDAI by $>100$ points since 1	haseline or final CDAI		
>150 points: need of s	urgeru: i	creased doses of st	eroids	basenne or milar CDAI		
Definition of musses	ligery, ll	(clinical and accord				
Definition of inucosal	of prim	ary outcome acces	$m_{1}$ , $m_{1}$			
Number of notions	or hum	ary outcome assess	<b>511CHL</b> , 1, 3, 0, 7, 12, and 24 mo			
rumber of patients	T-4-1	Flow on to 1	No intermedian and a	Intomation 2		
	Total	Elemental nutrition cross-	no intervention group	intervention 5 group		
Allogotod to	20	21	18	ΝΔ		
Anocated to	37	21	10	INA		
	25	17 (	10			
Analysed (specify	35	1 / (per	18	NA		
TTT and/or per		protocol)				
protocol)		21 (ITT)				
(If more than one						
follow-up, choose						
and specify the last						
one)						
Losses to follow.		4	0	NA		

up/drop out/sample						
attrition						
(II more than one follow up, aboase						
and specify the last						
one)						
Interventions						
				Descript	ion	
	(e.g	., formula manufact	turer, calorie cont	ent, type,	mode, dose, and durat	ion of administration)
		Diet			Co-interve	ention
Elemental nutrition	EO28 H	Extra powder contai	ining 443 kcal	Predniso	lone (mean range: 10.	5-17.5 mg/d)
group	energy,	, mixed with water	and taken orally	azathiop	rine (dose: NR)	
	in three	e separate portions of	laily; mean	5-ASA (	dose: NR)	
	intake (	(768.5, SD: 50.6 kc	al/d)	Duration	i: 12 mo	
	Duratio	on: 12 mo				
Intervention 2 group	In addi	rion to normal diet	al diat)	Dradnisa	long (magn: 13 / mg/	1) azathionrina (dosa:
intervention 2 group	Duratic	$n \cdot 12 \text{ mo}$	iai uiet)	NR)	none (mean. 15.4 mg/	i) azaunoprine (dose.
	Durant	n. 12 mo		5-ASA (	dose: NR)	
				Duration	: 12 mo	
Intervention 3 group	NA			NA		
Patient baseline chara	acteristic	cs				
	Elem	nental nutrition	No intervent	on group	(i.e., normal diet)	Intervention 3 group
	20.2 (2	group	42.0 (2.2)			N A
Age (years) Mean (SD)	39.2 (3	.9)	42.0 (3.3)			NA
Sex –female n/N (%)	14/21 (	66 6)	13/18 (72 2)			NA
Weight (kg)	59.4 (2	.9)	62.7 (2.8)			NA
Mean (SD)	0,2,1,1	,	0217 (210)			
<b>BMI</b> $(kg/m^2)$	20.0 (2	.2)	22.9 (0.9)			NA
Mean (SD)						
Smoking n/N (%)	NR		NR			NA
Previous bowel	NR		NR			NA
<b>resection</b> n/N (%)	60.3 (1	<b>9</b> <i>1</i> )	01.0 (14.8)			NA
(months)	00.5 (1	0.4)	91.0 (14.0)			INA
Mean (SD)						
Crohn's Disease	112.8 (	11.5)	94.6 (7.1)			NA
Activity Index						
(CDAI)						
Mean (SD)						
Crohn's Disease	NR		NR			NA
Endoscopic Index						
Mean (SD)						
Disease activity	NR		NR			NA
other than CDAI	1.11		1111			
(specify)						
Mucosal ulceration	NR		NR			NA
n/N (%)						
Other	NR		NR			NA
complications n/N						
(%)						
For each timing of ass	essment	nlease provide a ser	parate table			
For scores, extract onl	y total so	cores				
Post-baseline follow-u	p assessn	ment timing (Specif	y): 12 mo			
	Elem	nental nutrition	No interventio	n group	Intervention 3	Between-group
		group	(i.e., normal	diet)	group	difference

				p value
Patients remaining	10/21 (47.6)	4/18 (22.2)	NA	p=0.0003 (SS)
in remission n/N				RR=2.14 (0.81, 5.67),
(%)				p=0.18 (NS) calculated
Duration of remission (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Risk of relapse or recurrence n/N (%)	7/21 (33.3)	14/18 (77.7)	NA	p<0.00001 (SS) RR=0.50 (0.25, 0.98) calculated
<b>Time to relapse</b> (months) Mean (SD) or 95% CI	7.4 (0.9)	6.2 (0.4)	NA	NR (study report) MD=1.2 (0.35, 2.04), p=0.012 (SS) calculated
Survival rate (% patients in remission who have not relapsed) (Kaplan-Meier estimate and 95% CI)	NR	NR	NA	NA
Patients achieving mucosal healing n/N (%)	NR	NR	NA	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NA	NA
The Short Form Health Survey (SF- 36) Mean (SD) 95% CI	NR	NR	NA	NA
The Short Form Health Survey (SF- 12) Mean (SD) 95% CI	NR	NR	NA	NA
The Euro-Qol questionnaire (EQ- 5D) Mean (SD) 95% CI	NR	NR	NA	NA
Other HQOL (specify) Mean (SD) 95% CI	NR	NR	NA	NA
Weight (kg) Mean (SD) 95% CI	NR	NR	NA	NA
Weight gain (kg) Mean change (SD) 95% CI	NR	NR	NA	NA
Body mass index (kg/m <sup>2</sup> ) Mean change (SD) 95% CI	NR	NR	NA	NA
Height gain (cm)	NR	NR	NA	NA

Mean (SD) 95% CI				
Linear growth rate	NR	NR	NA	NA
(mean height-for-				
age Z-score)				
Adherence n/N (%)	17/21 (80.9)	18/18 (100.0)	NA	NR (study report) RR=0.81 (0.65, 0.99) calculated; in favour of
				No intervention group
<b>Need for surgery</b> n/N (%)	NR	NR	NA	NA
Steroid dose tapering n/N (%)	10/21 (47.6)	4/18 (22.2)	NA	NR (study report) RR=2.14 (0.80, 5.67)
				(NS) calculated
Withdrawal from steroids n/N (%)	4/21 (19.0)	0/18 (0.0)	NA	NR
Adverse events due	NR	NR	NA	NA
to treatment n/N				
(%)				
<b>Complications - Num</b>	ber (%) of patients with a	in event		
[if more than one foll	ow-up, choose and specify	the last follow up]	I	
[if more than one foll	ow-up, choose and specify Elemental nutrition	the last follow up] No intervention group	Intervention 3	Between-group
[if more than one foll	ow-up, choose and specify Elemental nutrition group	the last follow up] No intervention group	Intervention 3 group	Between-group difference
[if more than one foll	ow-up, choose and specify Elemental nutrition group	the last follow up]         No intervention group	Intervention 3 group	Between-group difference p value (or 95% CD)*
[if more than one foll Impaired growth	ow-up, choose and specify Elemental nutrition group NR	a the last follow up]         No intervention group         NR	Intervention 3 group	Between-group difference p value (or 95% CI)* NA
[if more than one foll Impaired growth n/N (%)	ow-up, choose and specify Elemental nutrition group NR	r the last follow up]         No intervention group         NR	Intervention 3 group NA	Between-group difference p value (or 95% CI)* NA
[if more than one foll Impaired growth n/N (%) Delay in pubertal development n/N (%)	ow-up, choose and specify Elemental nutrition group NR	the last follow up]         No intervention group         NR         NR	Intervention 3         group         NA         NA	Between-group difference p value (or 95% CI)* NA NA
[if more than one foll Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction	ow-up, choose and specify Elemental nutrition group NR NR	the last follow up]         No intervention group         NR         NR         NR         NR         NR         NR	Intervention 3         group         NA         NA         NA         NA	Between-group         difference         p value         (or 95% CI)*         NA         NA         NA         NA
[if more than one foll Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae	ow-up, choose and specify Elemental nutrition group NR NR NR NR	the last follow up]         No intervention group         NR	Intervention 3         group         NA         NA         NA         NA         NA	Between-group         difference         p value         (or 95% CI)*         NA         NA         NA         NA
[if more than one foll Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess	ow-up, choose and specify Elemental nutrition group NR NR NR NR NR NR	the last follow up]         No intervention group         NR	Intervention 3         group         NA         NA         NA         NA         NA         NA         NA         NA         NA	Between-group         difference         p value         (or 95% CI)*         NA         NA         NA         NA         NA         NA         NA
[if more than one foll         Impaired growth         n/N (%)         Delay in pubertal         development         n/N (%)         Bowel obstruction         Fistulae         Abscess         Colon/bowel cancer	ow-up, choose and specify Elemental nutrition group NR NR NR NR NR NR NR NR	the last follow up]         No intervention group         NR	Intervention 3         group         NA	Between-group         difference         p value         (or 95% CI)*         NA
[if more than one foll         Impaired growth         n/N (%)         Delay in pubertal         development         n/N (%)         Bowel obstruction         Fistulae         Abscess         Colon/bowel cancer         Intestinal infection	ow-up, choose and specify Elemental nutrition group NR NR NR NR NR NR NR NR NR NR NR	the last follow up]         No intervention group         NR	Intervention 3 groupNANANANANANANANANANANANA	Between-group         difference         p value         (or 95% CI)*         NA
[if more than one foll         Impaired growth         n/N (%)         Delay in pubertal         development         n/N (%)         Bowel obstruction         Fistulae         Abscess         Colon/bowel cancer         Intestinal infection         Others (Specify)	ow-up, choose and specify Elemental nutrition group NR NR NR NR NR NR NR NR NR NR	the last follow up]         No intervention group         NR	Intervention 3         group         NA         NA	Between-group         difference         p value         (or 95% CI)*         NA
[if more than one foll         [if more than one foll         Impaired growth         n/N (%)         Delay in pubertal         development         n/N (%)         Bowel obstruction         Fistulae         Abscess         Colon/bowel cancer         Intestinal infection         Others (Specify)         Authors conclusion	ow-up, choose and specify Elemental nutrition group NR NR NR NR NR NR NR NR NR NR	the last follow up]         No intervention group         NR	Intervention 3 groupNANANANANANANANANANANANANANA	Between-group         difference         p value         (or 95% CI)*         NA
[if more than one foll         Impaired growth         n/N (%)         Delay in pubertal         development         n/N (%)         Bowel obstruction         Fistulae         Abscess         Colon/bowel cancer         Intestinal infection         Others (Specify)         Authors conclusion         Over 12 mo, the EN gr	ow-up, choose and specify Elemental nutrition group NR NR NR NR NR NR NR NR NR NR	the last follow up]         No intervention group         NR         NR	Intervention 3 group         NA         NA	Between-group         difference         p value         (or 95% CI)*         NA         NA
[if more than one foll         Impaired growth         n/N (%)         Delay in pubertal         development         n/N (%)         Bowel obstruction         Fistulae         Abscess         Colon/bowel cancer         Intestinal infection         Others (Specify)         Authors conclusion         Over 12 mo, the EN gr         Reviewer's conclusion	ow-up, choose and specify Elemental nutrition group NR NR NR NR NR NR NR NR NR NR	the last follow up]         No intervention group         NR         Intervention group	Intervention 3 group         NA	Between-group         difference         p value         (or 95% CI)*         NA

BMI, or weight compared to the control group at 12 mo of FU; results for steroid tapering/withdrawals, adherence, and intolerance are inconclusive due to small sample number of events or sample size

Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Tara Gurung

**Study details** First author surname year of publication: Yamamoto 2007a,<sup>30</sup>; Yamamoto 2013,<sup>59</sup>; Yamamoto 2013,<sup>60</sup> Country: Japan Study design: non-randomised controlled trial Study setting (primary care/specialty clinic/other - specify): specialty clinic Number of centres: one Total length of follow up: 12 mo Funding (government/private/manufacturer/other - specify): other (no external funding received) Aim of the study To examine if long-term elemental nutrition infusion along with low fat diet is useful in reducing clinical and endoscopic recurrence rates after resection for CD **Participants Recruitment dates: NR** Total N of patients who received induction therapy: NR Total N of patients achieving remission after induction therapy: NR Total N of patients unable to achieve remission after induction therapy: NR Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): NR Total number of patients allocated to maintenance treatment: 40 Inclusion criteria: patients with endoscopic and histological diagnosis of CD, aged 15-75 yrs who had resection for ileal and ileocolonic (including ileocaecal) CD; received EN therapy including elemental nutrition infusion at least once before operation; agreed to continue assigned treatment (with or without enteral nutrition) for more than 1 year after operation Exclusion criteria: Patients with colonic Crohn's disease alone or with diffuse small bowel Crohn's disease Characteristics of participants (total study sample) Mean (range or SD) age (years): 32.0 (17.0) Women (n [%]): 14/40 [35.0] Race/ethnicity (n [%]): NR Diagnostic criteria for CD: endoscopic and histological (no specific criteria reported) Mean Crohn's Disease Activity Index (CDAI) (range or SD): NR CD location (n [%]): Terminal ileum (12/40 [30.0]), terminal ileum and colon (20/40 [50.0]), Ileocolonic anastomosis (8/40 [20.0]) Type of induction therapy (e.g., medical, surgical): bowel resection (40/40 [100.0]), corticosteroids (37/40 [92.5]), pentasa (32/40 [77.5]) Previous surgery (n [%]): 8/40 [20.0] Intervention Elemental nutrition group: elemental nutrition (with restricted food diet) Intervention 2 group: no intervention (i.e., normal unrestricted diet) Intervention 3 group: NA **Outcomes (study-based) Primary outcomes** (*list*): clinical and endoscopic recurrence Measure of disease activity (clinical, endoscopic): clinical (CDAI score), endoscopic (Rutgeerts score) Definition of remission (clinical, endoscopic): CDAI<150 (clinical), Rutgeerts score<2 (endoscopic) Definition of relapse/recurrence (clinical, endoscopic): clinical (at 6, 12 mo: CDAI≥150; at 60 mo: CDAI≥200), endoscopic (Rutgeerts score≥2) Definition of mucosal healing (clinical, endoscopic): NR Post-baseline timings of primary outcome assessment: 6 and 12 mo Number of patients Total Elemental No intervention group **Intervention 3 group** nutrition group Allocated to 40 20 20 NA treatment Analysed (specify 40 20 20 NA ITT and/or per (ITT) protocol) (If more than one

follow-up, choose and

specify the last one)					
Losses to follow-	0	0	0		NA
up/drop out/sample					
attrition					
(If more than one					
follow-up, choose and					
specify the last one)					
Interventions					
			Descr	iption	
	(	e.g., formula ma	nufacturer, calorie con adminis	ntent, type, mode, or stration)	lose, and duration of
		Die	et	Co-	intervention
Elemental nutrition	Elenta	l (Ajinomoto, To	okyo, Japan) with the	Pentasa 3000 mg	/day as a prophylactic
group	calorie	density of 1 kca	l/mL with an	medication	
	osmola	arity of 760 mOs	m/L. Infused at		
	home i	nasogastrically v	ia self-intubated	No corticosteroid	l, immunosuppressive
	tube in	the night-time 1	week after	drugs, or inflixin	ab except patients who
	operati	on. The concent	ration of the	relapsed	
	elemer	ntal nutrition was	s gradually increased		
	from o	ne-third to the fu	all strength over 10		
	days (a	idaptation phase	) to reduce side		
	effects	, such as diarrho	ea and abdominal		
	colic.	After the adaptat	ion phase, a		
	mainte	nance dose at the	t time (for 6, 10 h)		
	The ve	stered in the flig	nt-time (10f 0–10 ff).		
	infused	l per night was 1	$200_{1800} \text{ mJ}$		
	musee	i per ingitt was i	200–1000 IIIL		
	Restric	ted food diet: in	the davtime. low fat		
	foods	(20-30  g/day) we	ere taken according		
	to the	instructions of th	eir dieticians. The		
	daily c	alorie intake: 35	–40 kcal/kg body		
	weight	; about half of th	ne calorie was		
	obtaine	ed from the elem	ental nutrition		
	therap	у			
	Durati	on at least 12 mc	DS 1	<b>D</b>	/
No intervention group	No ele	emental nutrition	, only normal	Pentasa 3000 mg/day as a prophylactic	
	unresti	ficted diet		medication	
	Duroti	n > 12 mos		No corticostaroid	immunoquanraqqiya
	Durau	011 > 12 11108		drugs or inflixing	a) ab except patients who
				relansed	ab except patients with
Intervention 3 group	NA			NA	
Patient baseline chara	cteristic	s			
	Elem	ental nutrition	No Interve	ention group	Intervention 3 group
		group			
Age (years)	31.0 (1	6.5)	33.0 (17.4)		NA
Mean (SD)	0.000	0.0			
Sex –temale n/N (%)	8/20 (4	0.0)	6/20 (30.0)		NA
Weight (kg)	NR		NR		NA
$\frac{\text{Mean}(\text{SD})}{\text{DML}(1-t)^{2s}}$	ND		ND		
BMI (kg/m <sup>2</sup> )	NR		NK		NA
$\frac{\text{Mean}(SD)}{\text{Smoking } p(N(0))}$	2/20 (1	0.0)	2/20 (10.0)		N A
Drawiong harvel	2/20(1	0.0)	2/20(10.0)		
resection n/N (%)	20/20 (	100.0)	20/20 (100.0)		INA
Duration of CD	37.0.(2	17)	39.0 (36.7)		ΝΔ
(months)	57.0(5	1.()	57.0 (50.7)		
(monus)	I				

Mean (SD)				
Crohn's Disease	NR	NR		NA
Activity Index				
(CDAI)				
Mean (SD)				
Crohn's Disease	NR	NR		NA
Endoscopic Index of				
Severity (CDEIS)				
Mean (SD)				
Disease activity	NR	NR		NA
other than CDAI				
(specify)				
Mucosal ulceration	NR	NR		NA
n/N (%)	D: 1 11 11	ND		
Other complications	Diarrhoea, abdominal	NR		NA
n/N (%)	distension or			
	colic in most pts (n/N:			
Efficiency outcomes	INK)	<u> </u>		
Enicacy outcomes		a on anato tal·1-		
For each timing of asse	ssment piease provide a	separate table		
Post-baseline follow up	assessment timing (Sno	$e_{ifv} = 6 + 12 + 60 mo$		
1 Ost-Dasenne Tonow-up	Flemental nutritian	No Intervention	Intervention 2	Rotwoon grown
	group	group	aroup	difference
	group	group	group	n volue
				p value (or 95% CD*
Patients remaining	12 mo <sup>.</sup> 19/20 (95 0)	12 mo: 13/20 (65 0)	NA	n=NR
in remission n/N (%)	12 110. 17/20 (75.0)	12 110: 15/20 (05.0)	147 1	RR = 1.46 (1.04, 2.05)
				calculated: in favour of
				elemental group
Duration of	NR	NR	NA	NA
Duration of remission (months)	NR	NR	NA	NA
<b>Duration of</b> <b>remission (months)</b> Mean (SD) or 95% CI	NR	NR	NA	NA
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or	NR Clinical	NR	NA	NA Clinical at 12 mo
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0)	NR <u>Clinical</u> 12 mo: 7/20 (35.0)	NA	NA <u>Clinical at 12 mo</u> p=0.048 (SS) study
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0)	NA	NA <u>Clinical at 12 mo</u> p=0.048 (SS) study reported; RR=0.14
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0)	NA	NA <u>Clinical at 12 mo</u> p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated;
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) Endoscopic	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) Endoscopic	NA	NA <u>Clinical at 12 mo</u> p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0)	NA	NA <u>Clinical at 12 mo</u> p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental group
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0)	NA	NA <u>Clinical at 12 mo</u> p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental group
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA <u>Clinical at 12 mo</u> p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental group <u>Clinical at 60 mo</u>
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA <u>Clinical at 12 mo</u> p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental group <u>Clinical at 60 mo</u> p=0.11 (NS) study
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA <u>Clinical at 12 mo</u> p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental group <u>Clinical at 60 mo</u> p=0.11 (NS) study reported; RR=0.50
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA         NA         Clinical at 12 mo         p=0.048 (SS) study         reported; RR=0.14         (0.02, 1.00) calculated;         in favour of elemental         group       Clinical at 60 mo         p=0.11 (NS) study       reported; RR=0.50         (0.23, 1.07) calculated       Calculated
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA         NA         Clinical at 12 mo         p=0.048 (SS) study         reported; RR=0.14         (0.02, 1.00) calculated;         in favour of elemental         group       Clinical at 60 mo         p=0.11 (NS) study         reported; RR=0.50         (0.23, 1.07) calculated
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA         NA         Clinical at 12 mo         p=0.048 (SS) study         reported; RR=0.14         (0.02, 1.00) calculated;         in favour of elemental         group         Clinical at 60 mo         p=0.11 (NS) study         reported; RR=0.50         (0.23, 1.07) calculated         Endoscopic at 6 mo
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA         Clinical at 12 mo         p=0.048 (SS) study         reported; RR=0.14         (0.02, 1.00) calculated;         in favour of elemental         group         Clinical at 60 mo         p=0.11 (NS) study         reported; RR=0.50         (0.23, 1.07) calculated         Endoscopic at 6 mo         p=0.50 (NS) study
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA         Clinical at 12 mo         p=0.048 (SS) study         reported; RR=0.14         (0.02, 1.00) calculated;         in favour of elemental         group         Clinical at 60 mo         p=0.11 (NS) study         reported; RR=0.50         (0.23, 1.07) calculated         Endoscopic at 6 mo         p=0.50 (NS) study         reported; RR=0.62
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA <u>Clinical at 12 mo</u> p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental group <u>Clinical at 60 mo</u> p=0.11 (NS) study reported; RR=0.50 (0.23, 1.07) calculated <u>Endoscopic at 6 mo</u> p=0.50 (NS) study reported; RR=0.62 (0.24, 1.58) calculated
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Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA Clinical at 12 mo p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental group Clinical at 60 mo p=0.11 (NS) study reported; RR=0.50 (0.23, 1.07) calculated Endoscopic at 6 mo p=0.50 (NS) study reported; RR=0.62 (0.24, 1.58) calculated Endoscopic at 12 mo p=0.027 (SS) study reported; RR=0.42 (0.20, 0.80)
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA Clinical at 12 mo p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental group Clinical at 60 mo p=0.11 (NS) study reported; RR=0.50 (0.23, 1.07) calculated Endoscopic at 6 mo p=0.50 (NS) study reported; RR=0.62 (0.24, 1.58) calculated Endoscopic at 12 mo p=0.027 (SS) study reported; RR=0.42 (0.20, 0.88) calculated;
Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NA Clinical at 12 mo p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental group Clinical at 60 mo p=0.11 (NS) study reported; RR=0.50 (0.23, 1.07) calculated Endoscopic at 6 mo p=0.50 (NS) study reported; RR=0.62 (0.24, 1.58) calculated Endoscopic at 12 mo p=0.027 (SS) study reported; RR=0.42 (0.20, 0.88) calculated; in favour of elemental
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Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	NR <u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	NR <u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)	NA	NANAClinical at 12 mop=0.048 (SS) studyreported; RR=0.14(0.02, 1.00) calculated;in favour of elementalgroupClinical at 60 mop=0.11 (NS) studyreported; RR=0.50(0.23, 1.07) calculatedEndoscopic at 6 mop=0.50 (NS) studyreported; RR=0.62(0.24, 1.58) calculatedEndoscopic at 12 mop=0.027 (SS) studyreported; RR=0.42(0.20, 0.88) calculated;in favour of elementalgroupEndoscopic at 60 mop=0.21 (NS) study

				(0.42, 1.11) calculated
Time to relapse	NR	NR	NA	NA
(months)				
Mean (SD) or 95% CI				
Survival rate (%	NR	NR	NA	NA
patients in remission				
who have not				
relapsed)				
(Kaplan-Meier				
estimate and 95% CI)				
Patients achieving	NR	NR	NA	NA
mucosal healing n/N				
(%)				
Crohn's Disease	NR	NR	NΔ	NA
Activity Index			1471	1111
(CDAI)				
(CDAI) Mean (SD)				
The Short Form	NR	NR	NΔ	NA
Health Survey (SF.			1111	1111
36)				
Mean (SD)				
95% CI				
The Short Form	NR	NR	NA	NA
Health Survey (SF-				
12)				
Mean (SD)				
95% CI				
The Euro-Qol	NR	NR	NA	NA
questionnaire (EQ-				
5D)				
Mean (SD)				
95% CI				
Other HQOL	NR	NR	NA	NA
(specify) Mean (SD)				
95% CI				
Weight (kg)	NR	NR	NA	NA
Mean (SD)				
95% CI				
Weight gain (kg)	NR	NR	NA	NA
Mean change (SD)				
95% CI				
Body mass index	NR	NR	NA	NA
(kg/m²)				
Mean change (SD)				
95% CI				
Height gain (cm)	NR	NR	NA	NA
Mean (SD)				
95% CI	ND	ND	NT A	NIA
Linear growth rate	NK	INK	NA	INA
(mean neight-10f-age				
$\frac{\mathbf{L} \cdot \mathbf{S}(\mathbf{U} \mathbf{C})}{\mathbf{A} \mathbf{d} \mathbf{h} \mathbf{e} \mathbf{r} \mathbf{e} \mathbf{n} (\mathbf{N} (\%))}$	20/20 (100 0)	20/20 (100 0)	ΝΔ	- [12 mo]
	[12 mo]	[12 mo]		
	[12]			
	16/20 (80.0)	20/20 (100.0)		RR=0.80 (0.64, 0.99)
	[60 mo]	[60 mo]		calculated: in favour of
	[····]	[ · · · · · · · ]		the control group [60
				mo]
Need for surgery	1/20 (5.0)	5/20 (25.0)	NA	p=0.18 (NS) study

n/N (%)	[60 mo]	[60 mo]		reported; RR=0.20 (0.02, 1.56) calculated [60 mo]
Steroid dose tapering n/N (%)	NR	NR	NA	NA
Withdrawal from steroids n/N (%)	NR	NR	NA	NA
Adverse events due to treatment n/N (%)	NR	NR	NA	NA
Complications - Numl	per (%) of patients with w-up, choose and spec	n an event ify the last follow up]		
	Elemental nutrition	No Intervention	Intervention	3 Between-group
	group	group	group	difference
				p value (or 95% CI)*
Impaired growth n/N (%)	NR	NR	NA	NA
Delay in pubertal	NR	NR	NA	NA
development n/N (%)				
<b>Bowel obstruction</b>	NR	NR	NA	NA
Fistulae	NR	NR	NA	NA
Abscess	NR	NR	NA	NA
Colon/bowel cancer	NR	NR	NA	NA
Intestinal infection	NR	NR	NA	NA
Others (Specify)	NR	NR	NA	NA
Authors conclusion				
The long-term enteral n	utritional therapy signifi	icantly reduced clinical	and endoscopic re	ecurrence after resection
for Crohn's disease				
Reviewer's conclusion	l			
Assignment depended of	on compliance, i.e., pts w	with good compliance w	ere assigned to ele	emental nutrition group
and those with low com	ipliance to control group	b. I ne long-term enteral	nutritional therap	by significantly reduced
clinical and endoscopic	recurrence at 12 mo afte	er resection for Urohn's	disease: nowever	. at ou mo the rates of

clinical and endoscopic recurrence at 12 mo after resection for Cronn's disease; however, at 60 mo the rates of clinical/endoscopic recurrences as well as the need for operation were not significantly different between the two treatment groups; compliance rates were better in the control group

Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Tara Gurung **Study details** First author surname year of publication: Yamamoto 2007b<sup>57</sup> Country: Japan Study design: non-randomised controlled trial Study setting (primary care/specialty clinic/other - specify): NR Number of centres: one Total length of follow up: 12 mo **Funding** (government/private/manufacturer/other - specify): NR Aim of the study To investigate if long-term enteral nutrition (vs. no intervention) is effective in reducing clinical and endoscopic relapse rates and inhibiting mucosal cytokine production in patients with quiescent CD **Participants Recruitment dates: NR** Total N of patients who received induction therapy: NR Total N of patients achieving remission after induction therapy: NR Total N of patients unable to achieve remission after induction therapy: NR Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): NR Total number of patients allocated to maintenance treatment: 40 Inclusion criteria: patient with endoscopic/histological diagnosis of CD in the terminal ileum and/or the colon; age: 15-75 years; clinical remission (CDAI<150) after medical treatment; the duration from the induction of remission to entry<8 weeks; patient had experienced enteral nutrition therapy including elemental nutrition infusion at least 1 time before entry; patient agreed to continue with assigned treatment (with or without enteral nutrition) for >1year; and patient agreed to have ileocolonoscopy with multiple mucosal biopsies even if they did not have any clinical symptoms Exclusion criteria: diffuse jejunoileal or gastroduodenal; severe anorectal stricture or sepsis; tight bowel strictures or enteric fistulae even though clinical symptoms were quiescent; patient had received corticosteroids, immunosuppressive drugs, or infliximab at entry **Characteristics of participants (total study sample)** Mean (range or SD) age (years): mean 29.0-31.0 Women (n [%]): 13/40 [32.5] Race/ethnicity (n [%]): NR Diagnostic criteria for CD: endoscopic and histological (not specified) Mean Crohn's Disease Activity Index (CDAI) (range or SD): 97 (56-139) CD location (n [%]): terminal ileum (15/40 [37.5]), colon (4/40 [10]), terminal ileum and colon (21/40 [52.5]) Type of induction therapy (e.g., medical, surgical): 4 pts (5 mg/kg x 1 or x 3 prednisolone, infliximab), 6 pts (prednisolone with enteral nutrition), 10 pts (prednisolone alone), 20 pts (enteral nutrition alone), 36 pts (Pentasa, 750–3000 mg/day), and the majority of pts required parenteral nutrition at the start of the treatment. Previous surgery (n [%]): 8/40 [20] Intervention Elemental nutrition group: elemental nutrition (with restricted food diet) **Intervention 2 group:** no intervention (i.e., normal unrestricted diet) Intervention 3 group: NA **Outcomes (study-based) Primary outcomes** (*list*): CDAI score, cumulative proportion of pts maintaining clinical remission (CDAI<150), endoscopic severity of disease activity/mucosal inflammation, mucosal cytokine assays Measure of disease activity (clinical, endoscopic): CDAI (clinical), mucosal inflammation grade by Wardle et al. 1992 [0=macroscopically normal, 1= granular mucosa and contact bleeding, 2= erythematous and edematous mucosa, aphtoid or superficial ulcers, and 3=deep ulcers with slough and inflammatory pseudo polyps] (endoscopic) Definition of remission (clinical, endoscopic): CDAI<150 (clinical), NR (endoscopic; specific threshold for the mucosal inflammation grade NR) Definition of relapse/recurrence (clinical, endoscopic): CDAI ≥150 (clinical), NR (endoscopic; specific threshold for the mucosal inflammation grade NR) Definition of mucosal healing (clinical, endoscopic): endoscopic (specific threshold for the mucosal inflammation grade NR) Post-baseline timings of primary outcome assessment: 0, 6, and 12 mo Number of patients

	Total	Elemental	No interve	ention group	Intervention 3 group
Allocated to	40		p 20		NA
Anocated to	40	20	20		NA
A palysed (specify	40	20	20		NΔ
ITT and/or ner	40 (ITT)	20	20		
nrotocol)	(111)				
protocoly					
(If more than one					
follow-up, choose					
and specify the last					
one)					
Losses to follow-	0	0	0		NA
up/drop out/sample					
attrition					
(If more than one					
follow-up, choose					
and specify the last					
one)					
Interventions	1				
			Descri	ption	
	(	e.g., formula manu	ifacturer, calorie con	tent, type, mode, d	ose, and duration of
		D!-4	adminis	tration)	•
Elementel nutrition	Elama	Diet	tal (Alinamata	Dantaga 2000 mg	Intervention
crown	Elemen	ital nutrition: Elen	a 80 g of poudored	Pentasa 5000 mg	day as a prophylactic
group	alamar	, one pack contain	s so g of powdered	medication.	
	to give	300 mL of solutio	1200 = 1800	No corticosteroid	immunosuppressive
	mI /nic	the infused via self.	intubated	drugs or inflixin	ab except patients who
	nasoga	stric tube every nig	ht natients were	relansed	ab except patients who
	advised	to take 35–40 kc	al/kg ideal	Telupsed	
	body w	eight daily, and to	take		
	approx	imately half of the	calorie from the		
	enteral	nutrition			
	Restric	ted food diet: in th	e daytime, a low-		
	fat diet	(20-30 g/day) wa	s taken in accord		
	with di	eticians instructior	18		
	Duratio	n > 12  mo			
No intervention	No ele	emental nutrition, o	only normal	Pentasa 3000 mg/day as a prophylactic	
group	unrestr	icted diet		medication.	
	Dunati	an > 12 ma		No continentanoid	immunoquannaquiuq
	Duratio	n > 12  mo		No corticosteroid	a, immunosuppressive
				relepsed	lab except patients who
Intervention 3 group	NΔ			NA	
Patient baseline chara	cteristic	'S		1171	
	Elem	ental nutrition	No Interve	ntion group	Intervention 3
		group		8 1	group
Age (years)	29.0 (1	7.4)	31.0 (20.1)		NA
Mean (SD)					
Sex –female n/N (%)	6/20 (3	0.0)	7/20 (35.0)		NA
Weight (kg)	51.1 (8	5.5)	48.9 (7.6)		NA
Mean (SD)					
<b>BMI</b> (kg/m <sup>2</sup> )	19.2 (1	.3)	19.1 (1.8)		NA
Mean (SD)					
Smoking n/N (%)	2/20 (1	0.0)	4/20 (20.0)		NA
Previous bowel	4/20 (2	(0.0)	4/20 (20.0)		NA

resection n/N (%)				
Duration of CD	32.0 (35.3)	36.0 (38.9)		NA
(months)		~ /		
Mean (SD)				
Crohn's Disease	101.0 (28.2)	92.0 (21.5)		NA
Activity Index	101.0 (20.2)	92.0 (21.5)		1111
(CDAI)				
Mean (SD)				
Crohn's Disease	NR	NR		ΝΔ
Endoscopic Index of				
Soverity (CDFIS)				
Mean (SD)				
Disease activity	Grade 0: $8/20$ (40.0)	Grade 0: 9/20 (45 0	)	ΝΔ
other than CDAI	Grade 1: $7/20$ (35.0)	Grade 1: 7/20 (35.0)	)	1177
(andosconic mucosol	Grade 2: $3/20(15.0)$	Grade 2: $2/20(10.0)$	)	
inflommation grada	Grade 3: $2/20(10.0)$	Grade 3: $2/20$ (10.0)	)	
<b>0-3</b> )	Orade $5.2720(10.0)$	01adc 5.2720(10.0)	)	
Mucosal ulceration	NR (see above	NR (see above endo	scopic mucosal	NA
n/N (%)	endoscopic mucosal	inflammation grade	)	
	inflammation grade)	Entre Brand		
Other complications	Diarrhea abdominal	NR		NA
n/N (%)	distention or colic in			1111
1.11 (70)	most pts $(n/N \cdot NR)$			
Efficacy outcomes				
For each timing of asse	ssment please provide a se	parate table		
For scores. extract only	v total scores	1		
Post-baseline follow-up	assessment timing (Speci	fy): 12 mo		
	Elemental nutrition	No	Intervention	Between-group
	group	Intervention	3 group	difference
	8 1		• <b>8</b> • • <b>1</b>	
		group		n value
		group		p value (or 95% CI)*
Patients remaining	15/20 (75.0)	<b>group</b> 7/20 (35.0)	NA	p value (or 95% CI)* P=0.01 study reported
Patients remaining in remission n/N (%)	15/20 (75.0)	group 7/20 (35.0)	NA	p value (or 95% CI)* P=0.01 study reported SS
Patients remaining in remission n/N (%)	15/20 (75.0)	group 7/20 (35.0)	NA	p value (or 95% CI)* P=0.01 study reported SS
Patients remaining in remission n/N (%)	15/20 (75.0)	group 7/20 (35.0)	NA	<b>p value</b> (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10)
Patients remaining in remission n/N (%)	15/20 (75.0)	group 7/20 (35.0)	NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated: in favour
Patients remaining in remission n/N (%)	15/20 (75.0)	group 7/20 (35.0)	NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition
Patients remaining in remission n/N (%)	15/20 (75.0)	group 7/20 (35.0)	NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group
Patients remaining in remission n/N (%) Duration of	15/20 (75.0) NR	group 7/20 (35.0)	NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA
Patients remaining in remission n/N (%) Duration of remission (months)	15/20 (75.0) NR	group 7/20 (35.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95%	15/20 (75.0) NR	group 7/20 (35.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI	15/20 (75.0) NR	group 7/20 (35.0)	NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported)
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70)
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87)
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated (SS) in favour of
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated (SS) in favour of elemental nutrition
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated (SS) in favour of elemental nutrition group
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%)	15/20 (75.0) NR 5/20 (25.0)	group 7/20 (35.0) NR 13/20 (65.0)	NA NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated (SS) in favour of elemental nutrition group NA
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%) Time to relapse (months)	15/20 (75.0) NR 5/20 (25.0) NR	group 7/20 (35.0) NR 13/20 (65.0) 13/20 (65.0)	NA NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated (SS) in favour of elemental nutrition group NA
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%) Time to relapse (months) Mean (SD) or 95%	15/20 (75.0) NR 5/20 (25.0) NR	group 7/20 (35.0) NR 13/20 (65.0) NR	NA NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated (SS) in favour of elemental nutrition group NA
Patients remaining         in remission n/N (%)         Duration of         remission (months)         Mean (SD) or 95%         CI         Risk of relapse or         recurrence n/N (%)         Time to relapse         (months)         Mean (SD) or 95%         CI	15/20 (75.0) NR 5/20 (25.0) NR	group           7/20 (35.0)           NR           13/20 (65.0)           NR           NR           NR	NA NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated (SS) in favour of elemental nutrition group NA
Patients remaining in remission n/N (%) Duration of remission (months) Mean (SD) or 95% CI Risk of relapse or recurrence n/N (%) Time to relapse (months) Mean (SD) or 95% CI Survival rate (%	15/20 (75.0) NR 5/20 (25.0) NR	group 7/20 (35.0) NR 13/20 (65.0) NR NR	NA NA NA NA NA	p value (or 95% CI)* P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group NA OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated (SS) in favour of elemental nutrition group NA

who have not				group
relapsed)				
(Kaplan-Meier				
estimate and 95% CI)				
Patients achieving	Grade 0: 6/20 (30.0)	Grade 0: 2/18	NA	RR=2.70 (0.62, 11.72)
mucosal healing n/N		(11.1)		NS calculated
(%)				
Crohn's Disease	NR	NR	NA	p=0.04 (SS) in favour
Activity Index				of elemental nutrition
(CDAI) Maan (SD)				group
The Short Form	NP	ND	NA	ΝA
Hoolth Survey (SF-	INK	INIK	INA	NA
<b>36</b> )				
Mean (SD)				
95% CI				
The Short Form	NR	NR	NA	NA
Health Survey (SF-				
12)				
Mean (SD)				
95% CI				
The Euro-Qol	NR	NR	NA	NA
questionnaire (EQ-				
5D)				
Mean (SD)				
95% CI	ND	ND	N7.4	
Other HQOL	NK	NK	NA	NA
(specify) Mean (SD)				
95% CI Weight (kg)	NP	ND	ΝΔ	NS(n>0.05)
Mean (SD)	INK	INK	INA	NS (p>0.05)
95% CI				
Weight gain (kg)	NR	NR	NA	NA
Mean change (SD)		1.11	1.111	
95% CI				
Body mass index	NR	NR	NA	SS (p<0.05) in favour
$(kg/m^2)$				of elemental nutrition
Mean change (SD)				group
95% CI				
Height gain (cm)	NR	NR	NA	NA
Mean (SD)				
95% CI				
Linear growth rate	NR	NR	NA	NA
(mean height-for-				
age Z-score)	18/20 (00 0)	20/20 (100.0)	NTA	$= 0.40 \mathbf{F}' \cdot \mathbf{h} \cdot$
Adnerence n/N (%)	18/20 (90.0)	20/20(100.0)	INA NA	p=0.48 Fisher test (NS)
neea for surgery	0/20 (0.0)	2/20 (10.0)	INA	INK
Steroid dose	NΔ	NA	NA	NΔ
tapering n/N (%)	1111	11/17	11/1	1 1/ 1
Withdrawal from	NA	NA	NA	NA
steroids n/N (%)				
Adverse events due	NR	NR	NA	NA
to treatment n/N (%)				
<b>Complications - Num</b>	ber (%) of patients with an e	vent		
[if more than one follo	w-up, choose and specify the	e last follow up]		
	<b>Elemental nutrition</b>	No	Intervention	3 Between-group
	group	Intervention	group	difference
		group		p value

				(or 95% CI)*
Impaired growth	NR	NR	NA	NA
n/N (%)				
Delay in pubertal	NR	NR	NA	NA
development				
n/N (%)				
<b>Bowel obstruction</b>	NR	NR	NA	NA
Fistulae	NR	NR	NA	NA
Abscess	NR	NR	NA	NA
Colon/bowel cancer	NR	NR	NA	NA
Intestinal infection	NR	NR	NA	NA
Others (Specify)	NR	NR	NA	NA
Authors conclusion				

Long-term enteral nutrition in patients with quiescent CD has a clear suppressive effect on clinical and endoscopic disease activities and the mucosal inflammatory cytokine levels

#### **Reviewer's conclusion**

Assignment depended on compliance, i.e., pts with good compliance were assigned to elemental nutrition group and those with low compliance to control group. The maintenance rates of clinical remission, relapse rates, and CDAI scores were significantly better in the elemental nutrition vs. control group after 12 mos of follow-up

Name of first reviewe	er: Alexando wer: Tara (	er Tsertsvadze		
Study dotails		Julung		
First outhor surnome	ween of pul	bligation Vaman	note 2010 <sup>58</sup>	
Country: Japan	year of pu		1010/2010	
Study design: non ran	domised co	ntrollad trial		
Study design. non-ran		ltri alinia/athan	manifu), manialtu alinia	
Study setting (primary	v care/specia	aty chinc/other - s	specify): specially child	
Number of centres: of	ne			
Total length of follow	<b>up</b> : 14 mo	6 1		
Funding (government)	/private/mar	ufacturer/other -	specify): NR	
Aim of the study				
To assess the efficacy	of EN on the	e maintenance rate	e of clinical remission in patients with q	uiescent CD receiving
infliximab as maintena	nce therapy			
Participants				
Recruitment dates: N	R			
Total N of patients w	ho received	induction therap	oy: NR	
Total N of patients ac	hieving ren	nission after indu	iction therapy: 56	
Total N of patients ur	hable to ach	ieve remission af	ter induction therapy: NR	
Total N of patients ex	cluded befo	ore start of maint	enance therapy (e.g., in relapse, lost t	o follow up): NR
Total number of patie	ents allocat	ed to maintenanc	e treatment: 56	
Inclusion criteria: pat	ients diagno	sed with CD who	had achieved clinical remission (CDAI	<150 after infliximab
induction therapy) with	h time from	the induction of re	emission to entry <2 weeks patients wh	o had experienced EN
therapy including elem	ental nutriti	on infusion at leas	st one time before entry: and patients wh	a agreed to continue with
the assigned treatment	(with or wit	hout concomitant	enteral nutrition) for 56 weeks	to agreed to continue with
Exclusion criteria: pa	tients who h	ad severe aporect	al involvement: patients who had tight h	owel strictures or enteric
fistulae even if clinical	symptoms	au severe anoree	ar involvement, patients who had tight t	lower strictures of enterie
Characteristics of par	rtiginanta (t	otal study compl	0)	
Maan (range or SD) as	$(u_{2})$	otal study sampi	e)	
We are $(n [0]) > 20/5$	(years). 5.	$2(\mathbf{NK})$		
women (n $[\%]$ ): 20/30	[35./]			
Race/ethnicity (n [%])	NK			
Diagnostic criteria for	CD: NR			
Mean Crohn's Disease	Activity Ind	dex (CDAI) (rang	e or SD): 102.2 (NR)	
CD location (n [%]): si	mall bowel (	(22/56 [39.3]), sm	all bowel and colon $(34/56 [60.7])$	
Type of induction there	apy (e.g., me	edical, surgical): r	nedical (infliximab 5 mg/kg)	
Previous surgery (n [%	]): bowel re	section (19/56 [34	4.0%])	
Intervention				
Elemental nutrition g	roup: elem	ental nutrition + in	nfliximab 5 mg/kg + restricted low fat d	iet
Intervention 2 group:	Infliximab	5 mg/kg + unrestr	icted low fat diet	
Intervention 3 group:	NA			
Outcomes (study-base	ed)			
Primary outcomes (li	st): cumulat	ive proportion of i	ots maintaining clinical remission, CDA	I score
Measure of disease ac	etivity (clini	cal. endoscopic):	CDAI	
Definition of remissio	n (clinical.	endoscopic): CD	AI < 150	
Definition of relanse/	recurrence	(clinical endosco	(DAI > 150)	
Definition of mucosal	healing (cl	inical endosconi	c)· NR	
Post-baseline timings	of nrimary	outcome assess	nent haseline 8 16 24 32 40 48 and	156 wks
Number of nationts	or primary	outcome ussessi	<b>Hent:</b> Dusenne, 0, 10, 21, 52, 10, 10, and	200 WR5
Number of patients	Total	Flomontol	Inflivimah group	Intervention 3 group
	Total	Elemental nutrition	minxinao group	intervention 5 group
		inflining h		
		Inffiximation		
		group	24	NY 4
Allocated to	56	32	24	NA
treatment				
Analysed (specify	56 (ITT)	32	24	NA
ITT and/or per				
protocol)				
(If more than one				
follow-up, choose				
and specify the last				

	r	1	1		
one)					
Losses to follow-	0	0	0		NA
up/drop out/sample					
attrition					
(If more than one					
follow-up, choose					
and specify the last					
one)					
Interventions	•				
Interventions			Deserie	4	
	(	1	Descrip	tion	1
	(e.g., form	nula manufacturer	, calorie content, type	, mode, dose, and	duration of administration)
		Diet		Co	o-intervention
<b>Elemental nutrition</b>	Elemental	nutrition (1200–1	500 mL) nasogastric	Mesalazine (Per	ntasa 3 g/day), Azathioprine
+ infliximab group	tube infusi	ion during night-ti	ime; Brand: Elental	(Imuran 50–100	mg/day)
	(Ajinomot	to, Tokyo); One E	lental pack		
	contained	80 g of powdered	ED, which is to be		
	dissolved	in warm water to	give 300 mL of		
	solution be	efore administratio	on. The calorie		
	density 11	kcal/mL			
	action of the				
	Duration	56 wks (14 mo)			
	Duration.	50 WKS (14 IIIO)			
	Postrictod	diat low fat (20	30 g/day) diat		
	during day	ulet - IOW Tat (20-	-50 g/uay) ulet		
	during day				
	35–40 Kca	il/kg ideal body w	eight daily		
	T (1· · · 1		0 1 )		
	Infliximab	o (5 mg/kg, every	8 weeks)		
Infliximab group	Inflixima	b (5 mg/kg, every	8 weeks)	Mesalazine (Pentasa 3 g/day), Azathioprine	
	Unrestrict	ed diet		(Imuran 50–100 mg/day)	
	NA			NA	
Intervention 3 group	NA			NA	
Patient baseline char	NA acteristics			NA	
Patient baseline chart	NA acteristics Element	tal nutrition +	Inflixima	b group	Intervention 3 group
Patient baseline char	NA acteristics Element inflix	tal nutrition + imab group	Inflixima	NA b group	Intervention 3 group
Intervention 3 group         Patient baseline char:         Age (years)	NA acteristics Element inflix 31.0 (9.0)	tal nutrition + imab group	<b>Inflixima</b> 33.0 (7.8)	b group	Intervention 3 group
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)	NA acteristics Element inflix 31.0 (9.0)	tal nutrition + imab group	<b>Inflixima</b> 33.0 (7.8)	b group	Intervention 3 group NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex –female n/N (%)	NA           acteristics           Element           inflixi           31.0 (9.0)           12/32 (37.	tal nutrition + imab group 5)	Inflixima 33.0 (7.8) 8/24 (33.3)	b group	Intervention 3 group       NA       NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR	tal nutrition + imab group 5)	Inflixima 33.0 (7.8) 8/24 (33.3) NR	b group	Intervention 3 group       NA       NA       NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR	tal nutrition + imab group 5)	Inflixima 33.0 (7.8) 8/24 (33.3) NR	b group	Intervention 3 group       NA       NA       NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMU (kg/m <sup>2</sup> )	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           NR	tal nutrition + imab group 5)	Inflixima 33.0 (7.8) 8/24 (33.3) NR	b group	Intervention 3 group       NA       NA       NA       NA
Intervention 3 group         Patient baseline chara         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)	NA acteristics Element inflix 31.0 (9.0) 12/32 (37. NR NR	tal nutrition + imab group 5)	Inflixima 33.0 (7.8) 8/24 (33.3) NR NR	b group	Intervention 3 group       NA       NA       NA       NA       NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smeking n/N (%)	NA acteristics Element inflix 31.0 (9.0) 12/32 (37. NR NR	tal nutrition + imab group 5)	Inflixima 33.0 (7.8) 8/24 (33.3) NR NR	b group	Intervention 3 group       NA       NA       NA       NA       NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Densitions housed	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           NR           4/32 (12.5           11/32 (34	tal nutrition + imab group 5)	Inflixima 33.0 (7.8) 8/24 (33.3) NR NR 4/24 (16.6)	b group	Intervention 3 group       NA       NA       NA       NA       NA       NA       NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         magazing n (N (%)	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           NR           4/32 (12.5           11/32 (34.	tal nutrition + imab group 5) () 4)	Inflixima 33.0 (7.8) 8/24 (33.3) NR NR 4/24 (16.6) 8/24 (33.3)	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)	NA           acteristics           Element           inflixi           31.0 (9.0)           12/32 (37.           NR           NR           4/32 (12.5           11/32 (34.	tal nutrition + imab group 5)	Inflixima 33.0 (7.8) 8/24 (33.3) NR NR 4/24 (16.6) 8/24 (33.3)	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD	NA           acteristics           Element           inflixi           31.0 (9.0)           12/32 (37.           NR           A/32 (12.5           11/32 (34.           33.0 (24.8	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6)	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex –female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)	NA           acteristics           Element           inflixi           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8	tal nutrition + imab group 5) () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6)	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex –female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)	NA           acteristics           Element           inflixi           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6)	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex –female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5)	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5)	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5)	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)         Mean (SD)	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5)	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)         Mean (SD)         Crohn's Disease	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.           NR	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5) NR	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)         Mean (SD)         Crohn's Disease         Endoscopic Index	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.           NR	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5) NR	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)         Mean (SD)         Crohn's Disease         Endoscopic Index         of Severity (CDEIS)	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.           NR	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5) NR	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)         Mean (SD)         Crohn's Disease         Endoscopic Index         of Severity (CDEIS)         Mean (SD)	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.           NR	tal nutrition + imab group 5) () (4) (1)	Inflixima           33.0 (7.8)           8/24 (33.3)           NR           4/24 (16.6)           8/24 (33.3)           35.0 (19.6)           102.3 (22.5)           NR	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)         Mean (SD)         Crohn's Disease         Endoscopic Index         of Severity (CDEIS)         Mean (SD)	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           VR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.           NR	tal nutrition + imab group 5) () (4) (1) (1)	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5) NR	b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)         Mean (SD)         Crohn's Disease         Endoscopic Index         of Severity (CDEIS)         Mean (SD)         Disease activity         other than CDAI	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.           NR           NR	tal nutrition + imab group 5) 4) 1)	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5) NR NR	NA b group	Intervention 3 group         NA         NA <td< th=""></td<>
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)         Mean (SD)         Crohn's Disease         Endoscopic Index         of Severity (CDEIS)         Mean (SD)         Disease activity         other than CDAI         (specify)	NA           acteristics           Element           inflix           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.           NR           NR	tal nutrition + imab group 5) 4) 1)	Inflixima           33.0 (7.8)           8/24 (33.3)           NR           4/24 (16.6)           8/24 (33.3)           35.0 (19.6)           102.3 (22.5)           NR           NR	NA b group	Intervention 3 group         NA
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)         Mean (SD)         Crohn's Disease         Endoscopic Index         of Severity (CDEIS)         Mean (SD)         Disease activity         other than CDAI         (specify)	NA           acteristics           Element           inflixi           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.           NR           NR	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5) NR NR	NA	Intervention 3 group         NA         NA <td< th=""></td<>
Intervention 3 group         Patient baseline chars         Age (years)         Mean (SD)         Sex -female n/N (%)         Weight (kg)         Mean (SD)         BMI (kg/m²)         Mean (SD)         Smoking n/N (%)         Previous bowel         resection n/N (%)         Duration of CD         (months)         Mean (SD)         Crohn's Disease         Activity Index         (CDAI)         Mean (SD)         Crohn's Disease         Endoscopic Index         of Severity (CDEIS)         Mean (SD)         Disease activity         other than CDAI         (specify)         Mucosal ulceration         x (W)	NA           acteristics           Element           inflixi           31.0 (9.0)           12/32 (37.           NR           4/32 (12.5           11/32 (34.           33.0 (24.8           102.1 (18.           NR           NR           NR	tal nutrition + imab group 5) () () () () () () () () () () () () ()	Inflixima 33.0 (7.8) 8/24 (33.3) NR 4/24 (16.6) 8/24 (33.3) 35.0 (19.6) 102.3 (22.5) NR NR NR	NA	Intervention 3 group         NA         NA <td< th=""></td<>

Other	NR	NR		NA
complications n/N				
(%)				
Efficacy outcomes				
For each timing of ass	essment please provide a sep	arate table		
For scores, extract onl	ly total scores	(14 mo)		
r ost-baseline tonow-u	Flemental nutrition +	Inflivimab group	Intervention 3	Botwoon_group
	infliximah groun	ininxinao group	groun	difference
			group	p value
				(or 95% CI)*
Patients remaining	25/32 (78.1)	16/24 (66.6)	NA	p=0.51 (NS) study
in remission n/N				reported
(%)				RR=1.17 (0.83, 1.64)
				calculated
Duration of	NR	NR	NA	NA
<b>remission</b> (months) Mean (SD) or 05%				
CI				
Risk of relanse or	7/32 (21.8)	8/24 (33.3)	NA	p=0.51 (NS) study
recurrence n/N (%)				reported
				RR=0.65 (0.27, 1.56)
				calculated
Time to relapse	NR	NR	NA	NA
(months)				
Mean (SD) or 95%				
	ND	ND	NT A	
Survival rate (%	NK	INK	NA	p=0.32 (NS)
who have not				
relapsed)				
(Kaplan-Meier				
estimate and 95%				
CI)				
Patients achieving	NR	NR	NA	NA
mucosal healing n/N				
(%)	ND	ND	NT A	
Cronn's Disease	NK	NK	NA	p>0.05 (NS)
(CDAI)				
Mean (SD)				
The Short Form	NR	NR	NA	NA
Health Survey (SF-				
36)				
Mean (SD)				
95% CI			27.4	
The Short Form	NK	NR	NA	NA
12)				
Mean (SD)				
95% CI				
The Euro-Qol	NR	NR	NA	NA
questionnaire (EQ-				
5D)				
Mean (SD)				
95% CI	ND	ND	NIA	NT A
(specify) Moon (SD)	INK	INK	INA	INA
95% CI				
			1	

Weight (kg)	NR	NR	NA	NA
Mean (SD)				
95% CI				
Weight gain (kg)	NR	NR	NA	NA
Mean change (SD)				
95% CI				
Body mass index	NR	NR	NA	NA
$(kg/m^2)$				
Mean change (SD)				
95% CI				
Height gain (cm)	NR	NR	NA	NA
Mean (SD)				
95% CI				
Linear growth rate	NR	NR	NA	NA
(mean height-for-				
age Z-score)				
Adherence n/N (%)	25/32 (78.1)	NR	NA	NA
Need for surgery	NR	NR	NA	NA
n/N (%)		1.11	1.1.1	
Steroid dose	NR	NR	NA	NA
tapering n/N (%)		1.11		
Withdrawal from	NR	NR	NA	NA
steroids n/N (%)				
Adverse events due	NR	NR	NA	NA
to treatment n/N		1.11		
(%)				
(%) Complications - Num	ber (%) of patients with an	event		
(%) Complications - Num [if more than one follo	ber (%) of patients with an ow-up, choose and specify t	event he last follow up]		
(%) Complications - Num [if more than one follo	ber (%) of patients with an ow-up, choose and specify th Elemental nutrition +	event he last follow up] Infliximab group	Intervention 3	Between-group
(%) Complications - Num [if more than one follo	ber (%) of patients with an ow-up, choose and specify th Elemental nutrition + infliximab group	event he last follow up] Infliximab group	Intervention 3 group	Between-group difference
(%) Complications - Num [if more than one foll	ber (%) of patients with an ow-up, choose and specify th Elemental nutrition + infliximab group	event he last follow up] Infliximab group	Intervention 3 group	Between-group difference p value
(%) Complications - Num [if more than one foll	ber (%) of patients with an ow-up, choose and specify th Elemental nutrition + infliximab group	event he last follow up] Infliximab group	Intervention 3 group	Between-group difference p value (or 95% CI)*
(%) Complications - Num [if more than one foll Impaired growth	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group	event he last follow up] Infliximab group	Intervention 3 group	Between-group difference p value (or 95% CI)* NA
(%) Complications - Num [if more than one foll Impaired growth n/N (%)	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group	event he last follow up] Infliximab group	Intervention 3 group	Between-group difference p value (or 95% CI)* NA
(%) Complications - Num [if more than one foll Impaired growth n/N (%) Delay in pubertal	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR	event he last follow up] Infliximab group	Intervention 3 group NA NA	Between-group difference p value (or 95% CI)* NA NA
(%) Complications - Num [if more than one foll Impaired growth n/N (%) Delay in pubertal development	ber (%) of patients with an ow-up, choose and specify th Elemental nutrition + infliximab group NR	event he last follow up] Infliximab group	Intervention 3 group NA NA	Between-group difference p value (or 95% CI)* NA NA
(%) Complications - Num [if more than one follow Impaired growth n/N (%) Delay in pubertal development n/N (%)	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR	event he last follow up] Infliximab group	Intervention 3 group NA NA	Between-group difference p value (or 95% CI)* NA NA
(%) Complications - Num [if more than one folls Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR	event he last follow up] Infliximab group	Intervention 3 group NA NA	Between-group difference p value (or 95% CI)* NA NA
(%) Complications - Num [if more than one following in the second seco	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR	event he last follow up] Infliximab group NR NR NR NR	Intervention 3 group NA NA NA NA	Between-group difference p value (or 95% CI)* NA NA NA NA
(%) Complications - Num [if more than one foll Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR	Intervention 3 group NA NA NA NA NA	Between-group difference p value (or 95% CI)* NA NA NA NA NA NA
(%) Complications - Num [if more than one foll Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR NR NR	Intervention 3 group NA NA NA NA NA NA	Between-group difference p value (or 95% CI)* NA NA NA NA NA NA NA
(%) Complications - Num [if more than one follow Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR NR NR NR NR NR	Intervention 3 group NA NA NA NA NA NA NA NA	Between-group         difference         p value         (or 95% CI)*         NA
(%) Complications - Num [if more than one foll if more than one foll n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify)	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	Intervention 3 group NA NA NA NA NA NA NA NA NA	Between-group difference p value (or 95% CI)*       NA
(%) Complications - Num [if more than one follow Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclusion	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	Intervention 3 group NA NA NA NA NA NA NA NA NA NA	Between-group         difference         p value         (or 95% CI)*         NA
(%) Complications - Num [if more than one following Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclusion After 56 wks of follow	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	Intervention 3 group NA NA NA NA NA NA NA NA NA NA infliximab was no	Between-group         difference         p value         (or 95% CI)*         NA
(%) Complications - Num [if more than one folled Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclusion After 56 wks of follow the maintenance of rem	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	Intervention 3 group NA NA NA NA NA NA NA NA NA NA NA NA	Between-group         difference         p value         (or 95% CI)*         NA         It statistically significant for
(%) Complications - Num [if more than one folled if more than one folled Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclusion After 56 wks of follow the maintenance of rem Reviewer's conclusion	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	Intervention 3 group NA NA NA NA NA NA NA NA NA NA NA NA	Between-group difference p value (or 95% CI)* NA NA NA NA NA NA NA NA NA NA NA NA NA
(%) Complications - Num [if more than one folled if more than one folled Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclusion After 56 wks of follow the maintenance of rem Reviewer's conclusion Assignment depended	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR NR NR NR	Intervention 3         group         NA         NA         NA         NA         NA         NA         NA         NA         NA         infliximab was no         e assigned to element	Between-group difference p value (or 95% CI)*     NA     NA
(%) Complications - Num [if more than one follow if more than one follow Impaired growth n/N (%) Delay in pubertal development n/N (%) Bowel obstruction Fistulae Abscess Colon/bowel cancer Intestinal infection Others (Specify) Authors conclusion After 56 wks of follow the maintenance of ren Reviewer's conclusion Assignment depended those with low complia	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR NR NR NR	Intervention 3 group NA NA NA NA NA NA NA NA NA infliximab was no e assigned to element ates of clinical rem	Between-group         difference         p value         (or 95% CI)*         NA         It statistically significant for         ental nutrition group and         ission and CDAI scores
(%) Complications - Num [if more than one following in the second seco	ber (%) of patients with an ow-up, choose and specify the Elemental nutrition + infliximab group NR NR NR NR NR NR NR NR NR NR NR NR NR	event he last follow up] Infliximab group NR NR NR NR NR NR NR NR NR NR	Intervention 3 group         NA         e assigned to elementates of clinical remotol groups after 56	Between-group difference p value (or 95% CI)*         NA         Sopin and CDAI scores

rates

# 8.4 Appendix IV: The risk of bias assessment of included primary study reports

### **RCTs**

#### Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Paul Sutcliffe First author surname year of publication: Hanai 2012<sup>50</sup>

Bias	Source of bias		Support for judgment <sup>*</sup>	Authors'
uomam	Random sequ	uence generation	Group assignment was	Low ROB
Selection	Random seq		done by a random process	LOW ROD
bias	Allocation co	oncealment	No information provided	Unclear ROB
Performance	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	No information provided, but probably not blinded; their knowledge of the treatment likely to influence the outcome reporting	High ROB
bias		Objective (e.g., radiography, endoscopy)	Although participants and personnel not blinded, their knowledge of the treatment unlikely to influence the outcome reporting	Low ROB
Detection	Blinding of outcome assessors	Subjective (e.g., patient-reported)	No information provided, but even if blinded, the reporting of subjective outcomes may have already been influenced	High ROB
blas		Objective (e.g., radiography, endoscopy)	Even if not blinded, the assessment of objective outcomes unlikely to be influenced	Low ROB
Attrition	Incomplete outcome data	Subjective outcomes (e.g., patient- reported)	Although there were 11 withdrawals, the assessed data was complete (no missing outcomes)	Low ROB
bias		Objective outcomes (e.g., radiography, endoscopy)	Although there were 11 withdrawals, the assessed data was complete (no missing outcomes)	Low ROB
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		Cumulative probability (survival) of maintaining remission incompletely reported (only p values)	High ROB
Other bias	Funding sour type of analy important ch	rce, adequacy of statistical methods used, rsis [ITT/PP], baseline imbalance in aracteristics	No serious issues detected (funding source not reported, statistical methods adequate, no major baseline imbalance across the study groups	Low ROB

ITT=intention to treat; PP=per protocol; NA=not applicable; ROB=risk of bias

\* Statement, description or quote supporting the judgment \*\* Low risk of bias, high risk of bias, or unclear risk of bias

Outcome measure	Summary risk of bias across all domains within a study	
Subjective (list of outcomes): Maintenance of remission	Maintenance of remission (CDAI<150):	
(e.g., CDAI<150), occurrence of relapse/recurrence (e.g.,		
$CDAI \ge 150$ ), time to relapse/recurrence (e.g., $CDAI \ge 150$ ),	High ROB	
quality of life measures, clinical scores of severity (e.g.,		
CDAI)		
Objective (list of outcomes): Maintenance of remission	Occurrence of relapse/recurrence (CDAI $\geq$ 200 or	
(includes additional objective parameters besides clinical),	the need for an additional medication to suppress	
occurrence of relapse/recurrence (includes additional	worsening symptoms), need for surgery, adverse	
objective parameters besides clinical), time to	events:	
relapse/recurrence (includes additional objective parameters		
besides clinical), mucosal healing (endoscopic remission),	Low ROB	
weight gain, linear growth rate, complications, adverse		
events, adherence		
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias		

#### Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Paul Sutcliffe First author surname year of publication: Takagi 2006, <sup>52, 53</sup>Takagi 2009<sup>54</sup>

Bias	·	Source of bias	Support for judgment <sup>*</sup>	Authors'
domain				judgment <sup>**</sup>
	Random seq	uence generation	A block randomisation	Low ROB
			(block size of 10) was	
			made with a random	
			number table	
Selection	Allocation co	oncealment	Randomised allocation	Low ROB
bias			done independently of	
			the two clinical centres	
			by the randomisation	
			centre.	
	Blinding of	Subjective (e.g., patient-reported)	Participants and	High ROB
	participants		personnel not blinded:	8
	and		their knowledge of the	
	Personnel		treatment likely to	
	rensonner		influence the reporting	
Performance			of outcome	
hias		Objective (e.g., radiography	Although participants	Low ROB
blus		endoscony)	and personnel not	LOW ROD
		chuoscopy)	blinded their knowledge	
			of the treatment unlikely	
			to influence the	
			to influence the	
	Diadianaf	Subjections (a. a. matient new arts d)	Plinded (see heless) but	
	Blinding of	Subjective (e.g., patient-reported)	Blinded (see below), but	High KOB
	outcome		subjective outcomes	
	assessors		may have been already	
			influenced since patients	
			and personnel were not	
			blinded	
		Objective (e.g., radiography,	To blind the principal	Low ROB
Detection		endoscopy)	investigators at each	
bias			site, the results (lab	
			tests, CDAI) were	
			reviewed by co-	
			investigators who had no	
			contact with patients,	
			and these results were	
			reported in a separate	
			case report form	
	Incomplete	Subjective outcomes (e.g., patient-	No missing outcome	Low ROB
Attrition	outcome	reported)	data	
bias	data	Objective outcomes (e.g., radiography,	No missing outcome	Low ROB
		endoscopy)	data	
Reporting	Selective rep	orting of the outcome, subgroups, or	Remission rates not	High ROB
bias	analysis		reported	-
	Funding source, adequacy of statistical methods used.		No serious issues	Low ROB
	type of analy	sis [ITT/PP], baseline imbalance in	detected (i.e., no	
	important ch	aracteristics	external funding	
			received, statistical	
Other bias			methods adequate. ITT	
			analysis, no major	
			baseline imbalance	
			between the study	
			groups)	

ITT=intention to treat; PP=per protocol; NA=not applicable; ROB=risk of bias \* Statement, description or quote supporting the judgment \*\* Low risk of bias, high risk of bias, or unclear risk of bias

Summary risk of bias across all domains within a study			
Quality of life measure (IBDQ):			
High ROB			
Occurrence of relapse/recurrence (CDAI > 200,			
or the need for therapy to induce remission),			
adherence, adverse events:			
Low ROB			
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias; IBDQ= Inflammatory Bowel			

### Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Paul Sutcliffe First author surname year of publication: Verma 2001<sup>55</sup>

Bias	Source of bias		Support for judgment <sup>*</sup>	Authors'
Selection	Random sequ	lence generation	No information provided	Unclear ROB
bias	Allocation co	oncealment	No information provided	Unclear ROB
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	No information provided, but probably not blinded; their knowledge of the treatment likely to influence the outcome reporting	High ROB
		Objective (e.g., radiography, endoscopy)	Although participants and personnel not blinded, their knowledge of the treatment would not influence the outcome reporting	Low ROB
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)	No information provided, but even if blinded, the reporting of subjective outcomes may have already been influenced	High ROB
		Objective (e.g., radiography, endoscopy)	No information provided, but even if not blinded the assessment of objective outcomes unlikely to be influenced	Low ROB
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient- reported)	Although there were 6 (18%) withdrawals, the analysed data was complete (no missing outcome)	Low ROB
		Objective outcomes (e.g., radiography, endoscopy)	Although there were 6 (18%) withdrawals, the analysed data was complete (no missing outcome)	Low ROB
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		Outcomes were not pre- specified in Methods section, only in the abstract; need for surgery was not reported in Results section; selective reporting likely	High ROB
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP], baseline imbalance in important characteristics		No funding reported; statistical analyses adequate; there was some imbalance in the elemental nutrition group being on steroids for shorter period, higher CDAI, and lower weight than the control group	Unclear ROB

ITT=intention to treat; PP=per protocol; NA=not applicable; ROB=risk of bias \* Statement, description or quote supporting the judgment \*\* Low risk of bias, high risk of bias, or unclear risk of bias

Outcome measure	Summary risk of bias across all domains within a study		
Subjective (list of outcomes). Maintenance of remission	Qasumanas of malanas/masumanas (CDAL>200 or		
Subjective (list of outcomes): Maintenance of remission	Occurrence of relapse/recurrence (CDAI $\geq 200$ of		
(e.g., CDAI<150), occurrence of relapse/recurrence (e.g.,	increased by 100 points from baseline):		
$CDAI \ge 150$ ), time to relapse/recurrence (e.g., $CDAI \ge 150$ ),			
quality of life measures, clinical scores of severity (e.g.,	High ROB		
CDAI)	-		
Objective (list of outcomes): Maintenance of remission	Maintenance of remission (absence of diarrhoea		
(includes additional objective parameters besides clinical),	and abdominal pain, CDAI <150 in the 2 weeks		
occurrence of relapse/recurrence (includes additional	preceding the study, and ESR<20 mm/h),		
objective parameters besides clinical), time to	withdrawal from steroids, adherence:		
relapse/recurrence (includes additional objective parameters			
besides clinical), mucosal healing (endoscopic remission),	Unclear ROB		
weight gain, linear growth rate, complications, adverse			
events, adherence			
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias			

## Non-RCTs

### Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Paul Sutcliffe First author surname year of publication: Hirakawa 1993<sup>51</sup>

Bias domain		Source of bias	Support for judgment <sup>*</sup>	Authors'
Selection	The presence/absence of baseline between-group imbalance in important prognostic characteristics/factors (e.g., age, sex, CDAI, duration of CD, location of CD, complications during induction therapy, type of induction therapy, pre-study compliance, co-intervention, and/or smoking)		There was some imbalance in induction therapy and distribution of lesion across the study groups	High ROB
	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	Pure subjective outcomes: NR No information on blinding but probably not blinded	NA
Performance bias		Objective (e.g., radiography, endoscopy)	No information on blinding but probably not blinded. However, given the objective outcomes their knowledge of the treatment would not influence the outcome reporting	Low ROB
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)	Pure subjective outcomes: NR No information on blinding but probably not blinded	NA
		Objective (e.g., radiography, endoscopy)	No information on blinding but probably not blinded. However, given the objective outcomes their knowledge of the treatment would not influence the outcome reporting	Low ROB
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient- reported) Objective outcomes (e.g., radiography,	Pure subjective outcomes: NR 8 patients were excluded	NA High ROB
		endoscopy)	from the analyses (incomplete outcome data)	
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		The analyses for survival of remission, remission maintenance rates, and relapse rates were incompletely reported (no or partial numerical data)	High ROB
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]		Funding source not stated, PP analysis instead of ITT, possible imbalance in unmeasured prognostic factors	High ROB

ITT=intention to treat; PP=per protocol; NA=not applicable; CDAI=Crohn's disease activity index; ROB=risk of bias

\* Statement, description or quote supporting the judgment \*\* Low risk of bias, high risk of bias, or unclear risk of bias

Outcome measure	Summary risk of bias across all domains	
	within a study	
Subjective (list of outcomes): Maintenance of remission (e.g.,	NR (see below): NA	
CDAI<150), occurrence of relapse/recurrence (e.g.,		
CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150),		
quality of life measures, clinical scores of severity (e.g.,		
CDAI)		
Objective (list of outcomes): Maintenance of remission	Maintenance of remission (cumulative	
(includes additional objective parameters besides clinical),	survival): High ROB	
occurrence of relapse/recurrence (includes additional		
objective parameters besides clinical), time to	Adherence: Low ROB	
relapse/recurrence (includes additional objective parameters		
besides clinical), mucosal healing (endoscopic remission),		
weight gain, linear growth rate, complications, adverse		
events, adherence		
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias; IOIBD= International		
Organization for the Study of Inflammatory Bowel Disease: ESR=erythrocyte sedimentation rate; CRP=C-		
reactive protein		

#### Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Paul Sutcliffe **First author surname year of publication:** Verma $2000^{56}$

Bias	jui iluiile yeur	Source of bias	Support for judgment*	Authors'
domain		Source of blas	Support for Judgment	indoment <sup>**</sup>
uomum	The presence	vabsence of baseline between-group	The elemental nutrition	High ROB
Selection bias	imbalance in	important prognostic	group had shorter	ingii itob
	characteristic	cs/factors (e.g., age, sex, CDAL duration	disease duration (60.3	
	of CD. locati	ion of CD, complications during induction	vs. 91.0 months), greater	
	therapy, type	of induction therapy, pre-study	ESR, and longer steroid	
	compliance.	co-intervention. and/or smoking)	use compared to control	
	· · · · · · · · · · · · · · · · · · ·	, , , , , , , , , , , , , , , , , , , ,	group	
	Blinding of	Subjective (e.g., patient-reported)	No information on	High ROB
	participants		blinding but probably	U
	and		not blinded; their	
	Personnel		knowledge of the	
			treatment likely to	
			influence the outcome	
			reporting	
Performance		Objective (e.g., radiography,	No information on	Low ROB
bias		endoscopy)	blinding but probably	
			not blinded. However,	
			given the objective	
			outcomes their	
			knowledge of the	
			treatment would not	
			influence the outcome	
			reporting	
	Blinding of	Subjective (e.g., patient-reported)	No information on	High ROB
	outcome		blinding; the reporting	
	assessors		of subjective outcomes	
			may have already been	
			influenced	
Detection		Objective (e.g., radiography,	No information on	Low ROB
bias		endoscopy)	blinding; however, given	
			the objective outcomes	
			their knowledge of the	
			influence the sufference	
			reporting	
	Incomplete	Subjective outcomes (e.g. patient	Complete data analysed	Low POP
Attrition	outcome	reported)	Complete data analysed	LOW KOD
hias	data	Objective outcomes (e.g. radiography	Complete data analysed	Low ROB
0103	uutu	endoscony)	Complete data analysed	LOW KOD
	Selective ren	orting of the outcome subgroups or	No pre-specification of	High ROB
Reporting	analysis	soluting of the outcome, subgroups, of	outcomes (Methods	ingii KOD
bias	anarysis		section)	
	Funding sour	rce, adequacy of statistical methods used	No funder reported	Low ROB
Other bias	type of analy	sis [ITT/PP]	statistical analyses	200 100
Still Olus	spe of analy	500 [ +/+ + ]	adequate: ITT used	
ITT=intention	to treat. PP=r	per protocol <sup>.</sup> NA=not applicable <sup>.</sup> CDAI=Cr	ohn's disease activity index:	ROB=risk
of bias			see a and a a a a a a a a a a a a a a a a a	

\* Statement, description or quote supporting the judgment \*\* Low risk of bias, high risk of bias, or unclear risk of bias

Outcome measure	Summary risk of bias across all domains within a study	
Subjective (list of outcomes): Maintenance of remission (e.g.,	Maintenance of remission (CDAI<150), CDAI	
CDAI<150), occurrence of relapse/recurrence (e.g.,	score:	
CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150),		
quality of life measures, clinical scores of severity (e.g.,	High ROB	
CDAI)		
Objective (list of outcomes): Maintenance of remission	Occurrence of relapse/recurrence (increase in	
(includes additional objective parameters besides clinical),	CDAI by >100 points since baseline or final	
occurrence of relapse/recurrence (includes additional	CDAI >150 points; need of surgery; increased	
objective parameters besides clinical), time to	doses of steroids), time to relapse, adherence,	
relapse/recurrence (includes additional objective parameters	steroid dose tapering, withdrawal from steroids,	
besides clinical), mucosal healing (endoscopic remission),	adverse events:	
weight gain, linear growth rate, complications, adverse		
events, adherence	Unclear ROB	
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias		
#### Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Paul Sutcliffe

		<b>T T T T T T T T T T</b>
First outhor surnama	voor of nublication.	Vamamoto $2007a^{50}, 55, 60$
r ii st autiful sur name	veal of publication.	1 amamoto 2007 a

Bias domain		Source of bias	Support for judgment <sup>*</sup>	Authors'
uomam	The presence/absence of baseline between_group		No major imbalance	Unclear
	imbalance in	important prognostic	between the study	ROB
	characteristic	rs/factors (e.g. age sex CDAI duration	groups in the pre-	ROD
	of CD locati	on of CD complications during induction	specified important	
	thoropy type	of induction therapy, pro-study	prognostic factors	
	aompliance	an intervention and/or smalling)	However patients with	
	compnance,	co-intervention, and/or smoking)	nowever, patients with	
			good compliance were	
Selection			assigned to elementar	
bias			these with law	
			those with low	
			compliance to no	
			treatment group; this	
			selective assignment	
			may have generated	
			differences between the	
			groups in not otherwise	
			pre-specified factors	
	Blinding of	Subjective (e.g., patient-reported)	Not blinded; subjective,	High ROB
	participants		i.e., patient-reported	
Performance	and		outcomes reporting	
bias	Personnel		likely influenced	
0103		Objective (e.g., radiography,	Not blinded; objective	Low ROB
		endoscopy)	outcomes reporting	
			unlikely to be influenced	
	Blinding of	Subjective (e.g., patient-reported)	No information;	High ROB
	outcome		regardless of blinding	
	assessors		status, subjective, i.e.,	
			patient-reported	
Detection			outcomes reporting	
bias			likely influenced	
Ulas		Objective (e.g., radiography,	Endoscopic investigators	Low ROB
		endoscopy)	were blind to patient	
			status; objective	
			outcomes assessment	
			unlikely to be influenced	
	Incomplete	Subjective outcomes (e.g., patient-	Outcomes for all	Low ROB
	outcome	reported)	patients available	
Attrition	data		(complete data analysed)	
		Objective outcomes (e.g., radiography,	Outcomes for all	Low ROB
bias		endoscopy)	patients	
			available (complete data	
			analysed)	
Reporting	Selective reporting of the outcome, subgroups, or		Main outcomes pre-	Low ROB
	analysis		specified (Methods	
bias			section) and reported	
-	Funding sour	rce, adequacy of statistical methods used,	No external funding	Low ROB
01 1	type of analy	sis [ITT/PP]	received; statistical	
Other bias			methods adequate: ITT	
			analysis done	
ITT=intention	to treat; PP=p	er protocol; NA=not applicable; CDAI=Cr	ohn's disease activity index;	ROB=risk
of hias				

\* Statement, description or quote supporting the judgment \*\* Low risk of bias, high risk of bias, or unclear risk of bias

### Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains	
	within a study	
Subjective (list of outcomes): Maintenance of remission (e.g.,	Maintenance of remission (CDAI<150),	
CDAI<150), occurrence of relapse/recurrence (e.g.,	occurrence of relapse/recurrence (CDAI > 150,	
CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150),	CDAI≥200):	
quality of life measures, clinical scores of severity (e.g.,		
CDAI)	High ROB	
Objective (list of outcomes): Maintenance of remission	Occurrence of relapse/recurrence (Rutgeerts	
(includes additional objective parameters besides clinical),	score≥2), adherence, need for surgery:	
occurrence of relapse/recurrence (includes additional		
objective parameters besides clinical), time to	Low ROB	
relapse/recurrence (includes additional objective parameters		
besides clinical), mucosal healing (endoscopic remission),		
weight gain, linear growth rate, complications, adverse		
events, adherence		
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index;	ROB=risk of bias	

## Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Paul Sutcliffe First author surname year of publicatio

First author surhame year of publication: 1 amainoto 2007b					
Bias		Source of bias	Support for judgment	Authors'	
domain				judgment	
	The presence	/absence of baseline between-group	No major imbalance	Unclear	
	imbalance in	important prognostic	between the study	ROB	
	characteristic	cs/factors (e.g., age, sex, CDAI, duration	groups in the pre-		
	of CD, locati	on of CD, complications during induction	specified important		
	therapy, type	of induction therapy, pre-study	prognostic factors.		
	compliance,	co-intervention, and/or smoking)	However, patients with		
			good compliance were		
Selection			assigned to elemental		
bios			nutrition group and		
Ulas			those with low		
			compliance to no		
			treatment group; this		
			selective assignment		
			may have generated		
			differences between the		
			groups in not otherwise		
			pre-specified factors		
	Blinding of	Subjective (e.g., patient-reported)	Not blinded; the	High ROB	
	participants		knowledge of the	e	
	and		treatment could have		
	Personnel		influenced the outcome		
Performance	1 010011101		recording		
bias		Objective (e.g., radiography	Not blinded: the	Low ROB	
olus		endoscony)	knowledge of the	Low Rob	
		endoseopy)	treatment would not		
			have influenced the		
			outcome recording		
	Blinding of	Subjective (e.g. patient reported)	Lab investigators were	High POB	
	Difficing Of	Subjective (e.g., patient-reported)	blinded to the clinical	Tingii KOD	
	outcome		data: howayar the		
	assess015		callected patient		
			reported outcome date		
Detection			may have already been		
biog			influenced		
blas		Objective (e. e. rediography	Lab investigators were		
		objective (e.g., radiography,	hlinded to the aliniaal	LOW KOD	
		endoscopy)	data, the blinding status		
			uata, the binding status		
			unificery to influence the		
	T	S-histing automas (s. s. satisat	Outcome assessment	L DOD	
A *.*	Incomplete	Subjective outcomes (e.g., patient-	Outcome data for all	LOW KOB	
bias	outcome	reported)	patients was available	I DOD	
	data	Objective outcomes (e.g., radiography,	Outcome data for all	Low ROB	
	~	endoscopy)	patients was available		
Reporting	Selective reporting of the outcome, subgroups, or		All pre-specified	Low ROB	
bias	analysis		outcome (Methods)		
0100			were reported (Results)		
	Funding sour	ce, adequacy of statistical methods used,	No funding reported;	Low ROB	
Other bias	type of analy	sis [ITT/PP]	analyses were adequate;		
			ITT analysis done		
ITT=intention	ITT=intention to treat; PP=per protocol; NA=not applicable; CDAI=Crohn's disease activity index; ROB=risk				
of bias					

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of bias \* Statement, description or quote supporting the judgment \*\* Low risk of bias, high risk of bias, or unclear risk of bias

### Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study	
Subjective (list of outcomes): Maintenance of remission (e.g.,	Maintenance of remission (CDAI<150),	
CDAI<150), occurrence of relapse/recurrence (e.g.,	occurrence of relapse/recurrence (CDAI≥150),	
CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150),	CDAI score:	
quality of life measures, clinical scores of severity (e.g.,		
CDAI)	High ROB	
Objective (list of outcomes): Maintenance of remission	Mucosal healing (endoscopic remission),	
(includes additional objective parameters besides clinical),	weight, BMI, adherence, need for surgery:	
occurrence of relapse/recurrence (includes additional		
objective parameters besides clinical), time to	Low ROB	
relapse/recurrence (includes additional objective parameters		
besides clinical), mucosal healing (endoscopic remission),		
weight gain, linear growth rate, complications, adverse		
events, adherence		
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index;	ROB=risk of bias	

#### Name of first reviewer: Alexander Tsertsvadze Name of second reviewer: Paul Sutcliffe First author surname year of publicatio v.

<b>First author surname year of publication:</b> Yamamoto 2010 <sup>58</sup>					
Bias		Source of bias	Support for judgment <sup>*</sup>	Authors'	
domain				judgment	
Selection	The presence/absence of baseline between-group imbalance in important prognostic characteristics/factors (e.g., age, sex, CDAI, duration of CD, location of CD, complications during induction therapy, type of induction therapy, pre-study compliance, co-intervention, and/or smoking)		No major imbalance between the study groups in the pre-specified important prognostic factors. However, patients with good compliance were assigned to elemental nutrition group and those with low compliance to infliximab alone group; this selective assignment may have generated differences between the groups in not otherwise	Unclear ROB	
	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	pre-specified factors No information provided, but probably not blinded; their knowledge of the treatment likely to influence the outcome	High ROB	
Performance bias		Objective (e.g., radiography, endoscopy)	Although participants and personnel not blinded, their knowledge of the treatment would not influence the outcome reporting	Low ROB	
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported) Objective (e.g., radiography, endoscopy)	No information provided, but even if blinded, the reporting of subjective outcomes may have already been influenced No information provided, but even if not blinded the	High ROB	
	Incomplete	Subjective outcomes (a prosting)	assessment of objective outcomes unlikely to be influenced	Low DOD	
Attrition	outcome data	reported)	complete (no missing outcome)	LOW KOB	
bias		Objective outcomes (e.g., radiography, endoscopy)	The analysed data was complete (no missing outcome)	Low ROB	
Reporting bias	Selective rep analysis	orting of the outcome, subgroups, or	All pre-specified (in Methods section) outcomes were reported (in Results section)	Low ROB	
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]		No funding reported; statistical analyses adequate; ITT analysis reported	Low ROB	
ITT=intention to treat; PP=per protocol; NA=not applicable; CDAI=Crohn's disease activity index; ROB=risk of bias					

\*Statement, description or quote supporting the judgment \*\* Low risk of bias, high risk of bias, or unclear risk of bias

### Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission (e.g.,	Maintenance of remission (CDAI<150),
CDAI<150), occurrence of relapse/recurrence (e.g.,	occurrence of relapse/recurrence (e.g.,
CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150),	CDAI≥150), clinical scores of severity (CDAI):
quality of life measures, clinical scores of severity (e.g.,	
CDAI)	High ROB
Objective (list of outcomes): Maintenance of remission	Adherence: Low ROB
(includes additional objective parameters besides clinical),	
occurrence of relapse/recurrence (includes additional	
objective parameters besides clinical), time to	
relapse/recurrence (includes additional objective parameters	
besides clinical), mucosal healing (endoscopic remission),	
weight gain, linear growth rate, complications, adverse	
events, adherence	
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index;	ROB=risk of bias

# 8.5 Appendix V: Studies excluded with reasons

N	Study	Reason for exclusion
1	Belli DC, Seidman E, Bouthillier L, Weber AM, Roy CC, Pletincx M, et al. Chronic	<80% participants in
	intermittent elemental diet improves growth failure in children with Crohn's disease.	remission
	Gastroenterology. 1988;94(3):603-10	
2	Cucchiara S, Guandalini S, Staiano A, Ferola A, Romaniello G, Latte F, et al. Remission of	Case report
	colonic crohns-disease induced by elemental diet. Italian Journal of Gastroenterology.	
	1984; <b>16</b> (4):302-4	
3	Esaki M, Matsumoto T, Hizawa K, Nakamura S, Jo Y, Mibu R, et al. Preventive effect of	Unclear control
	nutritional therapy against postoperative recurrence of Crohn disease, with reference to	group
	findings determined by intra-operative enteroscopy. Scandinavian Journal of	
	Gastroenterology. 2005;40(12):1431-7	
4	Fukuda Y, Okui M, Tamura K, Shimoyama T. Serum fatty acid and disease activity in	Irrelevant
	Crohn's disease patients during maintenance therapy with elemental diet. 1999 [cited;	treatment/outcome
	Available from: <u>http://0-</u>	
	onlinelibrary.wiley.com.pugwash.lib.warwick.ac.uk/o/cochrane/clcentral/articles/882/CN-	
	00382882/frame.html]	
5	Geerling BJ, Badart-Smook A, van Deursen C, van Houwelingen AC, Russel M,	Irrelevant
	Stockbrugger RW, et al. Nutritional supplementation with n-3 fatty acids and antioxidants	treatment/outcome
	in patients with Crohn's disease in remission: Effects on antioxidant status and fatty acid	
	profile. Inflammatory Bowel Diseases. 2000;6(2):77-84	
6	Gorard DA, Hunt JB, Paynejames JJ, Palmer KR, Kumar PJ, Clark ML, et al. Relapse rates	Abstract
	in Crohns-disease after initial treatment with elemental diet or prednisolone. Gut.	
	1991; <b>32</b> (5):A582	
7	Harries AD, Jones LA, Danis V, Fifield R, Heatley RV, Newcombe RG, et al. Controlled	Participants with
	trial of supplemented oral nutrition in Crohn's disease. Lancet. 1983;1(8330):887-90	active CD
8	Herzog D, Deslandres C, Martin S, Rasquin A, Alvarez F, Bouthillier L, et al. Cyclical	Abstract
	exclusive semi-elemental diet therapy normalizes growth and decreases relapse rate in	
	pediatric Crohn's disease. Gastroenterology. 1997;112(4):A995	
9	Hunt JB, Payne-James JJ. A randomised controlled trial of elemental diet versus	Abstract
	prednisolone in treatment of new and recurrent Crohn's disease. 1989 [cited; Available	
	from: <u>http://0-</u>	
	onlinelibrary.wiley.com.pugwash.lib.warwick.ac.uk/o/cochrane/clcentral/articles/761/CN-	
	00258761/frame.html]	
10	Hunt JB, Payne-James JJ, Palmer KR, Kumar PK, Clark ML, Farthing MJ, et al. A	Abstract

	randomised controlled trial of elemental diet versus prednisolone in the treatment of new &	
	recurrent Crohns disease. 1989 [cited; Available from: http://0-	
	onlinelibrary.wiley.com.pugwash.lib.warwick.ac.uk/o/cochrane/clcentral/articles/382/CN-	
	00281382/frame.html]	
11	Imes S, Pinchbeck B, Dinwoodie A, Walker K, Thomson AB. Effect of Ensure, a defined	Participants with
	formula diet, in patients with Crohn's disease. Digestion. 1986;35(3):158-69.	active CD
12	Kamata N, Watanabe K, Tsukahara T, Hagihara Y, Morimoto K, Noguchi A, et al.	Abstract
	Concomitant elemental diet therapy is effective in sustaining infliximab scheduled	
	maintenance therapy in patients with crohn's disease to prevent loss of response.	
	Gastroenterology. 2013;1:S433	
13	Matsui T, Ueki M, Yamada M, Sakurai T, Yao T. Indications and options of nutritional	Abstracts of 3
	treatment for Crohn's disease. A comparison of elemental and polymeric diets. 1995 [cited;	studies
	Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/053/CN-	
	00123053/frame.html]	
14	Otley AR, Murray A, Christensen B, Williams T, Ste-Marie M, Rashid M. Primary enteral	Abstract
	nutrition therapy induces and maintains remission, and reduces steroid exposure in a	
	pediatric Crohn's disease population. Gastroenterology. 2005;128(4):A584	
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