Enteral nutrition feeding strategies and their impact on relapse rate and quality of life in paediatric Crohn's disease

Afzal, Nadeem Ahmad

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Nadeem Ahmad Afzal

M.D.

Barts and the London School of Medicine,
Queen Mary,
University of London

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Dedication

This thesis is dedicated to my beautiful wife, Munawara, with whom I will be in love forever.

Declaration

I declare that all work in this thesis is entirely my own.

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Abstract

Aims:
To study induction of remission and reduction in relapse rate of childhood Crohn's disease with quality of life (QOL) assessment in subjects on long term continuous oral supplementation with ACD004.

Methods:
This study was performed in two phases. In Phase A, ACD004 was used to assess effectiveness based on proportion of full remission at 8 weeks. Children then reintroduced food over a 4 week phase reducing their ACD004 intake to 30% RDA, subsequently enrolling into randomised controlled part of the trial (Phase B), to assess reduction in relapse rate whilst receiving continuous oral ACD004 supplementation compared to no supplementation. Secondary objectives of this study were to examine QOL, safety, tolerance and growth.

Results:
42 children were enrolled in Phase A with 78.6% (n=33) achieving remission with a significant improvement in endoscopic, histologic and QOL scores. One child developed refeeding syndrome. A further 8 children relapsed during the food reintroduction phase and 25 children were enrolled in the Phase B RCT. 12 were randomised to remain supplemented and 13 had no supplementation. Only 1/3rd of the calculated study power (n=72) was met due to collapse of trial following withdrawal of funding. 8/12 in the supplemented and 10/13 in the non-supplemented group relapsed by first year. At 2 years, 4/12 in the supplemented and 2/13 in the non-supplemented group were in remission. Deterioration in IBD and systemic QOL

symptoms related to disease were seen; however there was no change in emotional and social functioning.

Conculsions:
ACD004 is an effective remission inducing agent, which also improves QOL despite significantly limiting children's diet. Due to early collapse of trial, its role as a supplement remains uncertain; no benefit seen with limited trial recruitment. In the long-term, emotional and social domains in QOL remain unaltered, despite relapse which may be due to disease acceptance.

Publications based on this thesis

Abstracts

Afzal NA, Shergill-Bonner R, Arnaud-Battandier F, Paintin M, Murch S, Thomson M, Heuschkel R, Fell J. Clinical and mucosal responses to a new casein based enteral feed containing a higher ratio of n-3 : n-6 fats and lower level of total saturated fatty acids for treatment of acute Crohn's disease in children. Clinical Nutrition 2002

Afzal NA, Loonen H, Arnaud- Battandier F, Davies S, Murch S, Derkx B, Heuschkel R, Fell J. Assessment of quality of life in children with acute Crohn's disease after treatment with exclusive enteral nutrition. Journal of Pediatric Gastroenterology and Nutrition, 2003.
Archives of diseases in childhood, 2003

Afzal NA, Fagbemi A, Arnaud-Battandier F, Paintin M, Thomson M, Walker-Smith JA, Murch S, Heuschkel R, Fell JM. Enteral nutrition treats children with colonic Crohn's disease more effectively if the ileum is also involved. Arch Dis Child 2002

Papers

Afzal NA, Loonen H, Arnaud- Battandier F, Davies S, Murch S, Derkx B, Heuschkel R, Fell J. Assessment of quality of life in children with acute Crohn's disease after treatment with exclusive enteral nutrition.

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Afzal NA, Davies S, Paintin M, Davies S, Arnaud- Battandier F, Walker-Smith J, Murch SH, Fell JM. Exclusive enteral feeding for children with Crohn's disease: response rates for differing disease sites. Digestive Diseases and Sciences 2005 Aug; 50(8):1471-5

Abbreviations

AL110, CT3211 (Modulen IBD®) and ACD004 are three polymeric enteral feeds produced by Nestle®

ACCENT	a Crohn's disease clinical study evaluating Infliximab in a new long term treatment regimen
ACCESS	Software database package by Microsoft®
ANCA	Anti nuclear cytoplasmic antibody
ASA	amino salicylic acid medicines like sulphasalazine
ASCA	Anti saccharomyces cerevisiae antibody
ATP	adenosine triphosphate
AZA	azathioprine
CAM	complementary alternative medicines
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDEIS	Crohn's disease endoscopic index of severity
CRP	C-reactive protein
ENACT	evaluation of Natalizumab as continuous therapy
ESPGHAN	European Society of Paediatric Gastroenterology, Hepatology and Nutrition
ESR	erythrocyte sedimentation rate
FDA	US Food and drug administration
GETAID	Groupe d'Etude Therapeutique des Affections Inflammatories Digestive
GWAS	Genome wide Association Studies
HLA	human leukocyte antigen
HRQOL	health related quality of life
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
IC	indeterminate colitis
IGF	insulin like growth factor
IL	interleukin
IOIBD	international organization for the study of inflammatory bowel disease
MP	mercaptopurine
MWU	Mann Whitney U test
NBD	nucleotide binding domain
NFκB	nuclear factor kappa B
NG	nasogastric
PCDAI	paediatric Crohn's disease activity index

PML	progressive multifocal leucoencephalopathy
QOL	quality of life
RDA	recommended daily allowance
SDS	standard deviation score
SPSS	Statistical software package
TG	thioguanine
TNF	tumour necrosis factor
TPMT	thiopurine methyl transferase
TPN	total parenteral nutrition
UC	ulcerative colitis
WAZ	weight for age Z score
WHO	world health organisation

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Chapter 1. Background and definitions

1.1 Background and aims of the thesis

1.1.1 Background

Chronic inflammatory bowel diseases encompass a group of conditions which cause inflammation in the intestinal tract [1]. This group includes Crohn's disease and ulcerative colitis. Characteristically, Crohn's disease may involve any part of the gastrointestinal tract (compared to ulcerative colitis which is limited to the colon). Both are life long conditions commonly running a relapse and remitting course. As we begin to understand these conditions better, we now know that the aetiology is complex and multifactorial involving a combination of genetic predisposition, dysregulated immune response and environmental influences [2].

25% of inflammatory bowel disease patients present in childhood or adolescence [3,4]. The median age of presentation is between 10 and 14 years [5-9]. The reported incidence varies from 0.3-10.9/100,000 [7,10-15] with an increasing incidence most recently reported by Benchemol [16] in both Crohn's disease (23.9–31.6 / 100,000 and Ulcerative colitis (16.2–19.7 /1000,000) in Canada between the years 1994 - 2005.

Children with inflammatory bowel disease can present with a myriad of intestinal symptoms with some even being asymptomatic. Commonly reported symptoms of Crohns disease in children include abdominal pain, weight loss and diarrhoea [17]. As paediatric Crohn's disease commonly presents between the ages of 10-14, linear growth may be particualry impaired which may also be associated with lack of pubertal development. The relapsing and recurring bowel symptoms can affect day to day functioning which includes

education, social functioning and employment for young adults [18,19]. In addition, children face regular visits to the hospital, blood testing, endoscopies and treatments. The resulting quality of life (disease status forms one aspect of the total QOL assessment) may be poor.

The aim of treatment of inflammatory bowel disease in children is to achieve and maintain remission with the minimum of 'drug' side effects. Corticosteroids have always been the mainstay treatment for active disease but when used over long periods result in osteoporosis [20] and stunted growth [21]. Over years there has been a shift towards using nutritional treatments in Crohn's disease and in 1971 for the first time, enteral nutrition was used to improve nutrition of a child with active Crohn's disease [22]. Noticeable improvement in nutrition was associated with resolution of inflammation. The first feed Conded 72H®, was a sucrose based liquid elemental diet and did not taste nice; an issue with elemental feeds to date. It was administered as a continuous infusion via a nasogastric tube. Consequently, better tasting polymeric (whole protein) feeds were developed to avoid nasogastric tube usage [23]. Nutritional approach to treatment has significant advantages as it not only optimises nutrition but also controls active intestinal inflammation with a reduction in pro-inflammatory cytokines [24]. Although cross-sectional studies show a poor quality of life during active disease state [25], It however remains unknown if these therapies result in an improvement in quality of life over time during the course of the treatment. Also, retrospective studies show that supplement enteral feeding taken daily can help to maintain remission [26]. There are however no prospective studies to support its use as maintenance treatment.

More recently, there has been accumulating evidence of beneficial effects with n-3 fats and its anti-inflammatory properties [27]. Nestle produced a new polymeric feed ACD004 with higher n-3 : n-6 ratio compared to the used CT3211 feed (Modulen IBD®) with a view to offer better anti-inflammatory profile in an enteral feed. I used ACD004 in the study described in this thesis.

1.1.2 Study summary

Objective: Study induction of remission and reduction in relapse rate of childhood Crohn's disease with quality of life (QOL) assessment in subjects on long term continuous oral supplementation with ACD004.

Subjects: 27 children in phase A increasing to 72 children (aged 5 to 19 inclusive) with newly diagnosed or relapsing Crohn's disease.

Study design: the study will be performed in two phases and initiated in two centres.
Phase A: Prospective and open
Phase B: Prospective, open, controlled and randomised

Product: ACD004 exclusively for 8 weeks (Phase A), then ACD004 supplements versus usual diet (Phase B)

Treatment duration: Exclusive enteral supplementation with ACD004 for 8 weeks (Phase A), then gradual food re-introduction over a period of 4-6 weeks followed by a randomised intervention period of 2 years (108 weeks)(Phase B).

Evaulation criteria:

Phase A:

- Efficacy (remission or relapse after 8 weeks of treatment),
- short term safety,
- growth
- quality of life

Phase B:

- Reduction in relapse rate,
- long term safety,
- growth
- quality of life

1.2 Definition of inflammatory bowel disease

1.2.1 Introduction

All inflammatory bowel conditions are defined and differentiated mainly on the basis of histology. This underlies the importance of endoscopy and biopsy, in making a diagnosis. Each inflammatory disease can be further sub classified by anatomical distribution of inflammation such as proctosigmoiditis or pancolonic inflammation in cases of ulcerative colitis. Crohn's disease may also be classified on the basis of disease behaviour such as penetrating or fistulating. This has been discussed in detail in the following sections.

1.2.2 Crohn's disease

Crohn's disease is characterized by patchy transmural inflammation affecting any part of the gastrointestinal tract [28,29]. A secure or definite diagnosis can be made on the basis of following observations [30]:

- Presence of characteristic histology with non-caseating granulomata. When present these are a useful histological marker as they tend to be absent in other forms of inflammatory bowel disease. In a recent study granulomas were found to be present in 61% of the children at diagnosis [31]; however their significance on disease process remains unknown. In this study granulomas were more frequent in untreated children and their presence was not affected by age. Presence of a NOD2 mutation does not confer an increased risk to developing granulomas [32]. Equally its

presence does not predict future need for surgery [33]. It is important to consider that crypt associated giant cells and granulomas can occur in ulcerative colitis and are unreliable for differentiating between Crohn's and ulcerative colitis [34]. Although presence of pericryptal granulomas should alert one to the diagnosis of Crohn's disease, their presence is not itself diagnostic for Crohn's disease. Their presence in ulcerative colitis may be reflective of the mild nature of colitis [35]. Surawicz suggested that pericryptal granulomas may form as a result of mucin from damaged crypts, different from granuloma formation in Crohn's disease [36].

- The presence of terminal ileal ulceration on endoscopy and histological ileitis with a characteristic radiological appearance
- The presence of characteristic histology after intestinal resection (non-caseating granulomas and fissuring ulceration).
- A probable or presumptive diagnosis may be made when radiological investigations show the typical abnormalities found in Crohn's disease in a child who has clinical features to suggest its presence [30].

Crohn's disease may also be defined and described by location of inflammation (terminal ileal, ileocolonic, colonic, upper gastrointestinal) and pattern of disease (inflammatory, fistulating, structuring).

An international working party for the World congress convened in September 1998 and produced a classification of Crohn's disease called the 'Vienna classification'. A working party was formulated which included gastroenterologists (adult) from Europe, UK, Israel, Canada and USA. The classification content was debated as to

whether to include fixed or variable criteria. The fixed criteria are characteristics of the disease such as location e.g. colonic, ileal etc. The variable criteria include changing features like the symptoms of the disease. These may change on day to day basis. After an initial agreement the classification was based on fixed criteria and five international meetings were held between 1996 and 1998. The task force on disease quantitation of the International Organisation for the study of Inflammatory Bowel Disease (IOIBD) at the same time was considering the potential for developing a standardized IBD database and classification to assist in genetic studies and clinical trials. In January 1998 the IOIBD in conjunction with the Crohn's and Colitis foundation of America sponsored a meeting in New York City in which this working party was also represented.

After common consensus and a review of 413 consecutive cases three variables were selected. Two of these variables include location of inflammation and pattern of disease, which have been described in the preceding sections. A third variable, 'age at diagnosis' was also selected (age less than or above 40) which is not relevant to paediatric practice [37]. The Vienna classification is given in table 1.2.2.1.

Louis E et al have suggested that location of Crohn's disease as defined by Vienna classification is a relatively stable phenotype which seems suitable for phenotype-genotype analyses. The group studied 297 Crohn's patients and found ileal Crohn's disease to be more often stricturing, compared to colonic or ileocolonic Crohn's disease which was more often penetrating; this was already the case at diagnosis and became more prominent after 10 years [38].

Veloso et al in Porto in a study of 480 patients found that ileocolonic disease was diagnosed at a relatively earlier age which also had a lower probability of remaining in remission during the disease course; patients with colonic disease needed less surgical or steroid

treatments. They concluded that grouping of patients with Crohn's disease according to the Vienna Classification and/or the clinical activity in the year after diagnosis is useful in predicting the subsequent course of disease [39].

This phenotype classification has been validated for use in adults and has not been used to assess disease response to treatments or prognosticate future progress in any paediatric studies.

The ESPGHAN (European society of paediatric gastroenteorolology hepatology and nutrition) working group on paediatric IBD had its first meeting in Taormina, Italy in 2002. Various aspects of paediatric IBD from diagnosis to management with future plans of holding a database were discussed in this meeting. This was followed by 3 meetings in Porto and one in Prague. The final working group consisted of 23 working paediatric gastroenterologists from 19 centres in 12 European countries. Primary aims were to establish consensus based criteria for the diagnosis of IBD and to reach agreement regarding diagnostic work up in a new IBD patient. The second aim was to collect uniform phenotypic data on patients based on resources generally available throughout Europe. The Porto criteria for endoscopic and histologic diagnosis are listed in table 1.2.2.2 [40].

At the time of submission and writing of this thesis, very recently, the Montreal Classification has evolved which takes into consideration the younger age group [41]. A1 group described in the Vienna classification as < 40 years, has been redefined in the Montreal classification and further subdivided into A1 as below 17 years of age and A2 between 17 and 40 years of age. The general principles in the new classification particularly regarding definition of ileal, colonic and ileocolonic groups still remain the same, with additional allowance to incorporate coexistence of small bowel and distal disease in one group. This was decided as disease groups were

considered to be mutually exclusive with no allowance for overlap. The differences between the two classifications are highlighted in table 1.2.2.3. The Montreal classification has been used to characterise adult and early onset inflammatory bowel disease by Van Limbergen [42]. In this study childhood-onset inflammatory bowel disease was different to adult Crohn's disease by extensive instestinal involvement and rapid early disease progression. The natural history of Crohn's disease was described by the EPIMAD group using the Montreal classification who again described Crohn's disease to be more aggressive in the younger age group [43].

Table 1.2.2.1 The Vienna classification of Crohn's disease [37]

Age at diagnosis [1]:	A1, < 40 years
	A2, ≥ 40 years
Location [2]:	L1, Terminal ileum [3]
	L2, Colon [4]
	L3, Ileocolon [5]
	L4, Upper G I[6]
Behaviour:	B1, Non stricturing non penetrating [7]
	B2, Stricturing [8]
	B3, Penetrating [9]

[1] The age when diagnosis of Crohn's disease was first definitively established by radiology, endoscopy, pathology or surgery.

[2] The maximum extent of disease involvement for a location at any time before the first resection. Minimum involvement for a location is defined as any aphthous lesion or ulceration. Mucosal erythema or oedema is insufficient. For classification at least both, a small bowel and a large bowel examination are required.

[3] Disease limited to the terminal ileum (the lower third of the small bowel) with or without spill into caecum.

[4] Any colonic location between caecum and rectum with no small bowel or upper gastrointestinal involvement.

[5] Disease of the terminal ileum with or without spill over into caecum and any location between ascending colon and rectum.

[6] Any disease location proximal to the terminal ileum (excluding the mouth) regardless of additional involvement of the terminal ileum or colon.

[7] Inflammatory disease which never has been complicated at any time in the course of disease.

[8] Stricturing disease is defined as the occurrence of constant luminal narrowing demonstrated by radiologic, endoscopic or surgical pathologic methods with pre-stenotic dilatation or obstructive signs/symptoms without presence of penetrating disease at any time in the course of disease.

[9] Penetrating disease is defined as the occurrence of intra-abdominal or perianal fistulas, inflammatory masses and/or abscesses at any time in the course of disease. Perianal ulcers are also included. Excluded are postoperative intra-abdominal complications and perianal skin tags.

Table 1.2.2.2 Endoscopy and histology in inflammatory bowel disease – Porto criteria

	Crohn's disease	Ulcerative colitis
Endoscopy (& visualizations of oral and/or perianal lesions	Ulcers (aphthous, linear or stellate)	Ulcers
	Cobblestoning	Erythema
	Skip lesions	Loss of vascular pattern granularity
	Strictures	Friability
	Fistula	Spontaneous bleeding
	Abnormalities in oral and/ or perianal regions	Pseudopolyps
	Segmental distribution	Continuous with variable proximal extension from rectum
Histology*	Submucosal (biopsy with sufficient submucosal tissue) or transmural involvement (surgical specimen)	Mucosal involvement
	Ulcers, crypt distortion	Crypt distortion
	Crypt abscess	Crypt abscess
		Goblet cell depletion
	Granulomas (non-caseating, non-mucin)	Mucin granulomas (rare)
	Focal changes (within biopsy)	Continuous distribution
	Patchy distribution (biopsies)	

* Histology for both Crohn's disease and Ulcerative colitis included acute and chronic inflammation with architectural changes, loss of glands and branching of crypts. Crohn's disease abnormalities in oral region included lip swelling, gingival hyperplasia, aphthous ulcers; Crohn's disease abnormalities in perianal region included tags, fissures, fistulae and abscess.

Table 1.2.2.3 Differences between the Vienna and Montreal Classification

	Vienna	Montreal
Age at diagnosis	A1 below 40y A2 above 40y	A1 below 17y A2 between 17 and 40y A3 above 40y
Location	L1 ileal L2 colonic L3 ileocolonic L4 upper	L1 ileal L2 colonic L3 ileocolonic L4 isolated upper disease*
Behaviour	B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating	B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating p perianal disease modifier†

* L4 is a modifier that can be added to L1-3 when concomitant upper gastrointestinal disease is present
† "p" is added to B1-3 when concomitant perianal disease is present

1.2.3 Ulcerative Colitis

Ulcerative colitis is an important differential diagnosis of Crohn's disease and sometimes may be difficult to differentiate from Crohn's colitis. Definite ulcerative colitis is defined histologically by acute inflammation with severe crypt cell distortion and diffuse goblet cell depletion. Inflammation is generally diffuse and solely mucosal, with increased vascularity; not necessarily present in all cases [30].
Probable ulcerative colitis is indicated by [30]:
Diffuse mucosal inflammation with only mild or moderate crypt distortion, mucosal atrophy or mucous depletion
Diffuse acute and chronic inflammation with increased vascularity but little mucous depletion suggesting a resolving phase.

Both the Rome and Vienna classfications have not addressed subclassification of Ulcerative colitis. The Montreal classification incorporates a system of subclassifying Ulcerative colitis on the basis

of extent of disease extent and severity (see tables 1.2.3.1 and 1.2.3.2). Disesase definition based on disease extent is liable to change (progress or regress) with time. Sub-classification on based on disease severity may be useful to determine disease behaviour over time with direct relevance to clinical management.

Table 1.2.3.1 Montreal classification of extent of Ulcerative colitis

Extent	Anatomy
E1 Ulcerative proctitis	Involvement limited to the rectum (that is proximal extent of inflammation is distal to the rectosigmoid junction
E2 Left sided UC (distal UC)	Involvment limited to a proportion of the colorectum distal to the splenic flexure
E3 Extensive UC (pancolitis)	Involvment extends proximal to the splenic flexure

Table 1.2.3.2 Montreal classification of severity of Ulcerative colitis

Severity	Definition
S0 Clinical remission	Asymptomatic
S1 Mild UC	Passage of 4 or fewer stools (with or without blood), absence of any systemic illness and normal inflammatory markers (ESR)
S2 Moderate UC	Passage of more than 4 stools per day but with minimal signs of systemic toxicity
S3 Severe UC	Passage of at least 6 bloody stools daily, pulse rate of at least 90/minute, temperature of at least 37.5 C, Haemoglobin of less than 10.5 g/100ml and ESR of at least 30mm/hr

1.2.4 Indeterminate colitis and Inflammatory bowel disease unclassified (IBDU)

5-15% of patients with IBD affecting colon have some features of both Crohn's and ulcerative colitis but not classifiable in one particular category. This has been termed as indeterminate colitis [28]. This diagnosis is made after carefully considering clinical radiological endoscopic and pathological criteria for diagnosis.

Sands' has described a histological appearance of crypt atrophy to be definitively suggestive of IBD but crypt distortion a probable IBD. If there is mucin preservation at ulcer edge or in the crypts with infiltration of neutrophils, this would suggest indeterminate colitis [29]. Historically, Price introduced the term 'indeterminate colitis', for the first time in 1978, to refer to a subgroup of approximately 10–15% of IBD cases in which there was difficulty in distinguishing between ulcerative colitis and Crohn's disease in the excised colectomy specimen because features of typical severe ulcerative colitis were replaced by deep ulcers—often with knife-like fissures—relative rectal sparing, and transmural inflammation [44]. Transmural inflammation was present in most cases of indeterminate colitis but only related to areas of severe ulceration. Interestingly, 2/3rds of the cases from Price's series turned out to be ulcerative colitis in future follow up [45]. Approximately half of cases described by Price had uneven disease that fell into two patterns, both similar to Crohn's disease.

The Montreal working party has recommended that the term 'indeterminate colitis'should only be used for colectomy specimens where pathologists are unable to make a diagnosis after full examination. Instead they have introduced the term 'inflammatory bowel disease type unclassified' (IBDU) is suggested for patients in whom there is evidence on clinical and endoscopic grounds for

inflammatory bowel disease affecting the colon but not the small bowel. In addition there are no definitive histological and endoscopic features to favour either Crohn's disease or Ulcerative colitis.

The definition of IBDU may be difficult to adopt universally as it is most likely to be interpreted according to the level of available expertise. Some patients may have colitis that cannot be subclassified into Crohn's disease or Ulcerative colitis despite investigations at referral centres by a multidisciplinary team of gastroenterologists, pathologists and surgeons. IBDU may however be used loosely and more commonly in less specialized centres, which otherwise would have been diagnosed Ulcerative colitis or Crohn's colitis if investigated by a more expert team [46]. Needless to say this may therefore lead to inappropriate case ascertainment and prognostication.

One should be cautious in making a diagnosis of IBDU in the following circumstances:

- Fulminant or refractory IBD – in the initial cohort of indeterminate colitis, 2/3rds progressed to develop ulcerative colitis [45]
- Chronic phase of IBD – this is simply highlighted by the fact that when IBD is inactive, only minimal histological changes are found, making it difficult to diagnosis either Crohn's disease or ulcerative colitis [47]
- Treated cases of IBD – drugs like azathioprine and infliximab can induce mucosal healing [48,49]
- Earliest stages of IBD – UC especially in children may initially present with atypical features with relative or complete rectal sparing, with patchy disease [47,50-52]

Table 1.2.4.1 shows a list of conditions causing colitis in children. These should be diagnostically considered and excluded to avoid such patients being labelled as IBDU.

Lastly I would like to comment on role of serology in making an affirmative diagnosis in indeterminate colitis. Jossens et al prospectively studied 97 adult patients with indeterminate colitis with serology for ASCA and ANCA. Diagnosis changed to a UC/CD in 32% of these patients. A study of serology showed ASCA+/pANCA- to predict CD in 80% of patients and ASCA-/pANCA+ to predict Ulcerative Colitis in 63.6%. 48.5% did not show antibodies against ASCA or pANCA. Most of these patients remained diagnosed with IC during their further clinical course, defining perhaps not only a histological but also a distinct clinico-serological entity [46].

Table 1.2.4.1 Causes of colitis in children

- Inflammatory bowel disease (Crohn's disease and Ulcerative colitis)
- Infective colitis
- Amoebic colitis
- Cow's milk or allergic colitis
- Autoimmune colitis
- Chronic granulomatous disease
- Immunodeficiency
- Behcet's disease
- Hirschsprung's colitis
- Metabolic disorders

1.3 Epidemiology of paediatric Crohn's disease

1.3.1 Incidence of paediatric Crohn's disease

The incidence of paediatric Crohn's disease reported in the British Isles during 1998 and 1999 was 3.1/100,000 per year [53]. Although there are no previous prospective reports for comparison, retrospective studies from Scotland show a change in incidence from 2.3 to 2.5 [15,54-56]; the second study was conducted 7 years after the completion of the first. A more significant increase has been reported in Wales from 2.5 to 3.1 [57,58], the latter being a prospective report following the initial retrospective study, from the region. See table 1.3.1.1.

Reports from other centres in Europe, outside UK, show a similar increase in incidence in paediatric Crohn's disease. These are also listed in table 1.3.1.1 and include figures from France, Sweden, Norway and Denmark.

Table 1.3.1.1 Incidence of paediatric Crohn's disease in Scotland, Wales, UK and France

Location	Study years	CD	Study type
Scotland	1968-1983 [56]	2.3	R
	1990-1992 [54]	2.5	R
	1981-1995 [55]	2.5	R
	1981-1997 [15]	2.3	R
Wales	1989-1993 [57]	2.5	R
	Jan 1995 – 30th Mar 1997 [58]	3.1	P
British Isles	1998-1999 [53]	3.1	P
France Brittany	1994-1997 [59]	1.6	
France, Nord-Pas de Calais	1984-1989 [60]	2.1	P
	1988-1990 [61]	2.4	P
	1988-1999 [6]	2.3	P
Sweden	1984-1995 [8]	1.3	P
Sweden, Northern Stockholm	1990-2001 [7]	4.9	R
Norway	1984-1985 [9]	2.5	P
Denmark	1962-1987 [62]	0.2	R
Netherlands	1999-2001 [63]	2.1	P

Key: R= retrospective, P= prospective

1.3.2 Difficulty in interpreting and comparing different epidemiological studies

Comparison between different epidemiological studies is not easy and a change in incidence should be interpreted with care. Various factors may influence the reported incidence to vary from the true incidence of disease in a particular region. These are listed as follows:

Epidemiologic studies may be conducted retrospectively or prospectively. Data may be under-reported in retrospective studies, with an added disadvantage that there may be no way to cross-check and verify ambiguous facts. A previous retrospective report should certainly be compared with caution to for example, a present day prospective report.

The upper limit of paediatric age tends to vary in different practicing units and epidemiologic studies, from as low as 14 to as high as 17 years (Table 1.3.1.1). Because of the well described, steep rise in incidence in the teenage years this difference can be very important.

Crohn's disease will often present with non-specific symptoms and as a result there may be a delay in making the first diagnosis. In a recent study from the British Isles a median delay of 5 months (mean 11 months) has been described. One fifth of the children had symptoms for more than a year [17]. In the same context an adult gastroenterologist may not be skilled to recognise growth failure or pubertal delay and the subtle clinical features of non-classical Crohn's disease. Delay in diagnosis and recognition may have an impact on the reported incidence compared to a true incidence depending on the cut-off age used for a study. This is explained in the following hypothetical example:

Let us assume that an adolescent with onset of Crohn's disease at 15 year of age presents early to a specialist gastroenterology unit, undergoes initial investigations and is diagnosed without delay. The same child in a different area may ignore the initial symptoms, wait to be referred and seen by a specialist. The whole process in the second case may last well over a year; the patient will then be older than 16 years at the time of diagnosis. Even the best designed prospective study, with a cut off age of 16, would naturally include this child in one area but exclude in another. This illustrates that not only the differential cut off age in various studies may impact on the reported incidence, but also local practices and ease of availability of a paediatric gastroenterology service may influence it.

Similarly, caution is needed whilst comparing a study of 2000 with a study (for example) from the early 1970s. There is now increased awareness and ability to investigate suspected inflammatory bowel disease in children with use of gastroscopy, ileocolonoscopy and barium investigations. As these investigations were not readily available in the past this makes comparison of present day epidemiologic studies with studies from 20 years ago difficult.

True population based registries of paediatric Crohn's are scarce and most reports are a result of relatively crude hospital based figures.

As many as 15% of children are initially diagnosed as indeterminate colitis, which then may later evolve to become either CD or UC, which then may happen after the age of 16.

Lapidus's work highlights the above described fallacies [64]. In 1997 he showed an increase in Crohn's disease incidence between 10-14 years of age but a decrease between 15-19 years (comparison of years 1980-84 and 1985-89). The authors maintain that colonoscopy was adopted as early as the 1970's in Sweden; hence the diagnostic tools used to make a diagnosis have remained uniform. If

the diagnostic tool is a constant in this equation, then an alternative logical explanation, other than a true increase/decrease, is that the 15-19 year group in the 1985-1989 period had their diagnosis made earlier, reflecting a relative increase in incidence of the 10-14 year age group but relative decrease of incidence in the 15-19 year age group [64,65]. A true increase in this case should have reflected as an increased incidence not only in the 10-14 year age groups but also in the 15-19 year age groups.

1.3.3 Geographical variation

There is a striking geographical variation in distribution of Crohn's disease. It is recognized that Scandinavian descent confers an increased risk of inflammatory bowel disease. 'Viking' is a native Scandinavian term for Norse warriors who raided the coasts of Scandinavia, the British Isles, and other parts of Europe between the late 8th and 11th century. They travelled to the west and Varangians, who were best known as the Varangian Guards of the Byzantine emperors, to the east. This period of European history (generally dated to AD 793 - AD 1066) is referred to as the Viking age. History shows that the Vikings settled in Scotland, Scandinavia and Minnesota. These are areas with high incidence of inflammatory bowel disease (Table 1.3.1.1).

Earlier observations from the 1960s and 1970s show a north south gradient of inflammatory bowel disease. However, more recently (1991 – 1993), Shivananda et al in their 20 centre European collaborative study (EC funded) are less sure of the north south differences. They feel that at present there is a lesser difference possibly indicating an increase in incidence in the south in recent years followed by stabilisation of incidence in the north [66]. This

stabilization of incidence in the North, could represent better availability of diagnostic techniques during the period assessed. There is also a suggestion of a west east gradient within Europe. Adult studies show that the current incidence in Poland, Russia and the former Yugoslavia is similar to that of Western Europe in the 1940s and 1950s [67].

In Australia, there has been a recent report which shows a rising incidence in paediatric Crohn's disease. There seems to be a striking difference when figures from 2001 are compared with 1971 (0.128/100,000/year (1971)-2/100,000/year (2001). The study was conducted in children from Victoria (Australia) with data collection from Royal Children's Hospital, or Monash Medical Center, Melbourne, Victoria. As discussed in early sections of this chapter, availability of a paediatric gastroenterologist and use of endoscopy may have played a role in this increase [68].

Lastly, inflammatory bowel disease is relatively rare in continents of Asia and Africa. Recently there has been a report of ulcerative colitis from Punjab, India emphasizing that this may reflect a problem of under reporting rather than non-existence of the disease in the areas [69]. Stringent measures for diagnosis are scant due to unawareness of the disease and notable absence of any robust epidemiological data.

1.3.4 Gender and age

Crohn's disease tends to be commoner in adult females by 20-30% when compared to adult males [65]. Due to unexplained reasons, reports from paediatric studies generally show this ratio to be inversed [17,57]. This could suggest a different disease process but has yet to be established. The peak incidence for Crohn 's disease is

observed in late adolescence or young adulthood with a smaller second peak in the sixth decade [65].

1.3.5 Races and ethnic groups

Jews are susceptible to Crohn's disease and in particular Ashkenazi Jews are at an increased risk [70]. Ashkenazi Jews are descendants of the medieval Jewish communities of the Rhineland. Many later migrated eastward, forming communities in Germany, Poland, Austria, Eastern Europe and elsewhere between the 10th and 19th centuries. Interestingly in the 11th century the Ashkenazi comprised 3% of the world's Jewish population which increased to 92% by 1931. Currently they make up approximately 80% of the Jews world-wide. A significant proportion of Jews who migrated from Europe to other continents, particularly the United States, in the past two centuries are Eastern Ashkenazim. Their incidence rate for Crohn's disease varies in the world but nevertheless tends to be three to four times greater than the 'White' population.

In the UK it has been reported that the proportion of children with UC is higher in South Asian patients than Caucasian [53,71] however in one centre, with 100% ascertainment, the phenotype of IBD was identical between South Asian (of Bangladesh origin) and Caucasian children [72]. British children of Bangladeshi origin with IBD have equal proportion of Crohn's (58%) and UC/IC (42%) to Caucasian children. However children of Indian origin (resident in Leicester, UK) have a higher incidence of UC/IC (67%). The IBD phenotype in British children of South Asian origin varies by the country of their parent's birth. This implies important genetic differences between these countries and demonstrates that studies need to define the ethnicity more precisely both for genetic and epidemiological research [73].

1.3.6 Genetics

1.3.6.1 Genome wide linkage analysis (GWLA) and genome wide association studies (GWAS)

If a disease runs in the family, one can look for genetic markers (DNA sequence) that run exactly the same way in the family (for family specific traits). Genes causing disease, in proximity to these markers, can be identified by genome wide linkage studies. Nine IBD susceptibility loci have been discovered and replicated to varying extent (IBD 1-9). Some are specific for UC (such as IBD 2) [74-76] others for CD (IBD1) [77,78]. Despite initial promise shown by these linkage studies and the discovery of the NOD2 in 2001 subsequent progress has remained slow. This is due to low resolution of GWLS where areas millions of base pairs long are tested. In addition the strongest signals in this type of scanning tend to come from recessive and highly penetrant diseases.
This has however changed with the advent of Genome wide association studies (GWAS), which is an approach that involves looking at alleles different in the case population compared to the controls. It is now possible to look at differences in the whole genome with the completion of the Human Genome Project in 2003 [79] and International HapMap Project in 2005 [80-82]. To date over 50 IBD disease genes /loci have been identified.

1.3.6.2 Family History and early onset inflammatory bowel disease

One of the first clues towards a significant genetic component in IBD was the twin concordonce studies. In twins 44-58% concordance

has been reported for monozygotic twins compared with 0-3.8 % in dizygotic twins demonstrating the greater importance of genetic over environmental factors [83,84]. This is less strong in UC with monozygotic twins having 14-19 % concordance and 0-5 % in dizygotic twins [84,85]. The lifetime risk of Crohn's disease for first degree relatives has been shown to be 7 % in non-Jewish, white and 16.8 % in Jewish white families [86].

Polito et al reported that 30% of those presenting under the age of 20 had a family history compared with 14 % of those presenting over 40 [87]. Childhood onset inflammatory bowel disease appears to have a distinct phenotype with male predominance [6,7,88] compared to female preponderance in adults [89,90]. In addition there is evidence to support extensive intenstinal involvement (panenteric Crohn's disease [91,92] with rapid early progression with early requirement of immunomodulatory drugs. Children diagnosed below 8 years of age show significantly less ileal disease and more isolated colonic disease than their older counterparts [93-95].

Genetically, IBD5 variants have been shown to be associated with growth indices in early onset disease and a more severe phenotype [96,97]. Two SNPs, rs3024505 (IL10 region) and rs917997 (IL18R1, IL18RAP) showed genome wide significance for CD in early onset population, but not in the adult disease [98]. In addition SNPs near ORMDL3 and ICOSLG were shown to be significant for early onset UC having only previously been implicated in adult CD [99].

1.3.6.3 Defects in bacterial handling in Crohn's disease

1.3.6.3.1 NOD2

After fine mapping of the IBD1 region, seminal studies in 2001 identified the gene encoding NOD2 (which has now been renamed

as CARD15 (Caspase and Recruitment Domain) on chromosome 16q (IBD1 locus) as being important in white but not Asian patients [100]. 10-30 % of white CD patients are heterozygous for one of the three common variants of CARD15 (compared with 8-15% of controls); 3-15 % are homozygote or compound heterozygote (0-1 % of controls). Homozygous or heterozygous carriage of the common variants of CARD15 has been associated with early onset CD (as well as stricturing disease and ileal involvement) [101-103]. NOD2/CARD15 is an intracellular PRR (patern recognition receptor) that recognises muramyl dipeptide (MDP) a product of bacterial cell wall degradation. The recognition of MDP is facilitated through the LRR domain of the NOD2 protein [104]. This bond then triggers an intracellular signalling. It has been shown that NOD2/CARD15 has expression limited to Paneth cells [105] in the intestinal crypts.

1.3.6.3.2 NLRP3

The NLRP3 gene (1q44) encodes the cryopyrin protein which then regulates the enzyme caspase-1. Caspase-1 activates the pro-inflammatory cytokine IL1β. The NLRP3 gene thus controls inflammation. Villani and group recently reported effect of 6 CD mutations on NLRP3 expression on peripheral blood mononuclear cells [106]. The rs4353135 genotype has been significantly associated with altered expression and homozygosity of the risk allele at rs6672995 which results in decreased levels of IL1β following stimulation with lipopolysaccharides.

1.3.6.4 IL23 and Th17 signalling

Using GWAS, Duerr et al [107] reported a strong association between Arg381Gln (a non-synonymous SNP, rs11209026) in the IL23 receptor

gene (IL23R) and Crohn's disease susceptibility. This variant has shown to be protective for the development of IBD (like ankylosing spondylitis), although other signals within the gene also confer disease susceptibility idependent of the SNP [108]. Taylor et al [109] genotyped multiple SNPs in IL23R identifying IL23R risk and protective haplotypes compared to Arg381G1n alone.

Both IL23 and IL12 play an important role in development of naı¨ve Crohn's disease4+ T cell differentiation. Variations in the IL12 and IL23 pathways might lead to an aberrant early immune response to microbial encounter. IL12 drives naı¨ve Crohn's disease4+ T cells to a Th1 phenotype, however in the presence of IL23 they adopt the Th17 phenotype (drives autoimmune inflammation in animal models), characterised by the production of IL17, tumour necrosis factor and IL6 [110,111]. Some specific bacterial components such as peptidoglycan exert a differential regulatory effect on antigen presenting cells in increasing IL23 gene expression but not IL12 which explains that even subtle imbalances can result in inflammation [112]. Earlier in the differentiation of the Th17 subset, ICOSLG (the molecule inducible costimulator ligand also known as B7-H2) binds with T cell receptor (ICOS) leading to T cell activation [113]. ICOSLG is a member of the B7 family co-stimulatory molecules. It is a transmembrane protein with extracellular IgC and IgV domains. The ICOS and ICOSLG interaction is not only essential in early differentiation of the naïve T cells but is likely to be important in the careful balance between IL-10 producing regulatory cells and Th17 population [114]. Functional assays in IBD patients show that IL-17 producing cells and the levels of Th17 related cytokines IL-17 and IL-22 are increased in IBD patients [115-117].

1.3.6.5 Autophagy in pathogenesis of Crohn's disease

Autophagy is a process by which cell digests parts of their own cytoplasm for inhouse-keeping purposes. mTOR, is a kinase which critically regulates autophagy. Under starvation conditions, mTOR inhibition leads to activation of the autophage cascade to provide an alternative energy source by recycling intracellular organelles. Defective autophagy is now considered to play a role in pathogenesis of Crohns' disease. Two genes are associated, which are described as follows.

1.3.6.5.1 ATG16L1

GWAS have implicated association of Crohn's disease with ATG16L1 gene [118,119]. The ATG16L1 gene provides instructions for making a protein called ATG16 autophagy related 16-like 1. This protein is part of a larger family of proteins that are required for autophagy. At least one variation in the ATG16L1 gene is associated with an increased risk of Crohn disease. This increased risk has been found primarily in Caucasian (white) populations. The identified ATG16L1 variation changes a single protein building block (amino acid) in a critical region of the ATG16L1 protein. Specifically, it replaces the amino acid threonine with the amino acid alanine at protein position 300 (written as Thr300Ala or T300A) [118]. The gene is expressed in the intestine and particularly strongly in Crohn's disease, CD4+ T lymphocytes. Hampe and colleagues have demonstrated expression of ATG16L1 mRNA and protein in the colon, small intestine, intestinal epithelial cells and leucocytes [118]. Lees and colleagues have demonstrated downregulation of ATG16L1 mRNA in colonic CD biopsies compared with healthy controls in their large microarray dataset. Recently gene-trap mutations in ATG6L1 in two mouse lines have shown defective intestinal autophagy and disruption of granule exocytosis pathways in Paneth cells [120,121].

1.3.6.5.2 IRGM

IRGM was identified as a gene implicated in pathogenesis of Crohns disease in the WTCC GWAS. Two non-functional SNPs (rs13361189 and rs4958847) on chromosome 5q33.1 were strongly associated with CD [122]. The increased risk has been primarily found in Caucasian (white) populations. Although there is more work done on pathogenesis, simplistically IRGM gene variations may result in the cells ability to abrogate harmful bacteria effectively.

1.3.6.6 Developmental genes

Genetic studies show evidence that signalling pathways critical to normal mammalian gut development are dysregularted in IBD pathogenesis. There is a role for NK2 transcription factor-related, locus 3 (NKX2.3) [123,124] and glioma associated oncogene homolog 1 [125] (transcriptional regulator of the hedgehog signalling pathway) in inflammatory bowel disease.

1.3.6.7 Intracellular Tyrosine Phosphatases

1.3.6.7.1 PTPN2

The WTCCC study has identified PTPN2 as a CD susceptibility gene which encodes the cytosolic T-cell protein, tyrosine phosphatase (TCPTP). It acts by dephosphorylating and inactivating its targets, hence TCPTP is a key negative regulator of inflammatory responses [126].

T cell protein tyrosine phosphatase can regulate signalling pathways that are induced by various growth factors (eg EGF) and cytokines (eg TNFα). MAPK (mitogen activated protein kinases), a negative control for TNFα, is one of the target proteins inactivated by TCPTP [127]. MAPK inactivation results in propagation of inflammation.

1.3.6.7.2 PTPN22

Meta-analysis by Barrett [128] demonstrates evidence for association of PTPN22 gene with Crohn's disease. In Crohn's this SNP is protective [129] and is expressed on many haemopoietic cells, notably T cells. PTPN22 encodes a protein tyrosine phosphatase which affects the T cell receptor signalling pathway.

1.4 Paediatric Crohn's disease – symptoms, complications and assessment

1.4.1 Presenting symptoms

1.4.1.1 Introduction

Paediatric Crohn's disease classically presents with diarrhoea, weight loss and abdominal pain. A recent survey of paediatric Crohn's disease in Great Britain and Ireland, however, shows that only one quarter of CD present with these features and nearly half did not report diarrhoea [17]. There can be a delay in recognizing and making a diagnosis on the basis of classical features alone. A median delay of 5 months has been reported from the onset of symptoms to time of diagnosis. In addition, a fifth of these patients were reported to have symptoms for more than one year [17]. The commonest reported intestinal symptoms in order of frequency reported in this series were: abdominal pain (72%), weight loss (58%) and diarrhoea (56%) [17]. Moreover lethargy was found in 27%, of the children.

1.4.1.2 Abdominal pain

The abdominal pain is characteristically periumbilical and colicky. It may vary in character and site depending on location of inflamed bowel such as gastric inflammation may result in epigastric and extensive colonic disease in lower/ left-sided abdominal pain. Eating may not cause pain in gastritis alone but also trigger it via the gastrocolic reflex (presence of food in the stomach normally triggers

intestinal peristalsis). If this triggers contraction of inflamed bowel, it will cause pain. Urgency and tenesmus are well described in children with distal colitis. Acute appendicitis is a major differential diagnosis particularly in children with ileal and caecal involvement.

1.4.1.3 Anorexia, weight loss and growth

Anorexia is a symptom of Crohn's disease which may lead to misdiagnosis as these children may be considered to be suffering from anorexia nervosa. Of the children with Crohn's disease, 58% have lost weight at presentation [17]. This is likely to be due to decreased intake a consequence of raised pro-inflammatory cytokines (e.g.; TNF, IL-6) known to cause anorexia. Malabsorption seems to be only a minor factor contributing to weight loss. Mild steatorrhoea was found only in 24% of patients with ileal disease, 26% with ileocolonic involvement and 17% with Crohn's colitis [130].
A review of growth physiology shows that growth hormone mediates release of IGF-1 from the liver. IGF-1 in turn mediates the growth hormone's effects on growth plates. There is a well-recognised association between impaired growth in Crohn's disease and low IGF-1 [131,132]. Factors known to suppress IGF-1 include malnutrition [133], cytokines [134,135] and corticosteroids [136]. IL-6 mediated decrease in IGF-1 production represents a major potential mechanism of short stature [137]. IL-6 has also shown to have a direct adverse affect on the epiphyseal growth plate.
It is likely that appropriate linear growth in children with Crohn's disease may be best achieved by control of intestinal inflammation with adequate nutrition [138] and minimal use of corticosteroids. A recent Cochrane review reflects paucity evidence, though some growth benefit is shown with use of nutritional therapies in children with Crohn's disease [21].

1.4.2 Extraintestinal manifestations

1.4.2.1 Introduction

Crohn's disease does not only affect the intestine. It may cause systemic effects known as extraintestinal manifestations. The common target organs are skin, joints, liver, eye and bone. They tend to be commoner with colonic Crohn's rather than isolated small bowel disease [139,140]. The extraintestinal manifestations can be broadly divided into two groups; one which follows active Crohn's disease activity and a second group with manifestations un-related to active disease. For example erythema nodosum tends to be related to active disease although does not reflect severity of disease as opposed to pyoderma gangrenosum, which tends to be unrelated to the disease process.
There is also a third group of extraintestinal manifestations, which are a result of complications of the disease process. Examples include nephrolithiasis and ureteric obstruction [141,142].

These are described in detail as follows:

1.4.2.2 Joints

Arthralgias are commoner than arthritis and affect about 15% of patients with Crohn's disease [140]. The knees, hips and ankles are most commonly involved. These arthralgias are related to disease process and improve with treatment of disease. An exception to this is HLA B27 arthritis, a cause of juvenile ankylosing spondylitis, which is unrelated to disease activity [140,143]. In HLA B27 arthritides the

distribution of joint disease tends to be different with involvement of hips or sacroiliac joints [143].

Arthropathies can be pauciarticular (type I) when it affects less than 5 joints or polyarticular (type II) with involvement of more than 5 joints. The type I arthropathy is similar to the post dysenteric reactive arthritis and is self limiting. This, however also tends to coincide with episodes of active IBD. Type II arthropathy on the other hand generally persists for months or years and runs a course independent of IBD. It is also associated with uveitis but not the other extraintestinal manifestations. In contrast, type I arthropathy is associated with extraintestinal manifestations other than uveitis [143].

In adults 6% of patients with a seronegative spondyloarthropathy will develop IBD, but patients with normal gut histology at the time of the arthropathy do not go on to develop IBD [144-146].

1.4.2.3 Skin

Erythema nodosum and pyoderma gangrenosum are well-described skin complications in children [140]. In a recent series reported from the British Isles, 6/379 (0.02%) were reported to have erythema nodosum or some form of rash [17]. Erythema nodosum is the commonest skin lesion associated with inflammatory bowel disease and clinically appears in conjunction with active disease. Histological examination of the lower dermis of the skin lesion shows a moderate lymphohistiocytic infiltrate and direct immunoflorescence for immunoglobulins and complement may reveal perivascular deposits [147]. Erythema nodosum usually responds to treatment with corticosteroids.

Pyoderma gangrenosum is a chronic ulcerating skin disorder which can appear as a severe and debilitating complication sometimes more severe than the underlying inflammatory bowel disease.

Lesions typically occur on extensor surfaces of lower extremities and described in adult patients with severe disease and colonic involvement. High doses of steroids are effective but in severe cases successful use of cyclosporine, mycophenolate and infliximab has been described [148-152].

1.4.2.4 Eye

Ocular lesions may be present in young patients and comprise of episcleritis, uveitis and orbital myositis. Hofley reported uveitis in 6.2% of the children (n= 97) with Crohn's disease. These cases were mild, asymptomatic and self-resolving. Frequency of uveitis was found to be higher in children with IBD having other extraintestinal manifestations (15%) than in those without (3.1%; $p<0.10$) [153].

1.4.2.5 Liver

Primary sclerosing cholangitis is classically described with ulcerative colitis and rarely so with Crohn's disease. When present it may precede onset of bowel symptoms and tends to be unrelated to bowel inflammation [154-156].

1.4.2.6 Osteoporosis

The World Health Organisation defines osteoporosis as bone density (or bone mass) that is at least 2.5 standard deviations below peak bone mass (defined as, the bone mass achieved by healthy adults aged 18-30 years). There is yet no agreed definition for children as the bone density is difficult to quantify in children. Despite this, it has been shown that children with Crohn's disease have reduced bone

density [20] compared to normal controls [157] and children with ulcerative colitis [158]. The reported prevalence is variable ranging from as low as 11% to as high as 50% [20,158,159]. This variability may partly be explained by the inherent difficulty in interpreting DEXA scans. It is easy to over read using adult reference systems. These standard measures do not take regard of variability in stature, size, sex and race. Gafni et al have described over-reporting in more than 50% of the 34 cases referred to them with osteoporosis. Amongst other causes the most frequent error (62%) was use of T-score (SD score compared with young adults) to diagnose osteoporosis. After correction for body size, only 26% retained the diagnosis of low bone mineral density with 53% considered to be normal. Herzog [159] and Ahmed et al [160] have reported similar 'reporting' problems in paediatric Crohn's disease.
Several factors seem to be responsible for reduced bone mineral density. These include corticosteroid usage, release of cytokines such as IL-6, reduced calcium and vitamin D intake and relative immobility; all contributing to development of paenic bones. Sentongo found hypovitaminosis D in 16% of the 112 paediatric Crohn's patients. This was however, unrelated to bone mineral density or average dietary intake of vitamin D in this particular study [161].

Identifying and treating osteoporosis in children may produce dramatic results even when they have suffered vertebral fractures, as demonstrated by Thearle whilst treating a 12 year old boy with vertebral fractures at the time of first presentation of his Crohn's disease [162].

1.4.2.7 Other

Other rare complications include pancreatitis which can result secondary to inflammatory bowel disease or treatments like azathioprine and 6- mercaptopurine [163,164]. Renal complications of obstruction and stones [141], hypercoaguable states including DVT (deep venous thrombosis) [165], pulmonary emboli and cerebrovascular disease are well described complications [159,166].

1.4.3 Psychological issues

Crohn's disease is a complex chronic disease, affecting the psyche of the patient. There is no cure for the disease and it relapses without warning, with onset of undesirable symptoms. These symptoms may not only impair daily activities but also be socially unacceptable. These include, frequent diarrhoea and unexpected passage of gas and stool; usually difficult to control which may result in anxiety and depression. Lack of energy, a common symptom of active disease, makes it more difficult to cope. Diagnosis is made by painful blood tests and endoscopies, and the preparation for the performance of the latter can be particularly embarrassing. Treatments may be poorly tolerated as for instance enteral nutrition may need to be administered via a nasogastric tube. Medicines such as corticosteroids give a moon face, short stature and acne, unacceptable for teenagers. Uncertainty of the disease makes simple chores like planning holidays really difficult.
In a study of psychological issues affecting children with Crohn's disease from Leicester, 95% of the patients thought that their families were understanding and sympathetic [18]. However, there were some worrying findings in this study. Nearly 70% were unable to participate in sports on a regular basis, 60% unable to leave the house at all, 50% unable to play outside with their friends with 40% reporting concerns about going on holidays, 53% percent thought that their

teachers were ignorant of Crohn's disease and were treated unsympathetically. 80% felt that they had underachieved because of ill health. Children were worried about their future, and specifically about its effect on their schooling and prospects of getting a job. Akobeng et al from Manchester reported similar findings in their cohort [19]. In a previous study it has been shown that parents are concerned for their children in issues regarding future relationships, particularly marriage [167].
This is a brief description of Crohn's disease, and as we endeavour to learn about the disease and its treatments, it is obvious that quality of life issues are important in children with Crohn's disease. These concepts with tools used for assessment are discussed in detail in sub-chapter 1.7.

1.4.4 Tools used for assessment of clinical paediatric Crohn's disease

Several tools have been used and devised to assess disease severity in Crohn's disease [168]. In the 1970s Crohn's disease activity index (CDAI) was devised particularly aimed for adults. It included eight variables and involved maintenance of a 7 day diary, to reflect disease activity in that particular time frame, not easy to use in a single sitting. Lloyd-Still's scoring system evolved during this period. This not only included growth but also sigmoidoscopic and radiological evaluation [169]. Although CDAI has been extensively used as a research tool, difficulty in usage meant that these indices never became popular enough to be used in a clinic setting.
In the early eighties Harvey-Bradshaw devised a scoring system dependent on symptoms reported by the patients. It is short, simple and easy to score. Its completion does not require any laboratory data either. Although it has been incorporated in a few studies, it

perhaps is not applicable to paediatric practice for two reasons. First, the total score heavily depends upon correct symptom reporting, which may not be accurate particularly in the younger age group. Second, growth an important feature of paediatric Crohn's disease, is not represented by this scale [170,171]. Two further scales (OMGE, Index of the Organisation Mondiale de Gastro-Enterologié; The Cape Town index) were introduced; none ever became popular [172,173]. The CDAI, although cumbersome, remained the gold standard for majority of clinical trials conducted in paediatric Crohn's disease. A need for an easily usable, paediatric scoring system for assessment of Crohn's disease was desired.
In the 1990's Hyams working in conjunction with twelve paediatric gastroenterology centres, devised the PCDAI (paediatric Crohn's disease activity index) [174]. The PCDAI index was validated against the modified Harvey-Bradshaw scoring index with good correlation [175]. It comprises of clinical markers, laboratory tests and growth markers for assessment of disease and consists of 10 questions. This can be used and completed in a clinic sitting and has been incorporated in many paediatric studies. On the downside, filling a PCDAI form can be time consuming and requires a blood test to complete an assessment (see table 1.4.4.1).

Table 1.4.4.1 The paediatric Crohn's disease activity index (PCDAI)

History (Recall, 1 week)

Abdominal pain	
None	0
Mild- brief, does not interfere with activities	5
Mod/severe- daily, longer lasting, effects activities, nocturnal	10
Stools (per day)	
0 – 1 liquid stools, no blood	0
up to 2 semi-formed with small blood, or 2-5 liquid	5
gross bleeding, or ≥ 6 liquid, or nocturnal diarrhoea	10
Patient functioning, general well being (recall 1 week)	
no limitation of activites, well	0
occ difficulty in maintaining age appropriate activities below par	5
frequent limitation of activity, very poor	10

Laboratory

Hct (%)

< 10 years (males and females)		11-19 (Females only)	
33	0	≥ 34	0
28-32	2.5	29-33	2.5
< 28	5	< 29	5

11-14 (Males only)		15-19 (Males only)	
≥ 35	0	≥ 37	0
30-34	2.5	32-36	2.5
< 30	5	< 32	5

ESR (mm/hr)

<20	0
20-50	2.5
50	5

Albumin (g/dl)

≥ 3.5	0
3.1-3.4	5
≤ 3.0	10

Examination

Weight*	
Weight gain or voluntary weight stable/loss	0
Involuntary weight stable, weight loss 1-9%	5
Weight loss ≥ 10%	10

Height	
At diagnosis	
< 1 channel** decrease	0
≥ 1, <2 channel** decrease	5
> 2 channel** decrease	10
Follow up	
Height velocity *** ≥ -1SD	0
Height velocity*** < -1SD, >-2SD	5
Height velocity*** ≤ -2SD	10
Abdomen	
No tenderness, no mass	0
Tenderness, or mass without tenderness	5
Tenderness involuntary guarding, definite mass	10
Perirectal disease	
None, asymptomatic tags	0
1-2 indolent fistulae, scant drainage, no tenderness	5
Active fistula, drainage, tenderness or abscess	10

Extraintestinal manifestations (fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, erythema nodosum, pyoderma gangrenosum)

None	0
One	5
≥ two	10

TOTAL SCORE: _____

* Change in weight was based on a comparison of the patients current visit weight with one determined a minimum of 4-6 months previously.
**Channel decrease. For newly diagnosed patients a historical search was made of the patients past records to establish the premorbid height percentile. This value was then compared with the current height and a decrease in channels calculated. A decrease from 50th to 10th percentile would represent a 2 channel decrease.
***Height velocity was calculated as cm per year, based on patient's height on current visit compared with a height 6m - 1 year ago.

1.4.5 Prognosis

Unfortunately there is no known cure for the disease. With focused management the majority of children with Crohn's disease will lead an active life, being regularly followed up in a clinic, maintaining remission with medications. Anne Griffiths has reported a 5 year follow up in Toronto relating to the 'rule of thirds'. In her study approximately 1/3rd had a mild course, 1/3rd troublesome exacerbations but achieving remission and the remainder faced a difficult disease course, half of this last group eventually benefiting from surgery [176].

Despite use of timely, intensive medical treatments surgery is unavoidable in a majority of children. In 1984 Puntis reported 83% of children with Crohn's disease, requiring surgical intervention within 4 years of diagnosis [177]. These figures are high and in 2004 Freeman in his cohort, reported that, 56.3% required surgery within a mean time of 4.2 years; still a high proportion. More, newer studies are needed, as with availability of immunosuppressants like azathioprine and infliximab this figure may be lower. Whether genes will in the future predict the need for surgery it remains unknown; the three NOD2 mutations, associated with ileal disease, have not been linked with a greater need for surgery [178].

Crohn's disease presents with two peaks first in teens and then around fifties. Polito, retrospectively studied records of 552 adult patients and found greater small bowel involvement (88.7% vs. 57.5%), more stricturing disease (45.8% vs. 28.8%), and higher frequency of surgery (70.6% vs. 55.3%) associated with a younger age of diagnosis [179]. Freeman more recently reviewed 224 patients and has put down increased complications in the younger group simply to the fact that the disease has been there for a longer duration. His analyses showed that strictures (28.6%) and penetrating

complications (46.4%) in the younger group were similar to adults especially when both groups were followed up for a similar period of time [180].

Cancer is a rare complication in the paediatric population. Walker-Smith JA has reported 2 children developing cancer from his years in Queen Elizabeth children's hospital, London (Personal communication). Mortality has been described, as a complication of drug treatment or a post-surgical septic complication following surgery/resection [180].

1.5 Treatments for Crohn's disease

1.5.1 Introduction

Treatments for Crohn's disease may be grouped into two main categories; first, medicines used for acute active disease and second those used for maintenance of remission. Corticosteroids, enteral nutrition and infliximab are used for acute active treatment. 5 aminosalicylates, azathioprine and methotrexate in comparison are used to maintain remission. There may be some overlap and therapies like enteral nutrition (supplemental) and infliximab may fall into both categories.

1.5.2 Drugs used for inducing remission

1.5.1.1 Corticosteroids

Corticosteroids are the main stay treatment for acute active Crohn's disease in adults [181] and children [182]. A Cochrane review by Benchimol in 2008, shows corticosteroids to be superior to placebo or 5 ASA for inducing remission in all ages [183]. There remains little doubt about their effectiveness; though the side effects are universally accepted to be a major disadvantage. Steroid associated growth retardation is a concern to clinicians, parents and the child [184]. In addition, teenagers dislike development of acne, moon facies, striae and hirsutism, all well recognised side effects of steroids. Side effects such as steroid psychosis and pseudotumour cerebri have also been reported. In comparison enteral nutrition has a safer side effect profile an attractive option for children and parents and as a result has replaced corticosteroids

as an effective first line treatment in many paediatric gastroenterology centres.

Use of corticosteroids as a maintenance agent is unjustified. The long-term consequences with effects on growth and bones would be unacceptable. The risks for osteopenia are higher in paediatric Crohn's disease when compared with ulcerative colitis, even after adjustment for cumulative dose of prednisolone [158].

As an alternative to Prednisolone, gastroenterologists have attempted to use budesonide [185-187]. A special controlled ileal release formulation, allows budesonide delivery in the ileum and right side of the colon. Adult trials show it to be almost as efficacious as oral prednisolone with an added advantage of having a lesser side effect profile [188]. Recently, a paediatric trial of budesonide, which despite failure to recruit full numbers for the study, has echoed the adult trials results with significantly fewer side effects and comparatively lesser adrenal suppression in children. Although remission rates were not significantly different in the two groups (55% vs. 71%, p=ns), there was a clear trend for prednisolone to be more effective for inducing remission [189]. Unfortunately, oral budesonide like prednisolone affects growth. In another paediatric study reporting its use in a cohort of 32 children, 6 pre-pubertal children continued to receive 6 mg budesonide for 6 to 13 months. Although 5 of the 6 experienced only mild or no gastrointestinal symptoms and gained weight, their mean height velocity was only 2.3 +/- 1.0 cm/year, and none grew at a rate of more than 4cm/year whilst receiving budesonide [190]. A Cochrane review by Seow of use of Budesonide for induction of remission in all ages shows it to be superior to placebo and mesalamine but not to corticosteroids [191]. In a randomised double blind controlled study in children a better response was obtained in inducing remission with a dose of 12 mg in

comparison to a conventional dose of 9 mg without any reported increase in side effects [192].
Astegiona has reported use of another new steroid Beclomethasone, in Crohn's disease in a cohort of 34 patients with 66.7% achieving remission at 24 weeks [193]. Tursi reported Budesonide to be superior to Beclomethasone in inducing remission in patients diagnosed with Crohn's disease for the first time [194].

1.5.1.2 Enteral nutrition

Role of enteral nutrition in treatment of Crohn's disease is discussed in sub-chapter 1.6.

1.5.1.3 Antibiotics

Metronidazole was first reported in 1975, to be effective in treatment of Crohn's disease [195]. Studies have shown it be efficacious in Crohn's colitis but not for treatment of small bowel Crohn's disease [196-199]. Its long term use may result in peripheral neuropathy, with reported incidence as high as 50-75% [200].
Ciprofloxacin, a quinolone, is commonly used in conjunction with metronidazole. Where metronidazole is effective against Bacteroides, ciprofloxacin is efficacious against enterobacteriaciae and E Coli. Prantera et al in a retrospective review of 233 patients demonstrated use of combination of antibiotics for treatment of acute flare ups [201]. Interestingly, in this study combination therapy (remission in 70.6%) was found to be as efficacious as metronidazole (remission in 72.8%) and ciprofloxacin (remission in 69%) used individually.
Antibiotics are also commonly used for treatment for perianal Crohn's fistulae. Limited uncontrolled studies report success in adult

Crohn's disease. Bernstein in a study of 21 patients reported healing in 48% and advanced healing in 21% [202]. Similarly, Jacobovits reported a 50% success with treatment of 8 patients with metronidazole [203]. More recently, Dejaco et al have reported similar success in a prospective open label study using combination antibiotics (ciprofloxacin and metronidazole) and azathioprine in 52 patients [204]. 50% success was reported at week 8 (25% complete healing) with patients receiving azathioprine being more likely to achieve a response.

To date there are no randomised controlled trials published on use of antibiotics in acute inflammatory bowel disease in children. However in clinical practice i.e., treatment of children with active Crohn's disease, both metronidazole and ciprofloxacin tend to be used in tandem.

Recently, topical use of metronidazole has been reported for use in perianal Crohn's disease. In a randomised controlled study of 74 patients compared to placebo, although the perianal discharge and pain was reduced significantly there was no significant change in the CDAI (Crohns' disease activity index) scores [205].

1.5.1.4 Infliximab

Infliximab is an anti-chimeric anti TNF∝ monoclonal antibody. In 1995 Van Delleman, in an uncontrolled study showed infliximab to be effective in treatment of active Crohn's disease refractory to steroids [206]. Since then several studies have been undertaken and the ACCENT 1 trial is the largest to date. 573 adult patients were recruited in this trial. They received 3 infusion courses with 8 weekly infliximab used as maintenance treatment. At the end of 30 weeks the remission rates were 45% in patients receiving regular 8 weekly

courses, 39% who received a single 3 dose infusion course and 19% in patients receiving a single infusion [207].

Infliximab is contraindicated in patients suffering with infections such as general sepsis, pneumonia and tuberculosis as suppression of immunity results in rampant infection, associated with morbidity and mortality. Disseminated histoplasmosis and pneumocystis has been reported with use of infliximab [208]. In the ACCENT I study 5% had acute infusion reactions and 1% serious infusion reactions. These were more common in patients receiving more than one infusion and in those who had developed antibodies to infliximab. Localised tuberculosis may spread systemically and patients should be screened for the disease before its use [209].

Infliximab has been used in children and data suggest that it is as effective in children as in adults [210-213]. There is some suggestion that early use of Infliximab may be superior to late use in paediatric Crohn's disease, with children in early stages of their disease maintaining longer periods of remission (n=3) [214,215]. Numbers in these studies are small (total n=15) and these results should be interpreted with caution. In the UK, national guidelines are now in place with indications of use limited to severe active Crohn's disease refractory or intolerant to steroids, not treatable by surgery [216]. I, in another study have shown that 3 dose Infliximab infusion treatment in children may delay but not avoid need for surgery in severe resistant Crohn's disease [217].

More recently, Hyams and group have reported the REACH study [218] a large 112 children based RCT, demonstrating that paediatric patients responding to induction regimen of infliximab were more likely to be in clinical response and remission at week 54 when their maintenance therapy was given every 8 weeks rather than every 12 weeks. In another publication, in a post hoc analysis of the REACH study, Infliximab was found to be effective in reducing signs and

symptoms of concurrent perianal disease [219]. I have recently reported success with treatment of paediatric urogenital crohn's disease [220].

Till 2006, 8 cases of the rare and almost always fatal T cell hepatosplenic T-cell lymphoma were reported with use of Infliximab and concomitant Azathioprine and Prednisolone [221,222].

Infiliximab is one of the best known monoclonal antibodies used in treatment of Crohns disease and has been around for the longest. Infliximab is clearly effective but certainly this calls for caution in usage and prescription.

1.5.2 Drugs/ therapies used for maintaining remission

1.5.2.1 5-Aminosalicylates

5-Aminosalicylates have two components. 5-ASA is the active moiety of the drug and acting topically on the gut mucosa to prevent inflammation. It's absorbed rapidly from small intestine and excreted in the urine. The second part is a carrier used to deliver the 5-ASA at the desired place in the intestine, the ileum or the colon. In sulphasalazine (Salazopyrine®) the 5-ASA is joined to sulphapyridine by an azo bond which is cleaved by colonic bacteria. In Asacol®, there is a pH dependent coat around the 5-ASA whereas Pentasa® has a timed release mechanism helped by the individual coating of the microgranules.
Sulphasalazine compared to other 5ASAs is believed to have the most side effects mainly comprising of renal complications, liver toxicity, agranulocytosis or toxic epidermal necrolysis [223,224].
In a double blind randomised placebo controlled trial, mesalazine used at 50 mg/kg/day failed to prove to be an effective maintenance treatment [225]. A recent Cochrane review of use of sulphasalazine (meta-analysis of 6 trials), as maintenance agent for treatment of paediatric Crohn's disease, has not found any evidence in favour of its superiority over placebo [226].

1.5.2.2 Thiopurines

Azathioprine (AZA) is a purine metabolite and a pro-drug of 6-mercaptopurine (6-MP). AZA is converted to 6-MP during the first pass of this drug through the liver. 6-MP is further metabolized to 6-thioguanine (6-TG), the active metabolite that can be measured in

blood. 6-MP is eventually inactivated by 2 enzyme pathways: xanthine oxidase and thiopurine methyltransferase (TPMT).
A Cochrane review from 2000 shows an odds ratio of 2.04 for inducing remission with azathioprine in comparison to placebo. Treatment for more than 17 weeks increased this to 2.51 [227]. A more recent Cochrane review, 2009 continues to show superiority of thiopurine use over placebo in maintaining remission in 6 adult based trials [228]. Fuentes D et al have reported their retrospective experience of azathioprine use in Royal Free hospital in UK. They reported bone marrow toxicity in 8.6% of cases, leading to treatment stoppage, whilst using doses of 3 mg/kg/day [229]. Fraser has reported well-sustained efficacy over five years and a good safety record with use of azathioprine in a retrospective review of 30 years of practice [230]. More recently a meta-analysis of six studies showed an approximate fourfold increased risk of lymphoma in IBD patients treated with azathioprine/6-MP. The authors attributed this increased risk of lymphoma to be multi-causal; result of medications, severity of underlying disease, or combination of the two [231]. It is generally agreed that the overall benefits of use of azathioprine far outweigh any possible risks of developing lymphoma.
Markowitz has reported a placebo controlled multicentre RCT evaluating combination of 6 MP and Prednisolone in children with moderate to severe CD [232]. 55 children were randomised to 6MP or placebo within 8 weeks of diagnosis. Although remission was induced in 89% of children in both groups, over an 18 month period, only 9% of the remitters in the 6MP group relapsed compared to 47% of controls.
A meta-analysis of four placebo controlled trials demonstrates thiopurines to be superior to placebo in preventing post operative recurrence in adults [233].

1.5.2.3 Cyclosporin

Cyclosporin has no proven therapeutic value in treatment of Crohn's disease [234]. In a study on newly diagnosed children with Crohn's disease cyclosporin was not found to be as effective as corticosteroids [235]. In fact, Stange in a multicentre one year follow up study of 182 patients did not find cyclosporin to be significantly different from placebo [236]. Similar results were achieved by Feagan in an eighteen month randomized double blind placebo controlled trial of more than 300 patients and found cyclosporin similar in effect to placebo [237].

1.5.2.4 Methotrexate

Methotrexate has been shown to be effective in treatment of active Crohn's disease [238]. In a meta-analysis of 3 trials high dose intramuscular methotrexate was shown to be effective in steroid dependent patients. In another study 141 steroid dependent patients were randomized to intramuscular treatment and placebo for 16 weeks. 39% compared to 19% were able to come off steroids [238-242]. An adult based Cochrane review in 2009 shows intramuscular methotrexate to be comparable to mercaptopurine, but superior to placebo for maintaining remission in Crohn's disease. One study in the meta-analysis found the oral 'Methotrexate' formulation to be ineffective [243].

Methotrexate has been rarely used in paediatric Crohn's disease. Mack et al showed that 11/14 children and adolescents previously intolerant or refractory to azathioprine or 6-MP improved with methotrexate [244].

In 2000 a French study looked at use of Methotrexate in 41 adults with Crohn's disease. Methotrexate may adversely affect the liver

and in this study, 11/41 had a liver biopsy with mild steatosis found in 5. There was one patient each, with mild sinusoid dilatation, granulomatous hepatitis with mild portal fibrosis and slight periportal fibrosis [245].

Uhlen S and group retrospectively looked at 61 children in a 3 year multicentre study [246]. Indications to use Methotrexate included a non response to or relapse under azathioprine or azathioprine intolerance/toxicity. Methotrexate improved or induced complete remission in 80% of whom 29.5% relapsed after 13 +/- 10 months of treatment. It was possible to discontinue corticosteroids in 35 patients. Prospective studies are needed, however this study with others supports and suggests Methotrexate to be a viable second line alternative to thiopurines.

1.5.2.5 Thalidomide

Thalidomide lost popularity in the sixties because of its teratogenic affects (major limb deformities) found during treatment of morning sickness in pregnancy. After the initial fall out, it has now been found to have a suppressive activity on TNF production and used for treatment of Crohn's disease. Two open label adult trials with refractory Crohn's disease have been published [247,248]. At week 12 a response was achieved in about 70% of the patients in both studies showing thalidomide to be effective for treatment of acute and chronic active disease. It was also shown that lower doses are as effective, and, better tolerated than higher doses. Recently it has been used as maintenance treatment with 83% remission rate at the end of 12 months [249].

There are very few reports of use of thalidomide in paediatric Crohn's disease in the literature. Sensory neuropathy remains a major concern [250-254]. In a 2009 Cochrane review no randomised

controlled trials were identified to make any recommendation regarding usage of thalidomide or the newer lenalidomide for maintenance therapy in Crohn's disease [255].

1.5.2.6 Infliximab

Rutgeerts [256] in 1999 first showed in a double blind placebo controlled randomised trial that Infliximab was effective as maintenance therapy. At week 44, 62% patients receiving 2 monthly Infliximab (10 mg/kg) maintained remission compared to 37% receiving placebo. Following this study, Hanauer in 2002 [207] in a large double blind RCT, recruited 573 patients from 55 European centres showed remission rates were higher in the infliximab groups (receiving 5mg/kg and 10mg/kg) compared to placebo. Success was reported with use of infliximab in another placebo controlled RCT for treatement of fistulising Crohn's disease by Sands in 2004 [257]. Hyams and group have reported the REACH study [218] a 112 children based RCT, demonstrating that paediatric patients responding to induction regimen of infliximab were more likely to be in clinical response and remission at week 54 when their maintenance therapy was given every 8 weeks rather than 12 weeks. More recently Hyams [258] reported a larger multicentre study on maintenance treatment with Infliximab in children. A total of 158 infliximab treated children received maintenance therapy. Following maintenance therapy initiation, 26%, 44%, and 33% of patients continuing on maintenance infliximab over 0-1, 1-2, and 2-3 years, respectively, had clinically inactive disease not requiring corticosteroids or surgery. The recently published NICE guidance in 2010 also describes role of Infliximab as a maintenance agent particularly when it has been effective in inducing remission [259].

In the recent Cochrane review, Infliximab was found to be superior to placebo for maintenance of remission (RR 2.50) and clinical response (RR 2.19) in Crohn's disease [260]. In addition it was also superior in complete healing of perianal and enterocutaneous fistulas (RR 1.87).

1.5.3 New therapies

1.5.3.1 CDP571

CDP 571 is a genetically engineered human antibody to TNF∝, with the advantage it being less immunogenic than chimeric antibodies. In a recent placebo controlled trial in 169 patients with moderate to severe Crohn's disease, the rate of clinical response at 2 weeks was significantly higher compared to the placebo group (45% vs. 27%). Week 4 response rates similarly favoured the drug – 36.9% to 24.2% (p=0.014). However, at week 28, CDP571's 30.4% to 23.5% response rate advantage failed to reach statistical significance. Though, these results are disappointing, it was generally well tolerated with anti CDP 571 antibodies developing in 7% of the patients [261]. Sandborn in a larger study from 2004 of 396 patients [262], and Feagan [263] in a study of 269 patients in 2006 did not find CDP571 different to placebo for use in maintaining remission in Crohns' disease.
There is one published study on use of CDP 571 in paediatric Crohn's disease. 13/20 children with Crohn's disease responded to the treatment with a fall of > 10 in the PCDAI score. Mild to moderate side effects were documented in 14 patients with development of antibodies in 6 patients [264].

1.5.3.2 Etanercept

Etanercept is a TNF ∝ binding protein made by fusing the P75 TNF receptor tail to immunoglobulin G1. A recent trial of its use in an uncontrolled pilot study in 43 patients with moderate to severe Crohn's disease shows no efficacy [265].
Etanercept has been sporadically used in paediatric Crohn's disease but there are no published trials regarding its use. Early reports show it to be a disappointment and is certainly not as effective as its in other inflammatory conditions [266].

1.5.3.3 Natalizumab

Natalizumab is a recombinant humanized anticlonal antibody (IgG4) to ∝4 integrin. ∝4 integrin is an important mediator for leukocyte migration across vascular endothelial cells in the intestine and is up-regulated in acute inflammation. The multi-centre ENACT-1 and ENACT-2 trials are the largest studies on use of Natalizumab. In the ENACT-1 study, 905 patients were randomized to natalizumab (3 infusions timed at week 0, 4 and 8) or placebo. There was no difference in efficacy on comparison of the two groups at 10 weeks. The ENACT-2 study was a longer term study in which Natalizumab responders from ENACT-1 were enrolled. 339 patients were randomized to receiving Natalizumab (administered every 4 weeks through week 56) or placebo. Patients receiving Natalizumab showed a better response to treatment at week 36 compared to placebo (remission 44% vs. 26%) [267].
Two UK based placebo controlled trials of use of Natalizumab one in a group of 30 patients with mild to moderate active Crohn's disease showed it to be effective in 7 patients (39%) remission compared to one receiving placebo. The study's primary end point was CDAI at

week 2 [268]. In another placebo controlled study in 248 patients with moderate to severe Crohn's disease a 44% remission was achieved and shown to be superior to placebo. A dose of 6 mg/kg was found to have a similar efficacy to a dose of 3 mg/kg [269]. A recent Cochrane review taking the three, to date trials into account concluded that, Natalizumab may be effective for induction of clinical response. A greater response was seen in those with elevated CRP, active disease despite use of immunosuppressants, prior to use of anti TNFa therapy [270].

In a multicentre single arm study, Natalizumab has been used in 38 adolescent patients and assessed for safety, tolerability and efficacy [271]. Although remission was achieved in only 29% of the patients (PCDAI ≤ 10) a clinical response was seen in 55% (≥ 15 point decrease in PCDAI from baseline). 5 patients suffered from acute infusion reactions consisting of pyrexia and abdominal pain commonly. Serious adverse effects were noticed in 8 patients and considered to be unrelated to the drug. The planned study follow up was for a period of 32 weeks.

Natalizumab was withdrawn from the market on February the 28th 2005. The FDA issued a public health advisory to inform patients and health-care providers about the suspended marketing of Natalizumab while the agency and the manufacturer evaluated two serious adverse events reported with its use in patients. The FDA received a report of one death and one possible case of progressive multifocal leukoencephalopathy in Crohn's disease. In addition two cases were reported after treatment, their underlying diagnosis being multiple sclerosis [272]. Progressive multifocal leukoencephalopathy is a rare and serious progressive neurological disease with no known effective treatment.

The patient with Crohn's disease was 60 years old and had long standing Crohn's disease, presented with confusion and

disorientation in July 2003. He had been treated with natalizumab (eight infusions) since March 2002 in ENACT-1 and ENACT-2 trials (phase III trials of natalizumab in Crohn's disease). A brain biopsy was interpreted as astrocytoma. He died in December 2003, three months after treatment with corticosteroids. An autopsy was not performed. The brain biopsy was re-examined and the diagnosis revised to progressive multifocal leucoencephalopathy (PML). Retrospective analysis of serum samples detected JC virus in May 2003; the viral load increased by a factor of 10 after two further injections of natalizumab, confirming a temporal relation between PML and natalizumab [272].

1.5.4.4 Certolizumab (CDP870)

Certolizumab is a humanized IgG4 monoclonal antibody against TNFa. In a placebo-controlled study, 292 patients with moderate to severe Crohn's disease received subcutaneous certolizumab 100, 200, or 400 mg or placebo at weeks 0, 4, and 8. At all time points, the clinical response rates were highest for certolizumab 400 mg, the greatest response was at week 10 (certolizumab 400 mg, 52.8%; placebo, 30.1%; P = .006) but not significant at week 12 (certolizumab 400 mg, 44.4%; placebo, 35.6%; P = .278) [273]. In a larger multicentre study (PRECISE) in 2007 Schreiber reported a large multicentre placebo controlled RCT in 668 patients. The patients received Certolizumab every 4 weeks through to week 26 at which point a higher proportion of patients were in clinical remission compared to placebo (48% v 29%) [274]. To date, there are no paediatric studies of its use.

1.5.4.5 Adalimumab

Adalimumab is a fully human IgG1 monoclonal antibody to TNF that is administered subcutaneously. In 2004, Sandborn conducted an uncontrolled trial in 24 patients with Crohn's disease who had lost responsiveness or developed intolerance (acute or delayed infusion reactions) to infliximab. Patients were enrolled in a 12 week uncontrolled trial and treated with subcutaneous adalimumab 80 mg at week 0 and then 40 mg every other week starting at week 2. None of the patients experienced acute or delayed hypersensitivity reactions during treatment. Of the 17 patients, those with baseline CDAI scores > or =220: clinical remission occurred at weeks 4 and 12 in 2 (12%) and 5 (29%), respectively; and clinical response occurred in 7 (41%) and 10 (59%), respectively [275].

The results of the CLASSIC 1 trial on 299 patients (naïve to anti-TNF therapy) have been published in 2006. It is a randomized, double-blind, placebo-controlled, dose-ranging trial was performed to evaluate the efficacy of adalimumab induction therapy in patients with CD. The rates of remission at week 4 in the adalimumab 40 mg/20 mg, 80 mg/40 mg, and 160 mg/80 mg groups were 18% (P = .36), 24% (P = .06), and 36% (P = .001), respectively, and 12% in the placebo group. Adverse events occurred at similar frequencies in all 4 treatment groups except injection site reactions, which were more common in adalimumab-treated patients. Adalimumab was superior to placebo in this group of adults with moderate to severe Crohn's disease [276]. The CLASSIC II study (the study of maintenance Adalumimab) 44% in the placebo group were in remission at week 56. In comparison 79%, were in remission when receiving 2 weekly therapy and 83% when receiving weekly therapy at week 56 [277]. Colombel, in a large multicentre study (CHARM) of 854 patients, reported superiority of Adalumimab over placebo for maintenance therapy of Crohn's disease. In week 56 of maintenance treatment phase 29% were in remission while receiving 2 weekly treatments,

23% when receiving weekly and only 6% in the placebo arm were in remission [278].

Mian has reported a case of a 15 year old girl with Crohn's disease diagnosed at the age of 4. She was steroid dependent, had pancolonic involvement with the duodenum and stomach and although infliximab was initially successful (at the age of 10 years) subsequent usage had resulted in a reaction. Adalimumab was successfully used (3 doses over 4 weeks) with symptomatic and macroscopic improvement [279].

The RESEAT study [280] in States reported a retrospective paediatric experience in 115 patients from 12 centres. The most popular maintenance dose was 40mg alternate weeks (88% of patients). Treatment with Infliximab preceded Adalimumab use in 95% of the patients. The commonest reasons for discontinuation were loss of response (47%) and reactions to the infusion (Infliximab) (45%). Clinical response reported by physician global assessment was 65% at 3 months, 71% at 6 months and 70% at 12 months. Overall Adalimumab was found to be well tolerated and an effective resuce therapy for moderate to severe paediatric CD.

These initial results show promise and suggest that adalimumab may be an alternative option to infliximab especially if the patient has shown resistance to treatment. Viola reported effective use of Adalimumab in 23 children as maintenance therapy with remission rate of 65.2% at week 48 [281].

1.5.4.6 Miscellaneous

Anti-interleukin 12, interleukin 11, interleukin 10, anti-interleukin 6, CNI-1493, BIRB-796, RDP-58, Asis 2302, MLN-02, Onercept and MRA (anti-interleukin 6 receptor antibody) are currently at experimental stages [282-289]. Of these, initial studies on Fontolizumab (anti-interferon γ) [290],

Etanercept [291], Onercept [292], MLN-02(LDP-02), Isis 2302 (Alicaforsen) [293], interleukin 11 [287,288], BIRB-796 and RDP-58 have been a disappointment.

1.6 Enteral nutrition in treatment of Crohn's disease

1.6.1 Introduction

The first enteral feed used in treatment for Crohn's disease was an elemental feed [22]. Feeds may be elemental, semi-elemental or polymeric depending on state of hydrolysation of protein in the feed explained further in section 1.6.2.
The first elemental feeds were developed as part of the US space exploration programme and were not intended for any treatment. The idea was to produce a highly absorbable feed which would result in a low faecal residue in space. When it was first chosen to be used in a child with Crohn's disease it again was never intended to be used as treatment but to correct the state of malnutrition. Giorgini in February 1973, for the first time reported success with treatment of an Italian boy who had anorexia, weight loss, perianal fistulae, 3-5 loose bowel movements, erythema nodosum and regional enteritis seen on a barium enema. The boy diagnosed a couple of years earlier had relapsed on 15 mg alternate days of prednisolone. As an inpatient Conded 72H®, a sucrose based liquid elemental diet, was used concurrently with corticosteroids and salicylazosulfapyridine (an aminosalicylate) for a period of 42 days. This was preferred over high dose steroids due to the child's short stature and Cushingoid appearance. The purpose of the liquid diet was to provide nutrition by medically 'by-passing' the diseased intestinal loops. The patient gained 24 pounds, the fistula healed and the nitrogen balance became positive during this period [22].

1.6.2 Different types of enteral feeds

Enteral feeds are classified on the basis of the hydrolysation of the protein in the feed and may be elemental, semi-elemental or polymeric. Elemental feeds are amino acid based feeds, semi-elemental oligopeptides and polypeptides and polymeric feeds are based on whole protein. Any of these feeds can be a specialised feed, for eg: ACD004 with the added TGF beta (and higher n-3 ratio) used in Crohn's disease is a specialised polymeric feed. Feeds used in renal disease will also fall in the same category.

Elemental formulas contain individual amino acids and are usually low in LCTs and are thought to be minimally stressful for the intestine and exocrine pancreatic function. MCT is the predominant fat souce in many products which can be absorbed directly into the portal vein in the absence of lipase or bile salts. There are considered to be useful for malabsorptive states.

Semi-elemental feeds comprise of proteins that have been hydrolysed into oligopeptides of varying lengths, dipeptides and tripeptides. The di- and tri- peptides have a specific uptake transport mechanism considered to be more efficient than amino acids or whole proteins [294].

Polymeric formulas contain intact proteins, complex carbohydrates and larger proportion of LCT fats in majority of cases. Whole protein 'polymeric' feeds taste better than amino acid based feeds. Sudies have shown that these feeds are as effective as elemental feeds for treatment of Crohn's disease in children [295-297]. In a randomised controlled trial comparing use of a peptide based enteral formula v a standard formula, in patients with hypoalbuminaemia, no differences were found with regards to tolerance/side effects and effectiveness [298]. Rodrigues in a randomised controlled trial demonstrated similar (p=ns) remission rates for elemental (64%) and

polymeric (51%) enteral feeds. Nasogastric feeding was more frequently required for administration of elemental feeds [299].
The opinion regarding choice continues to remain divided as paediatric gastroenterologists prescribe both elemental feeds (eg: EO28 ®) and polymeric feeds for treatment of acute active Crohn's disease.

1.6.3 Enternal nutrition in paediatric Crohn disease

Since Giorgini, enteral nutrition use has gained popularity as a first line treatment for paediatric Crohn's disease in many centres of the world.
Morin in Quebec in 1980 used elemental diet to treat 4 growth retarded children with Crohn's disease who showed acceleration of growth post treatment. All patients achieved clinical remission and 3 out of the 4 continued to grow during the 67 weeks of supplemental treatment and follow up; the fourth required surgery [300]. Morin in 1982, used continuous elemental feeding (via pump) in 10 children for 3 weeks. All of them achieved remission with a drop in disease activity index from a mean of 307 to 69.2. 8/10 children were still in remission 3 months after cessation of treatment with Vivonex® [301]. This was re-demonstrated by O'Morain in 1983 whilst using Vivonex® [302]. Navarro (1982) in France opted to use a feed based on oligopeptides; because of its comparatively lower osmolality. Again, the feed was administered via a nasogastric tube constantly (continuously) over a period of 2 to 7 months in 17 children. This was termed as 'constant rate enteral nutrition'. Remission was successfully introduced with an increase in growth rate, never before possible on a child taking continual corticosteroids [303].

Sanderson et al (1987), in the first ever randomized controlled trial of enteral nutrition and corticosteroids in paediatric Crohn's disease, showed that a semi-elemental feed (Flexical®, Mead Johnson) was as efficacious as corticosteroids in inducing remission in small intestinal Crohn's disease. The authors as before once again demonstrated improved growth using this form of treatment; a clear edge over use of corticosteroids [304].

Undesirable taste of these elemental feeds necessitated insertion of a nasogastric tube. Later a better tasting, polymeric feed AL110® was used by Beattie et al in a cohort of 6 children [305]. This study was duplicated by Fell et al (1997) using Modulen IBD®. During treatment a mucosal cytokine assessment demonstrated a fall in the pro-inflammatory cytokines IL-1β, IL-8 and IFN-γ at completion of 8 weeks of treatment [24]. Over recent years development of polymeric feeds have included improvement in taste with further acceptance of this mode of treatment in children [305-308]. Rodriques and colleagues showed that although polymeric nutrition did not affect adherence to the dietary treatment, its use was associated with a significantly less use of nasogastric tube compared to the elemental formula [309]. Over the past two decades the superiority of enteral nutrition and corticosteroids over each other has been disputed. In 1995, a meta-analysis performed by Griffiths et al showed corticosteroids to be superior to enteral nutrition [310]. These findings were further re-affirmed by Zachos in a Cochrane review in 2001 [311]. An update of this Cochrane review was made in 2007 [312]. Meta-analysis of ten trials comprising 334 patients demonstrated no difference in the efficacy of elemental versus non-elemental formulas (OR 1.10; 95% CI 0.69 to 1.75). Further analysis of seven trials including 209 patients treated with EN formulas of differing fat content (low fat: < 20 g/1000 kCal versus high fat: > 20 g/1000 kCal) demonstrated no statistically

significant difference in efficacy (OR 1.13; 95% CI 0.63 to 2.01). Similarly, no differences were found regarding the effect of very low fat content (< 3 g/1000 kCal) or type of fat (long chain triglycerides). However corticosteorids were found to be superior to enteral nutrition for treatment of Crohn's disease. Importantly, these meta-analyses included adult patients to increase the yield of these analyses. A paediatric IBD oriented meta-analysis was performed by Heuschkel et al in 2000 to compare corticosteroid treatments with enteral nutrition. A total of 194 children formed the basis of this analysis and the authors failed to show corticosteroids to be superior to enteral nutritional treatment [182]. A more recent meta-analysis by Dziechciarz in 2007 showed no difference in the remission rates between enteral nutrion and steroids groups in paediatric Crohn's disease [313].

Management of Crohn's disease in the paediatric population involves issues besides treatment of disease; most important being to maintain remission through puberty with a view to maximise growth. Even though the superiority of either treatment (enteral nutrition vs. corticosteroids) remains in dispute, enteral nutrition has a superior side effect profile as it is growth sparing. In addition investigators have demonstrated that corticosteroids, in comparison to enteral nutrition, do not achieve mucosal healing of the inflamed intestine [314]. The mucosal (intestinal) healing in children using exclusive enteral nutrition is associated with a fall in mucosal pro-inflammatory cytokines [24]. Additionally Buchanan and colleagues have reported remission with use of exclusive enteral nutrition irrespective of the Crohn's disease site [315].

1.6.4 Enteral nutrition in adult Crohn's disease

O'Morain in 1984 reported a randomized controlled trial of use of elemental feed Vivonex ® and corticosteroids in 21 patients. After 4 weeks of treatment, 8/10 in the steroid and 9/11 in the enteral feeding group achieved remission. At three months, a single patient in each group was considered to be a treatment failure. Interestingly one patient in the steroid group was treated with enteral feeding and responded very well to the treatment. One patient in the feeding group had a perforation once returning to free food. In this study O'Morain has clearly outlined poor palatability of the feed. Also, these feeds were expensive costing £9-12 per day.

Since O'Morains work there are now three published meta-analyses and a Cochrane database review comparing use of enteral nutrition with corticosteroids [310,311,316,317].

The Cochrane meta-analyses of Griffiths and Zachos reported in 2001 [310] and then more recently updated in 2007 [311] show clear advantage of use of corticosteroids over enteral nutrition. These results are contrary to O'Morain's small successful study and the paediatric experience in centres skilled in administering enteral nutrition, and use enteral nutrition as primary therapy. It is important to realize that O'Morain's group too were highly motivated and aimed at administering enteral feeding. The above mentioned meta-analyses are based on trials administering treatments (corticosteroids and enteral feeds) on an intention to treat basis. Patients unable to complete the treatment (enteral nutrition) course were considered to have failed the treatment even if in remission. It is notable that analyses limiting to patients successfully completing the enteral feed treatment achieved comparable remission rates to corticosteroids. There is little doubt that motivation of the clinician and the patient is essential to ensure successful enteral nutritional

treatment. This is a key factor to consider in any trial using enteral nutrition.
Motivation is important from a patient perspective as no one likes a radical change in their diet, particularly adults. Despite personal preferences, it is now being recognized that adults 'at risk' should still be strongly considered for treatment with enteral nutrition rather than corticosteroids.

The 'at risk' group includes:

- Adults who are particularly going to stay on corticosteroids for a long time
- Adults who are steroid refractory or dependent

Additionally it should be offered to:

- Patients requesting treatment with a safer profile
- Patients seeking alternative treatments

A view is now emerging that patients with active Crohn's disease should be encouraged to make decisions regarding their treatments, based on full awareness of pros and cons of medications used.

1.6.5 Use of supplemental enteral nutrition as maintenance therapy

There is some evidence that enteral nutrition works when used as a maintenance therapy. This involves patients who once in remission continue to take enteral nutrition alongside normal diet which accounts for 1/3rd to ½ of their total RDA.
Two adult studies report use of supplemental enteral nutrition as maintenance therapy in Crohn's disease.

Verma [318] reported use of supplemental nutrition in a series of 39 adult patients with Crohn's disease in clinical remission. Of these, 21 patients (Group 1) received oral nutritional supplementation, taken in addition to their normal diet. Their outcome (relapse rate, Crohn's disease activity index, inflammatory markers) was compared with that of 18 patients (Group 2), who were maintained on a normal unrestricted diet over an observation period of 12 months. On an intention-to-treat basis, 10 patients (48%) in the supplement group remained in remission for 12 months, compared to 4/18 (22%) patients in the non-supplemented group. Seven patients in Group 1 and 14 in Group 2 relapsed at a mean of 7.4+/-0.9 and 6.2+/-0.4 months, respectively.

Takagi [319] has also reported their experience of use of enteral nutrition (elemental) as as a supplement in adults. Supplement consisted of half of total daily intake and 51 patients were randomised to supplemental/non-supplemental groups. The primary outcome was relapse over 2 years. The relapse rate in the half elemental diet group was significantly lower [34.6% vs. 64.0%; multivariate hazard ratio 0.40 (95% CI: 0.16-0.98)] than that in the free diet group after a mean follow-up of 11.9 months.

There are published studies in children as well.

Belli has demonstrated significant height and weight gain in a small prospective study of 8 children with growth failure. The elemental feed was administered for one month out of four via continuous nasogastric infusion at home [320]. Aiges used a year long nocturnal supplementatal nutrition via nosogastric tube and demonstrated significant growth spurt in a group of 16 children receiving enteral nutrition via gastrostomy [321]. Wilschanski in his retrospective study compared relapse rate at 1 year in two groups of children (28 on supplement and 19 no supplement), found 12/28 relapsing in the supplemented group compared to 15/19 in the non-supplmentened

group [26]. The study was biased as the choice to type of feeds was made by patients (non-randomised study).

Akobeng has included the two adult studies in the recently published Cochrane review in 2007, concluding that despite a small number of studies there may be an advantage in using supplemental enteral nutrition [322].

1.7 Quality of life (QOL) in paediatric Crohn's disease – background and basic concepts

1.7.1 Background

A physician endeavours to achieve health, for instance in Crohn's disease, by maintaining remission, a desirable end point for all treatments. Importantly, for patients, mucosal healing and a fall of paediatric Crohn's disease activity index score all indicative of remission, though momentarily reassuring, is of little consequence. Patients are concerned about their health and more importantly what it means to them i.e., their personal feelings.
Health status, functional status, and quality of life are three concepts often used interchangeably to refer to the same domain of "health". Quality of life is a broader concept and will encompass health and functional status in it. It is important to explain health status and functional status of the patient before discussing quality of life is. These concepts are described as follows:

1.7.2 The health and functional status

Health status reflects an individual's level of wellness and illness. It is about the physical well-being of the patient in reference to biological or physiological dysfunction (bowel inflammation) and symptoms (pain, bloody diarrhoea). Poor health and symptoms may in turn cause functional impairment, such as patient's inability to participate in sports or even walk (arthritis). This now leads to us to define functional status.

Functional status of the patient describes an individual's ability to perform daily duties to meet basic needs, fulfil usual roles and maintain health and well-being [323]. Assessment of functional status would be based on two fundamental concepts. One is functional capacity, which is an individual's maximum capacity to perform daily activities in the physical, psychological and social domains of life. The other concept is of functional performance, which comprises of activities people actually do, during the course of their daily life [324]. Both variables can be affected by biological or physiological impairment, symptoms, mood, and specific health perceptions of the individual. These factors are intertwined and quite often a change in one variable would affect another, causing a change in balance of the whole equation.

Importantly, tools assessing functional and health status, focus on assessment of negative health states. It is important that measures of well-being that focus on positive aspects of health are also used in such assessments. Analysis of positive aspects would give an idea about an individuals' coping mechanism, an important attribute which helps to counter events in life. In practice, it is difficult to analyse these concepts.

It is also important to realize that health and functional status are often not rated by patients but by physicians or healthcare workers. This fundamentally differs from quality of life, which primarily encompasses patient's perceptions about their health status. Good health and functional status may simply just not equate to quality of life. In a simplistic example, physical functioning may be more important for a professional athlete than a novel writer. Limitation of physical functioning by disease (say arthralgia of the ankle joints reasonably controlled with used of medications) will affect the two people differently, certainly their perception about it and hence their quality of life.

1.7.3 What is quality of life?

With some understanding of the functional and health status assessment, it will now be easier to explain the concept of quality of life. It is based on the idea that every individual has their own unique perspective on quality of life. Quality of life is multi-dimensional and encompasses several domains; focusing on both objective and subjective perspectives within each domain [325]. Objective assessment focuses on what an individual can do and defines degree of health as explained above. Subjective assessment includes what it actually means to the individual.
Quality of life has been defined as the physical, psychological and social domains of health influenced by a person's experiences, beliefs, expectations and perception [325].
Disease well-being is only one factor which determines quality of life. Other factors include characteristics of a person, their coping abilities, environmental situation and available social support; all important determinants for well-being. It is difficult to develop a tool simple enough to use, which would incorporate and accurately assess quality of life with due consideration to all of these factors.

Based on the above *a good quality of life is said to be present when hopes of an individual are matched and fulfilled by experience* [326].

Gill and Fenstein lay emphasis on three areas in which quality of life may be assessed in the health context [327].

- Use of objective measures such as clinical indices that patients would not necessarily use or be aware of.
- Functional performance

- Patient's own evaluation of their subjective experience. This becomes harder to assess in younger age groups.

In summary, quality of life assessment should encompass the three main domains;

- physical (functional status, disease and treatment related symptoms)
- psychological and
- social aspects of life

1.7.4 History of paediatric quality of life assessment

Evaluation of quality of life in adults has taken place in many studies since the 1960's. However, the importance of this concept in children only gained recognition in the eighties. Until 1998 only 13% of the total number of publications concerning quality of life were related to children [328]. Ditesheim and Templeton performed one of the earliest studies on assessment of quality of life in children following surgical repair of high imperforate anus [329]. This assessment was based on school attendance, social relationships and physical abilities. In another study, Herndon and co-workers reported quality of life in children surviving major burns [330]. They demonstrated that children have remarkable energy and capabilities to adapt to disabilities.

Other issues were also highlighted during these early years of paediatric quality of life assessment. In another study by Henning and co-workers, children with renal failure were shown to be concerned about their height even though their average height was normal [331]. This highlights how quality of life can be affected by self-perception of children, an integral part of any quality of life assessment.

1.7.5 Concept of quality of life in children

It is clear that children differ from adults in their views about quality of life. For young children quality of life is not about achievement of basic functional tasks like in adults [332]. More so it is about having lots of friends, play football like Wayne Rooney or perhaps have the shiniest hair. It is obvious that adults cannot rate a child's quality of life, the thoughts and perceptions are inherently different.
Second it is important to realize that children may make judgements in a manner different to adults. Parents are known to differ in scoring their child's quality of life when compared to the clinician [333].
Children are likely to differ from their parents in the same regard [334].
Interestingly in a quality of life study on asthma in children in Ontario, Canada [335] children's global rating of change in symptoms correlated strongly with changes in quality of life (0.54 to .67) but not with measures of airway calibre or asthma control, while parents' global ratings did not correlate with children's quality of life but showed moderate correlations with airway calibre (0.29 to .48) and asthma control (0.50). Differences were more obvious in children over the age of 11, correlations with all clinical variables were higher for their own than their parents' global ratings.
Proxy measurements by parents can be strongly influenced by how much the subject's health condition is a burden to the caregivers themselves [336]. Although it is important to recognise parental burden of a child's illness it still needs to be measured separately to the quality of life of the child [337].
Finally, children's views about quality of life do change with age [338]. An adolescent's perception of quality of life is different from that of a younger child. It may be influenced by their cognitive development as well as peer group perceptions and a myriad of

influences that result from achievement of adolescent developmental tasks such as body self integrity and personal identity, autonomy and independence and educational and vocational goals.

1.7.6 How to assess quality of life in children? Use of generic and disease specific questionnaires

Having described the fundamental concepts, there are several questions that arise regarding assessment of quality of life in children. The first question is who should assess quality of life? Majority of previous studies have used parents and then clinic staff to make the assessment, which unfortunately undermines the true reliability of the assessment (as discussed above). The most common problem seen is variability and inconsistency in the parents report [339]. It has been shown and suggested that children with chronic illnesses (a study on children with diabetes) have a more sophisticated and mature understanding of their illness compared to well peers and are therefore capable of making their own assessments [340].
There is ample number of available adult quality of life questionnaires, which one may be tempted to use in children. It is important to emphasize that children are not small adults. They differ in their understanding of health, cause of illness and beliefs regarding working of medications [341]. In addition they have different coping mechanisms. From a practical point of view reading age is an important pre-requisite to enable the individual to read, understand and complete any questionnaire. Furthermore, a questionnaire has to be valid for use in the children age group. Moreover the questionnaire may contain a difficult response scale, use of long questions and finally their item content may include questions about sex life, which would be inappropriate [342].

It is thus imperative that quality of life questionnaires are designed and developed for children. Such questionnaires/ assessment tools will fall into two main categories. The first category entails assessment of 'generic measures' and second assessment of 'disease specific measures'.

'Generic measures' are designed to be broadly applicable across a host of conditions regardless of a particular disease or use of any particular treatments. This compares quality of life of a disease in a child with another healthy child. It is therefore not specific and is based on more general measures. As a result it may not be responsive to small changes in children's conditions and a clinically relevant aspect related to a specific condition may be easily overlooked. By general principle, these questionnaires tend to be longer in length and are more difficult to fill in.
In contrast 'disease specific measures' may be used in a questionnaire, which are designed to be valid for a specific condition e.g.; PAQLQ (paediatric asthma quality of life questionnaire) for asthma in children. The main advantage of disease specific measures is that it maximizes 'content validity'. Content validity is a term used to describe the variables used in the questionnaire. It is defined as the extent to which a variable measures i.e., what it is supposed to measure. Clearly disease specific measures would provide greater sensitivity and specificity. This gives it an advantage to be used in trials to compare treatments of a disease and measure indices in different time frames.
With all limitations, disease specific instruments cannot be used to compare quality of life in children with different conditions/ diseases. This will become important when one patient suffers from more than one disease/disorder. In these cases a single 'disease specific questionnaire' would not fulfil the purpose and it may be necessary

to use multiple disease specific tools. A simpler/ alternative option may be to use 'generic questionnaires' in such cases.

1.7.7 Characteristics of an ideal 'quality of life' tool

1.7.7.1 Construct validity

In this section, I will discuss two important concepts, validity and reliability. An ideal quality of life tool should be 'valid'. Central to this, is the term 'construct validity', explained in figure 1.7.7.1 and as follows.

The easiest way to understand 'construct validity', would be to divide it into two imaginary portions or territories (lands); the 'land of theory' constituting top half of figure 1.7.7.1 and the 'land of observations' constituting the lower half of figure 1.7.7.1.

The land of theory represents what goes inside the mind and one's attempt to articulate this to others. It constitutes the main idea, the theory and hypothesis. In the land of observations one makes/forms the actual questionnaire i.e., the actual measures or observational procedures. This is constructed and based on the thought processes from the 'land of theory'. The 'land of observations' is based on ideas from the 'land of theory'. It is like developing a program to reflect the kind of programme one has in mind.

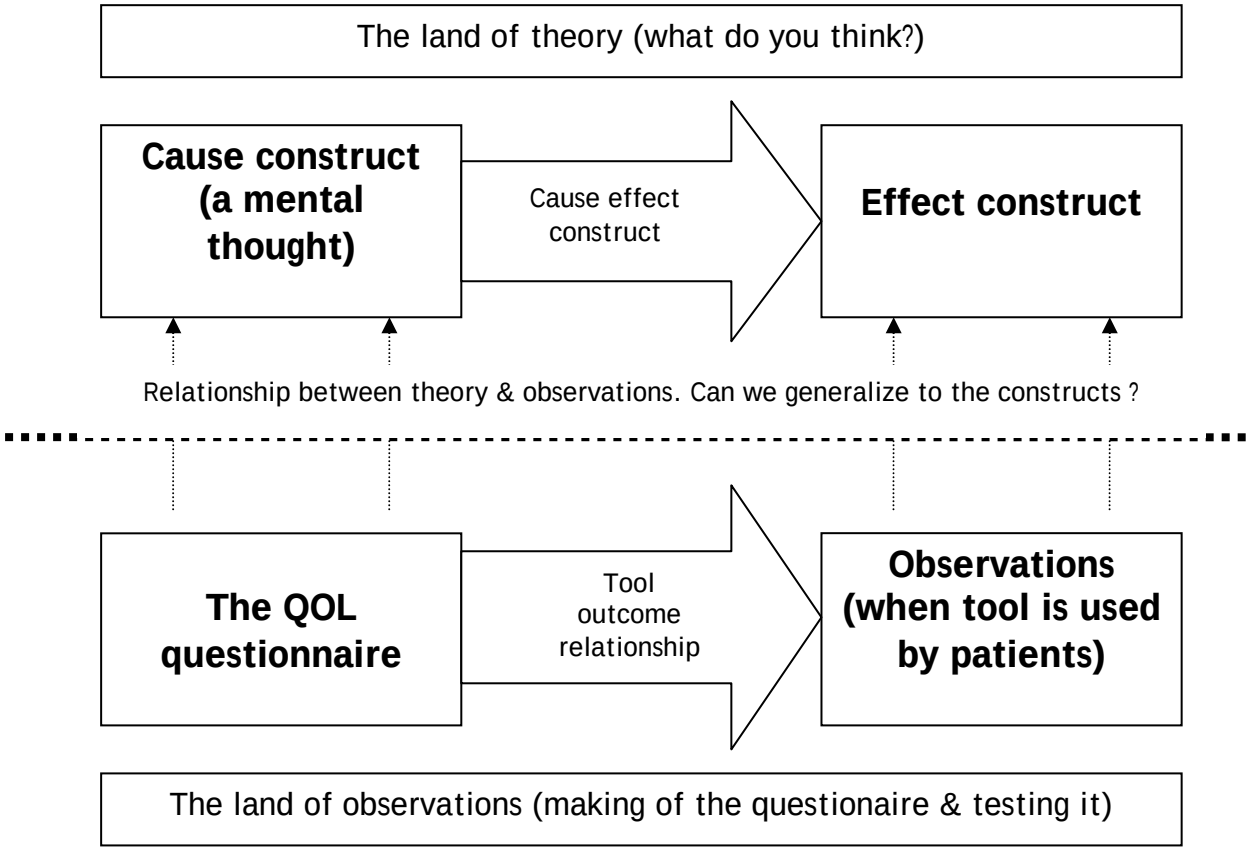


Figure 1.7.7.1. The concept of construct validity

Any time one translates (puts into operation) a concept or construct into a functioning and operating reality (the operationalisation) one needs to be concerned about how well the translation works.
Hence in terms of quality of life, the concept of quality of life is the 'construct' and the 'QOL questionnaire' the operationalisation.
Construct validity encompasses all these concepts and refers to translating any construct into operationalisation.
A list of 'validity' terms encompassed under the broad umbrella of construct validity is shown in table 1.7.7.1 and described as follows.
These terms are used and applied when one talks about quality of measurement.

Table 1.7.7.1 Components of construct validity

- Construct validity
- Translation validity
- Face validity
- Content validity
- Criterion related validity
- Predictive validity
- Concurrent validity
- Convergent validity
- Discriminant validity

In translation validity one focuses on whether the operationalisation is a good reflection of the construct. It assumes that one has a good detailed definition of the construct and that the operationalisation can be checked against it. This approach is definitional in nature. However, in criterion related validity one examines whether the operationalisation behaves the way it should, given the theory of the construct. This is a relational approach to construct validity. It assumes that the operationalisation based upon theory of construct should function in predictable ways in relation to other operationalisations based upon theory of construct.

1.7.7.2 Translation validity

The two types of translation validity are face and content validity. In face validity one looks at operationalisation and to see whether 'on face' it seems like a good translation of the construct. This is probably the weakest way to demonstrate construct validity as the researcher relies on his/her subjective judgement here.

In content validity one checks the operationalisation against the relevant content domain (i.e., questions asked to assess quality of life contain appropriate content to assess quality of life) for the construct. This approach assumes that a good detailed description of the content domain is available. This is a direct comparison and usually done by experts in the field. The criteria used for comparison are the construct definition itself (the formulated theoretical concept e.g.; the concept of quality of life in our case). Validity is easier to test where a gold standard exists.
Unfortunately, in real life 'criterion measures' (gold standard) often do not exist and in such cases criterion related validity tests are best regarded in assessment of construct validity.

1.7.7.3 Criterion related validity

In this, one checks performance of operationalisation against some criterion. It is different from content validity as it is not a direct comparison but the researcher makes a prediction about how the operationalisation will perform based on the theory of construct; this would particularly apply when a gold standard is not available.
The differences among the criterion related validity sub-types are in the criteria they use as standard for judgement.
Predictive validity is about the operationalisation's ability to predict something it should theoretically be able to predict. In concurrent validity we assess the operationalisation's ability to distinguish between groups that it should theoretically be able to distinguish between. Convergent validity relates to the degree to which the operationalisation is similar to other operationalisations that it theoretically should be similar to. In discriminant validity we examine the degree to which the operationalisation is not similar to (diverges

from) other operationalisations that it theoretically should not be similar to.

Finally, a quality of life tool needs to be 'valid' and 'reliable'. This means that children would respond to the questionnaire similarly on different occasions. Reliability may be tested in three different ways:

- Internal consistency. It is the extent to which the items of a domain or scale assess the same dimension and is measured using Cronbach's alpha. This is a statistical assessment of the correlation between items within a dimension and tests whether items within a scale correlate positively (i.e., they all test the same thing).
- Test-retest reliability. This is established where individuals complete a measure on two separate occasions and those two sets of scores are then positively correlated. This may be tested using intra-class correlation.
- Inter-rater reliability. It is an assessment of the consistency of an instrument when administered by different interviewers to the same patient.

1.7.8 Quality of life assessment in paediatric inflammatory bowel disease

A choice of disease specific instruments are available for quality of life assessment in adults with IBD (The rating form of IBD patient concern [343], UC/CD health status scale [344], Cleveland clinic questionnaire [345] and IBDQ [346]). Dorssman et al in his studies in 1991 on adult quality of life in inflammatory bowel disease showed that clinical disease activity is unrelated to patients perception of their health status [347,348]. Unfortunately, the choice for quality of life assessment in paediatric IBD is limited.

Recently IMPACT, a disease specific quality of life questionnaire was developed by Anne Griffiths in Toronto Canada for use in children

[349]. It comprises of 33 questions answered using a 7 cm visual analogue scale. These questions are organised under six domains: IBD symptoms, systemic symptoms, emotional functioning, social functioning, body image and feelings towards treatments and interventions. The total score can be converted linearly to range from 0-100, with higher scores representing a better quality of life. The readability statistics and number of unanswered questions were assessed among 147 patients (97 CD, 50 UC) with mean age 14.4 +/- 2.2 years (range 9.2-18.0 years) using the self-administered questionnaire. In the absence of a previous 'gold standard', construct validity was based on, a priori hypotheses.

IMPACT was further developed into IMPACT II by Loonen et al [350]. The original in Dutch has been translated into Canadian English, UK English and French. The researchers reported difficulty in use of the original IMPACT questionnaire, based on a pilot study in Netherlands. These difficulties were:

The questionnaire was found to consist of many long double barrelled and multi interpretable questions and answers. Answering phrases were simplified and changed to 'very much' and 'not at all' or 'very often' 'never', where applicable.

The absence of a specified time frame in the questions was considered sub-optimal.

The format with the answer representing the most impairment on the visual analogue scale on the left side was found to be leading and upsetting to the children.

Below is an example of how a question from IMPACT I changed to its new form in IMPACT II:

Q: Put a mark on the line to tell how much your stomach has been hurting recently

_____

A	B
My stomach has been hurting so much, the pain is as bad as it has ever been, and comes all the time; it's really hard to deal with	I have not had any stomach cramps at all recently

(New) Q: How much has your stomach been hurting you during the last two weeks?

A	B
Not at all	Very much

Hence, evolution into IMPACT II involved simplifying double barrelled questions, addition of a 2 weeks time frame to questions specifically related to frequency of problems/symptoms and switching of answering anchors with the answers representing least impairment, to the left side of the visual analogue scale. The IMPACT II comprises of 35 questions instead of the original 33 in IMPACT I. The questionnaire takes about 5-10 minutes to complete.

The IMPACT II has also undergone the validation process. Reliability coefficient was good for 5/6 domains and measures of test-retest stability in clinically stable patients were good for all domains. Good discriminant validity was demonstrated between symptom groups and disease course severity in all domains [25].

Another version of the IMPACT tool with a Likert scale has been developed in a pilot study in addition to the current visual analogue scale [351]. Further to its use in the study on enteral nutrition the IMPACT tool [307] has been more recently used in the joint Natalizumab study [271].

Details of IMPACT II are listed in table 1.7.8.1.

Table 1.7.8.1 Items and scales of IMPACT II questionnaire

Scale	Items
IBD symptoms	Stomach aches Not being able to eat what you want because of disease Diarrhoea Worried about blood with bowel movement Being sick Afraid to soil pants Having to pass gas
Systemic symptoms	How much energy How did you feel How tired did you feel
Emotional functioning	Worried about having a flare up Worried about having a chronic condition Worried about health in future Thinking it is unfair to have this disease Being angry to have this disease Being ashamed Being happy
Social functioning	The influence of the disease upon the family Having to miss out on hobbies Having rules imposed because of the disease Having fun Is it harder to make friends Worries not to be able to go out on dates Teased or bullied because of the disease or treatment Does the disease make it harder to travel or go on holiday Try and keep your disease a secret Able to talk to anyone about worries Able to play sports as much as you would like Able to go to school
Body image	How do you feel about height How do you feel about weight How do you feel about the way you look
Treatment/ interventions	How do you feel about taking medicines How do you feel about investigations Worried about ever having an operation

1.8 Hypothesis and aims of the thesis

1.8.1 Hypothesis

Enteral nutrition is a well-established treatment for acute Crohn's disease in childhood. This has been previously discussed in section 1.6. Fell et all demonstrated a clinical remission rate of 79% in 29 children with active intestinal Crohn's disease using a polymeric feed Modulen (CT3211) [24]. As, there has been an accumulating evidence of beneficial effects with n-3 fats and its anti-inflammatory properties [27], a new polymeric feed ACD004, with a higher n-3 : n-6 ratio compared to the commonly used CT3211 feed (Modulen IBD®), was produced with a view to offer better anti-inflammatory profile in an enteral feed. With this new feed being used for the first time, the first hypothesis to be tested is that use of ACD004 is efficacious in children with acute and active Crohn's disease.

Supplemental enteral nutrition has been prescribed and used in maintaining remission in children with Crohn's disease. Wilschanski and workers, in a retrospective study, showed that a relapse rate of 70% at one year was halved by enteral supplementation [26]. There are however no prospective studies of use of supplemental nutrition in children with Crohn's disease. The second hypothesis of this thesis is that use of daily enteral supplementation (ACD004) helps to maintain remission in children with Crohn's disease.

Physical measures of disease activity and degrees of mucosal inflammation, in isolation, are of limited interest to patients with inflammatory bowel disease. A successful therapy should ideally both improve a patient's quality of life and reduce the long-term consequences of the disease by modifying its course. Some

paediatric gastroenterologists believe that enteral nutrition therapies and strategies compromise quality of life in children as it affects the day to day eating habits. The third hypothesis of this thesis is that there is an improvement in quality of life of children receiving enteral nutrition not only for treatment of active disease but also when used as a supplement for maintenance of remission.

1.8.2 Aims

The aims of this thesis are:

- Assess efficacy based on the proportion of full remission at 8 weeks in children with Crohn's disease receiving ACD004.

- Assess reduction in relapse rate in Crohn's disease in children on long-term continuous oral ACD004 supplementation as part of their total daily requirements (TDR) compared to a control group receiving the same energy intake, as usually food, over a period of 104 weeks.

- Assess quality of life in children with Crohn's treated with enteral feed during the acute phase and whilst using the feeding as a supplement.

Chapter 2. Use of a new enteral feed for treatment of paediatric Crohn's disease – Phase A

2.1 Background

Enteral nutrition is a preferred first line treatment for acute active paediatric Crohn's disease in many paediatric gastroenterology centres. This is due to its beneficial effects on nutritional status and growth, with lack of 'steroid like' adverse effects. Enteral feeding, down-regulates mucosal pro-inflammatory cytokines, resulting in mucosal healing [24,314,352]. Use of enteral nutrition in children has been discussed in previous sections.
ACD004 is amongst the newer generation of enteral feeds and is a newly developed enteral feed used in this trial. It is produced by Nestle and is a whole protein polymeric feed. This feed evolved from the previous CT3211 (marketed as 'Modulen IBD®'). The main difference is an altered increased n-3 fat ratio. n-3 fats are known for their anti-inflammatory properties [27]. The n-6: n-3 ratio in ACD004 has been decreased towards the lower recommended value with a view to derive maximum benefit from an enteral feed. This is discussed in further details in section 2.2.
Chapter 2 describes the first part of this study looking at induction of full remission with ACD004. This is a prospective and open study of use of enteral nutrition for a period of 8 weeks in children with acute and active Crohn's disease. This treatment period is followed by food reintroduction over 4-6 weeks. We have called this 'phase A' of the treatment trial.

2.2 What is ACD004 ?

As mentioned before ACD004 was developed as a next step up to the currently used Modulen IBD® feed produce by Nestle, Switzerland. There are considerable similarities to Modulen feed, particularly from the protein, carbohydrates, calorific value and electrolytes point of view. Both feeds provide 1 Kcal/ml of energy and are casein based. The carbohydrate source is glucose.

There is however a considerable difference in the fat blend of the feeds. The fat source in ACD004 is vegetable oil comprising of high oleic sunflower and low erucic rapeseed oil. In comparison Modulen IBD® (CT3211) derives its fats from vegetables particularly corn oil. This results in a shift in the n-6:n-3 ratio, decreasing it to 5.2: 1 (10.8: 1 in Modulen IBD ®). This also results in a decrease in the saturated fat ratio providing a saturated fat to unsaturated fat ration of 0.50:1. As a result there is an increase in monounsaturated fats to 50% and MCT (medium chain triglycerides) to 5.75 g/100 mls. This is within the recommended daily allowance (RDA) of saturated fats.
The constituents of the feed are enlisted in table 2.2.1.

Table 2.2.1 Major constituents in the polymeric feed ACD004

Energy density (Kcal/L)	1000
Protein (g/L)	40
Carbohydrates (g/L)	110
Na (mg/L)	600
K (mg/L)	1400
Cl (mg/L)	930
Ca (mg/L)	800
P (mg/L)	550
Ca/P	1.5
Mg (mg/L)	250
Mn (µg/L)	1000

2.3 Aims

The primary object of this phase was to assess efficacy based on proportion of full remission at 8 weeks. Secondary objectives were to demonstrate short-term safety with tolerance of the feed. Other secondary measures included assessment of growth, development and quality of life.

2.4 Methods

2.4.1 Description

Patients were recruited prospectively and consecutively over a 2 year period. Children with symptoms suggestive of inflammatory bowel disease seen in the 'inflammatory bowel disease' paediatric gastroenterology outpatient clinic were admitted for further investigations. On admission, all had a detailed clinical assessment which included a detailed history, informed consent for the study and examination with measurement of heights and weights. This was followed by blood tests to check for blood count, liver function, and inflammatory markers with serology for Yersinia and Amoebiasis. Suspected cases were screened for tuberculosis and were further investigated with a Mantoux test and a chest radiograph. All children had a diagnostic upper gastrointestinal endoscopy, ileocolonoscopy and a barium meal and follow through. Once the results of investigations were available PCDAI with mucosal disease scores (as seen on endoscopy) were recorded. Finally children on admission completed the quality of life questionnaire form in presence of the investigators (see chapter 3).
The admission checklist is given in table 2.4.1.1 and figure 2.4.1.2.
A diagnosis of Crohn's disease was made using previously described criteria (see chapter 1.2).
A multi-disciplinary team comprising of paediatric gastroenterologists, nurses, dieticians and child psychiatrists were responsible for care of the children. The paediatric dieticians assessed each child, calculated and prescribed ACD004 (enteral feed) at the rate of 110-120% of the recommended daily allowance (RDA). The calculation of RDA is based on FAO/WHO/UNU values (1985). 110-120% of RDA would approximate to the increased daily calorific requirement in a child unwell with Crohn's disease [353 307]. The children were given a minimum volume to drink each day and

asked to keep a daily diary record of their intake. The daily intake was supervised by the nursing and dietetic team. Standard feed preparation instructions (followed by staff members and given to parents) are given in table 2.4.1.3.

Children were followed up at week 4 when they were assessed clinically, had a PCDAI score and blood tests (please see figure 2.4.1.2 for details) with a weight check. Patients were called telephonically by the dieticians, in between, to ensure compliance and troubleshoot any problems which children and parents may encounter at home. This was also to adjust the ACD004 dosage according to the children's demand and wellbeing.

After 8 weeks of exclusive enteral feeding children were re-assessed (PCDAI score and ileocolonoscopy). Remission was defined as a fall in PCDAI to less than 20. Children treated with antibiotics, immunosuppressants or needing surgery at or before 8 weeks irrespective of the PCDAI score were considered to have failed the treatment (see table 2.4.1.2 for inclusion and exclusion criteria of the study).

At week 8 children were readmitted for assessments as on week 0. These included history, examination, blood tests, endoscopy (mucosal disease assessment), dietary assessment, quality of life assessment and PCDAI scores. Food reintroduction was planned on discharge with each food group introduced over three days. Those in remission continued with the study and were given a date for review in paediatric outpatients for recruitment into phase B.

The investigations and clinical assessment details are listed in figure 2.4.1.2. This period of 8 weeks intensive treatment is termed as 'phase A' (see flow diagram 2.4.1.1).

Table 2.4.1.1 Admission checklist (week 0) for a child entering phase A of the ACD004 study

- Written informed consent
- Inclusion/ exclusion criteria

- Demography (sex, age, race)
- Clinical and dietary assessment
- Medical and surgical history
- Concomitant medication

- Height and body weight
- Pubertal status

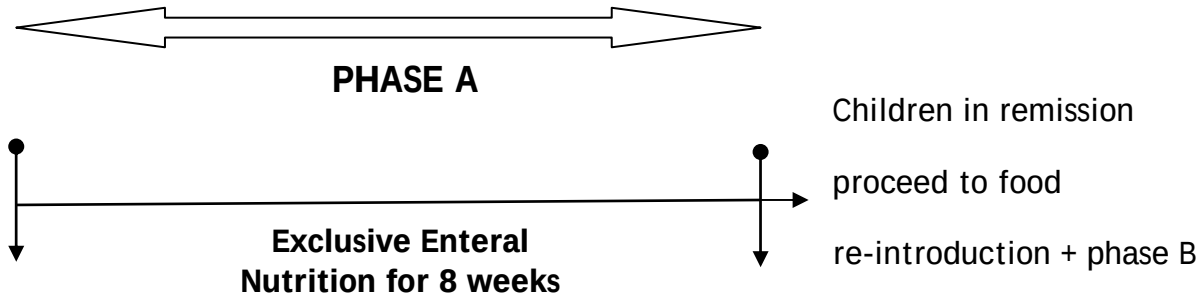
- PCDAI to assess disease activity
- Quality of life

- Biochemical assessment
- Hb & Hct, Platelet count
- CRP, ESR
- Albumin, Electrolytes

- Radiographic assessment of disease site using barium meal and follow through

- Histology and colonoscopy (microscopic and macroscopic assessment)

Figure 2.4.1.1 Design of study (Phase A)



Wk0

Recruitment

Ileo-colonoscopy + gastroscopy

(endoscopic + histologic scores)

PCDAI

Wk8

End of this part of study

Ileo-colonoscopy + gastroscopy

(endoscopic + histologic scores)

PCDAI

Bloods

PHASE A ⟷					PHASE B (randomized controlled study) ⟷							
	Diagnosis	**3 weeks**	**9 weeks**	**13 weeks**	**0 month**	**2 months**	**4 months**	**8 months**	**12 months**	**16 months**	**20 months**	**24 months**
Inclusion Criteria	X											
Informed Consent	X											
Randomisation				X								
Hb	X	X	X	X			X	X	X	X	X	X
Hct	X	X	X	X			X	X	X	X	X	X
Platelet count	X	X	X	X			X	X	X	X	X	X
ESR	X	X	X	X			X	X	X	X	X	X
CRP	X	X	X	X			X	X	X	X	X	X
Albumin	X	X	X	X			X	X	X	X	X	X
Urea	X	X	X	X			X	X	X	X	X	X
Height (cm)	X		X				X	X	X	X	X	X
Weight (kg)	X	X	X	X			X	X	X	X	X	X
PCDAI	X	X	X	X			X	X	X	X	X	X
Quality of Life	X	X	X	X			X	X	X	X	X	X
Barium Meal & Follow Through	X											
Colonoscopy	X		X									
Histology	X		X									
Dietetic Assessment	X	X	X	X			X	X	X	X	X	X
Weighed food intake						X						

Figure 2.4.1.2 Investigations flow chart for phase A and B

Table 2.4.1.2 Inclusion and exclusion criteria for the study

Inclusion Criteria

- Age: 5 to 19 years
- Males or females
- Diagnosis of Crohn's disease as confirmed by:
    - histology
    - colonoscopy
    - barium follow-through
    - PCDAI $\geq$ 20 in the acute phase
    - All subjects with a new diagnosis or known patients of Crohn's disease who have just been treated with 5-ASAs, not taking part in any other study and been in remission for at least 4 months, are included.
- All subjects will take enteral nutrition as their sole source of nutrition during the first 8 weeks of the initial phase of the study
- All subjects recruited will be attending their respective paediatric inflammatory bowel disease clinic and available for follow-up
- Written informed consent obtained from subject or legal guardian

Exclusion Criteria

Subjects will be considered ineligible for enrolment in the study if any of the following are met:

- Immunosuppressive drugs and steroids
- Exclusive oral disease
- Exclusive perianal disease
- Subjects already included in other clinical trials or who have taken part in a clinical trial within the previous 4 weeks
- Subjects who are unable to comply fully with study requirements

Early end of study

- Subjects will be prematurely discharged from the study if any of the following circumstances occur:
- Not in full remission at the end of Week 8 (end of exclusive feeding)
- Relapse of the disease (PCDAI > 20)
- Non compliance (defined as a reduction or interruption of prescribed enteral product to 20% or more over the 8-week exclusive feeding phase
- Onset of life threatening adverse event
- Death of the patient
- Is life threatening
- Requires hospitalization or prolongation of current hospitalization
- Results in persistent or significant disability/incapacity
- Subject's request
- Enrolment in another investigational study

Table 2.4.1.3 Preparation of the polymeric enteral feed for administration

a. Instructions for use of polymeric feed

- Wash hands thoroughly. Follow instructions carefully and select volume of feed required.
- Measure boiled and cooled water and pour into a clean jug, bowl or shaker.
- Measure corresponding amount of powder, either use scoop or weigh powder in grams. Level off scoop with the back of a knife.
- Add powder to the water. Immediately stir or shake until well mixed.
- Use immediately or cover and refrigerate and use within 24 hours.

b. Mixing table

Volume of feed required	Water	Powder
2 litres	1800 mls	Whole tin
1 litre	900 mls	207 grams (or 41 scoops)
750 mls	675 mls	153 grams (or 31 scoops)
500 mls	450 mls	103 grams (or 21 scoops)

1 scoop = 5 grams
(Once reconstituted, 100 mls = 100 kcal)

2.4.2 Clinical disease scoring using PCDAI

This clinical tool has been previously described in sub-chapter 1.4 and I also used PCDAI to assess severity of disease [174]. There are 11 items in the index with each question carrying an individual score (see table 1.4.4.1). At completion, the scores are totalled and net value gives an indication of the severity of disease. In the original article Hyams et al defined a score of greater than 10 to be representative of active disease, 11-30 as mild

disease and 31 or more representative of severe disease. In this thesis a cut off score of 20 was used to define active disease out of a possible allowable score of 110.

We have often observed, in clinical practice, that a PCDAI score of 10 or 15 may inappropriately include children who are in clinical remission. An illustrative example would be of a child presenting with abdominal pain secondary to viral infection which results in a raised ESR. This child would score at least 10 on the PCDAI scale and hence by definition would fall in the category of active disease. This would result in increased number of false positives in the study. Viral infections are common in children and inappropriate diagnoses may compromise this long term study as relapse is the end point of this prospective trial. Recently Otley et al have addressed the issue of re-validation of the PCDAI scores for definition of active disease [354]. This group used similar methodology as employed in paper by Hyams et al and also correlated the PCDAI scores with the physician's global score. They concluded that a cut-off of 10 was too low. They arrived at the minimum figure of 18.7 $\pm$ 7.3 as definition for active disease. Therefore, we defined relapse as a PCDAI of 20 or more.

2.4.3 Endoscopic (macroscopic) scoring [355] (table 2.4.4.1)

For endoscopic scoring (mucosal inflammation visualised by endoscope) in this thesis, I have used a previously used scoring system. This system described by Williams CB is not validated but has been used in local research methodology. This method was originally chosen due to absence of a robust endoscopic scoring system suitable for use in children. Reasonings for this chioice have been discussed in detail in the 'discussion' section (section 2.8).

This endoscopic scoring system is a simple system based on inflammation visualized endoscopically, scored on a scale ranging from 0-3; with a score of 0 representing no inflammation and 3 active inflammation with

ulceration (see table 2.4.4.1) [355]. Therefore, each segment of the large and small bowel can be scored individually for inflammation. The worst colonic score from any segment was considered to be representative of the total colonic score. This scoring technique is discussed in more detail in the 'discussion' section.

2.4.4 Histology (microscopic) scoring [352] (table 2.4.4.1)

This system, similar to the endoscopic scoring system, is unvalidated. This was devised and used in previous investigations in the paediatric gastroenterology departments of St Bartholomew's and Royal Free hospital. As this method uses a similar scoring method (and scale) to endoscopic inflammation scoring, it was adopted to maintain conistency and comparibility. The histological scoring scale also ranges from 0-3. The ileum and each area of the colon receiving a score described in table 2.3.4.1 [352]. Again, each segment of the large and small bowel can be scored individually for inflammation. The worst colonic score from any segment was considered to be representative of the total colonic score. The specimens were all examined and scored by the same technique for inflammation by paediatric gastroenterology histopathologists in Royal Free and Chelsea Westminster Hospitals. Histopathologists at both centres were blinded to the identity, clinical/endoscopic details and timing of biopsy.

Table 2.4.4.1 Endoscopic and histologic grades for scoring intestinal inflammation in Crohn's disease in children

ENDOSCOPIC SCORING [355]

0 – No inflammation
1 – Mild inflammation, with erythema and/or occasional aphthoid ulcers
2 – Moderate inflammation, with extensive superficial ulceration and/or occasional deep ulcers
3 – Severe inflammation, with extensive deep ulceration

HISTOLOGY SCORING [352]

0 - Normal or minor chronic inflammation
1 - Prominent chronic inflammation (not lymphoid follicles) and / or focal cryptitis/ surface inflammation
2 - Prominent active inflammation with crypt abscess or crypt destruction
3 – Inflammation with ulceration

2.4.5 Adverse Event and adverse event reporting

2.4.5.1 Adverse event (or adverse experience)

An adverse event is defined as any untoward occurrence in a subject or clinical investigation subject administered as investigational product and which does not necessarily have to have a causal relationship with this treatment.
An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease temporarily associated with the use of an investigational product whether or not considered related to the investigational product. It may or may not lead to withdrawal of the subject from the study.

2.4.5.2 Adverse reaction

Adverse reaction is an unintended response to an investigational product related to any dose. The phrase 'response to an investigational product'

means that a causal relationship between the product and the adverse event cannot be ruled out.

2.4.5.3 Serious adverse event

Serious adverse event is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or
- Is a congenital anomaly/birth defect

2.4.5.4 Non-serious adverse events

All other adverse events not included within the serious adverse event definition are considered as non-serious. They can be mild, moderate or severe.
Mild events are usually transient require no special treatment and do not interfere with the subject's clinical conditions.
Moderate events usually introduce a low level of inconvenience or concern to the subject and may interefere with clinical conditions, but are usually improved by simple therapeutic measures.
Severe events deteriorate subjects clinical condition and generally require systemic drug therapy or other treatment.

2.5 Funding, study site/dates and ethics

2.5.1 Funding sources

The phase A was fully funded by Nestle, Switzerland.

2.5.2 Dates and site of the study

The study for Phase A was conducted between, March 2000 to September 2002.
The study was carried out at Royal Free and Chelsea Westminster Hospitals, London. I managed all appointments at the two centres and conducted these studies in person.

2.5.3 Data collection

Data was collected in CRFs (case report forms) provided by Nestle. The data was cross checked by the supervisor, in relation to clinical notes and laboratory results on the computer systems. Carbon copies of these records were retrived after cross checking. I retained the original CRFs in the hospital and transferred information to patient secured database to Excel and SPSS for analyses.

2.5.4 Ethics

Patient information sheet and patient consent forms given in appendix A and B, were devised using previously described guidelines used in the hospital. These, along with the complete study protocol, were reviewed and approved by the ethical committee. The phase A and B studies were approved by LREC, the local research ethics and research committees of Royal Free and Chelsea and Westminster hospitals.

2.6 Statistics

2.6.1 Power calculation

The power calculation was done a priori.

The criterion used for null and alternative hypotheses were:
Ho: the proportion of subjects with complete remission is 0.85
Ha: the proportion of subjects with complete remission is < 0.85
In the previously conducted study CT3211, the observed proportion of total remission was 0.85. A proportion of 0.60 is defined by the investigators as the clinically meaningful proportion. In the current study a minimum total of 27 subjects is needed in the 2 year recruitment period to complete phase A to obtain alpha = 5% and 90% power in the ability to detect a difference between the proportion of remission with ACD004 as compared to 0.85 (CT3211).

The investigators agreed that although a minimum total of 27 subjects were needed for phase A, recruitment would continue throughout the two year period, thus enabling us to collect more information about the feed.

2.6.2 Description of statistics analyses

All analyses were done on an intention to treat basis. Statistical software, SPSS v 11.01 was used for all statistical tests. The data was rechecked with SPSS v 16.0.0 for the repeat submission following the MD thesis examination interview (viva).
All power calculations were done by statisticians based at Nestec, Luassane. Statistcal analyses were carried out by me, as guided by Dr Corrine Hager (statistician in Nestec) and Dr Richard Morris, Reader in

Medical Statistics and Epidemiology, based at University College of London.
Databases were maintained in Microsoft® Excel 2000 and 2003 and SPSS v 11.0.0 and 16.0.0. Normally distributed continuous data has been described using mean and standard deviation whereas non-normally distributed continuous data as median (range or interquartile range-IQR). All categorical results are a number (%). 't test' and 'ANOVA' were used to assess parametric data; 'Kruskall Wallis' and 'Wilcoxon Rank' test to analyse non parametric data.
Significance was defined as $p < 0.05$.

2.7 Results

2.7.1 Demographics

Forty two children were recruited over a 2 year period in Royal Free and Chelsea Westminster Hospitals, London (March 2000 – February 2002). Thirty nine were newly diagnosed and three had been previously diagnosed having now presented with relapsed disease but had been in remission for a mean period of 1.2 yrs (0.6-2 yrs) – see inclusion criteria, table 2.4.1.2. They were not on any concomitant immunosuppressants.
The median age of children in the study was 13.6 years (IQR = 11.4 - 15.1 yrs). 28 males and 14 females were recruited. 18 were pre-pubertal, 9 in mid puberty and 15 at end of their pubertal development. 34 (81%) had severe disease (PCDAI > 30) and 8 (19%) mild to moderate disease (defined by PCDAI < 30). Table 2.7.1.1 gives details of children recruited in the study with date of births, decimal age at presentation and gender.

Table 2.7.1.1 Details of children recruited in phase A of the study with coded serial for the study, date of births, gender and decimal age at presentation (years)

Serial	DOB	Sex	Decimal age at presentation (yrs)
SJ 01	3/7/89	m	10.866
BK 02	26/9/86	f	13.644
MB 03	7/9/84	m	15.707
LR 04	25/7/90	m	9.901
SM 05	17/10/86	m	13.879
CO 06	10/9/84	m	15.819
CO 07	17/12/85	m	14.660
PB 08	10/12/84	m	15.693
DT 09	1/9/86	f	13.986
AW 10	2/9/89	m	10.986
CM 11	22/9/86	m	13.934
AW 12	18/12/91	m	8.764
SH 13	19/8/85	m	15.115
KC 14	11/3/86	f	14.597
LH 15	5/3/87	m	13.647
VS 16	9/3/92	f	8.655
WS 17	26/12/90	m	9.890
GD 18	29/4/90	f	10.592
KH 19	28/1/85	f	15.890
VR 20	31/1/87	f	13.934
AE 21	23/10/90	m	10.211
GK 22	2/2/88	m	12.948
PD 23	25/8/87	m	13.403
LS 24	28/1/85	f	15.997
AH 25	9/1/87	m	14.066
SO 26	4/7/88	m	12.581
SN 27	22/3/91	f	9.871
GL 28	23/12/86	f	14.173
JR 29	24/8/88	m	12.510
EE 30	24/1/89	m	12.110
JW 31	10/1/89	f	12.178
DC 32	26/2/88	m	13.060
OS 33	7/12/85	m	15.359
MY 34	23/2/87	m	14.290
SW 35	16/12/89	m	11.482
LH 36	2/4/86	f	15.225
RK 37	29/6/85	f	16.005
BH 38	5/1/86	m	15.518
BB 39	14/6/89	f	12.077
PG 40	5/10/84	m	16.805
AE 41	22/02/90	m	11.970
FS 42	18/12/87	m	14.112

2.7.2 Response to treatment

2.7.2.1 Follow up at 4 weeks

All patients were followed up at 4 weeks into treatment. There was a significant fall in ESR, CRP and PCDAI at this stage ($p < 0.0001$) with a significant increase in weight (WAZ) and albumin ($p < 0.0001$).

Table 2.7.2.1 PCDAI, WAZ and blood marker changes at week 4 of commencing enteral nutrition.

	Week 0	Week 4	p
PCDAI	43.8 (32.5-50.6)	7.5 (5-15)	$p < 0.0001$
ESR	32 (16.3-67.3)	10 (7-16)	$p < 0.0001$
CRP	27 (5.3-71.3)	2 (0-8)	$p < 0.0001$
WAZ	-1.08 (-1.82 - -0.24)	-0.66 (-1.6 – +0.1)	$p < 0.0001$
Albumin	32 (29-36.3)	41 (38-42)	$p < 0.0001$

There was a significant change in all paramenters with drop in PCDAI and inflammatory markers, and increase in albumin at week 4.

Table 2.7.2.2 PCDAI, WAZ and blood marker changes at week 8 after commencing enteral nutrition.

	Week 4	Week 8	p
PCDAI	7.5 (5-15)	7.5 (5 - 10.6)	ns
ESR	10 (7-16)	10 (4 - 20)	ns
CRP	2 (0-8)	1 (0 - 9.5)	ns
WAZ	-0.66 (-1.6 – +0.1)	-0.81 (-1.49 - 0.1)	$p = 0.023$
Albumin	41 (38-42)	40.5 (37.3 - 43)	ns

There was no change in in PCDAI, inflammatory markers, or albumin at week 8 (compared to week 4). Although there was significant fall in weight (WAZ) at week 8 (from week 4), there was an overall significant improvement in weight when compared to week 0 ($p < 0.0001$).

2.7.2.2 Follow up at 8 weeks

At completion of 8 weeks of enteral nutrition treatment, 33/42 children were in remission (78.6%).

There was no significant change in PCDAI, ESR, CRP and albumin between week 4 and week 8 (see table 2.7.2.2 and figures 2.7.2.1, 2.7.2.2 and 2.7.2.3). However, in the latter 4 weeks, there was a significant decrease in weight (p=0.023) from a median z score of -0.66 (IQR= -1.6 - +0.1) to -0.81 (-1.49 - +0.1) - See table 2.7.2.2. Despite the drop in WAZ scores in the latter 4 weeks there was an overall increase in weight from week 0 to week 8 ($p < 0.0001$)

There was an overall endoscopic and histologic healing in the ileum and colon of children. The scores significantly improved at completion of 8 weeks of treatment (WR, $p < 0.01$) – see table 2.7.2.3.

Table 2.7.2.3 Mucosal inflammation assessment at completion of treatment. Comparative scores pre and post treatment. Median scores are given with interquartile ranges in brackets. Wilcoxon Rank test was used for analysis.

	Pre - treatment	Post treatment	p
Ileum endoscopy	2 (0.5 – 2.5)	0 (0 – 1)	0.000
Ileum histology	1 (1 - 3)	1 (0 – 1)	0.002
Colon endoscopy	2 (1 – 3)	1 (0.25 – 1)	0.000
Colon histology	2 (1 – 3)	1 (1 – 1)	0.001

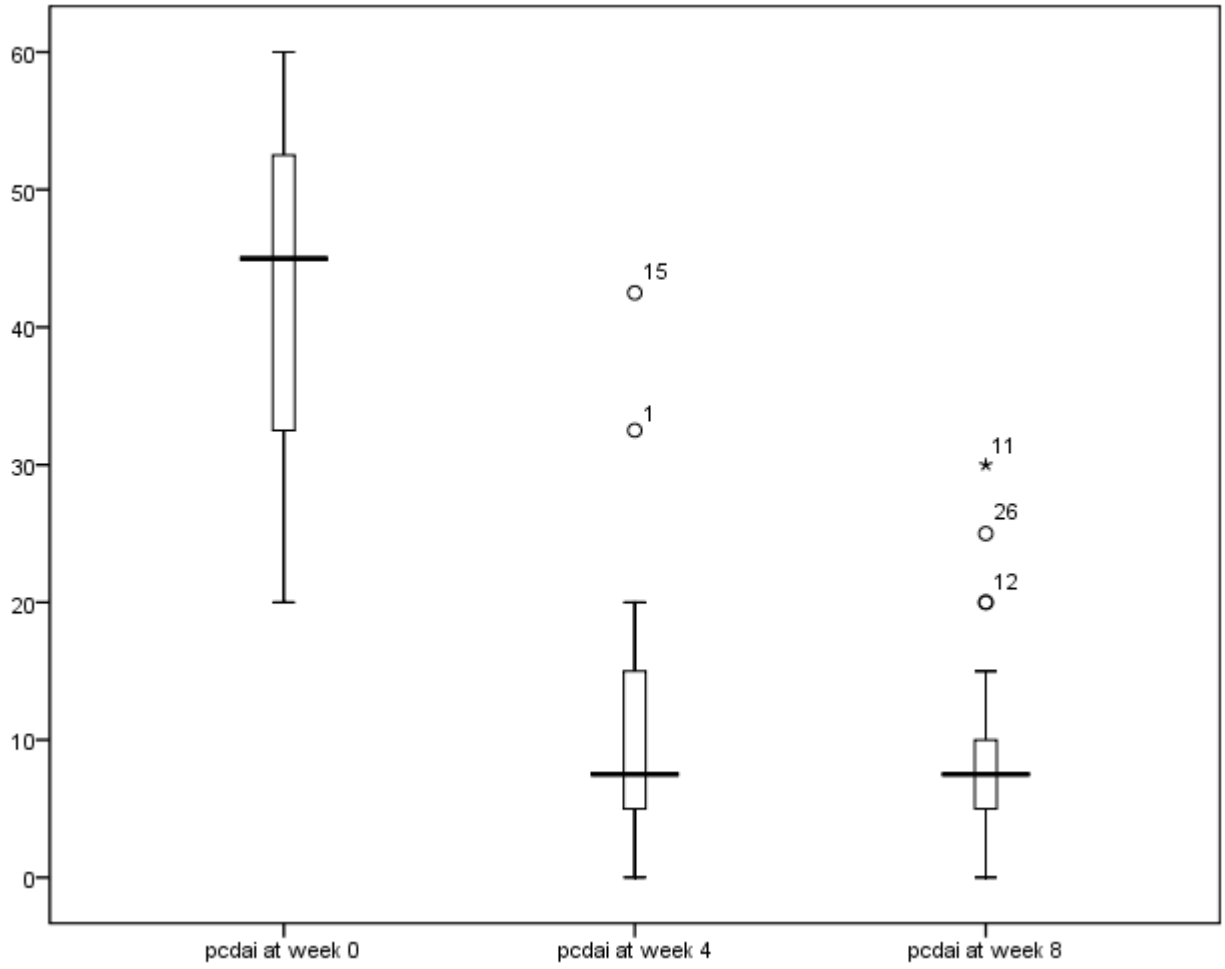


Figure 2.7.2.1 Significant fall in PCDAI in the first 4 weeks of treatment which then does not change over the subsequent 4 weeks

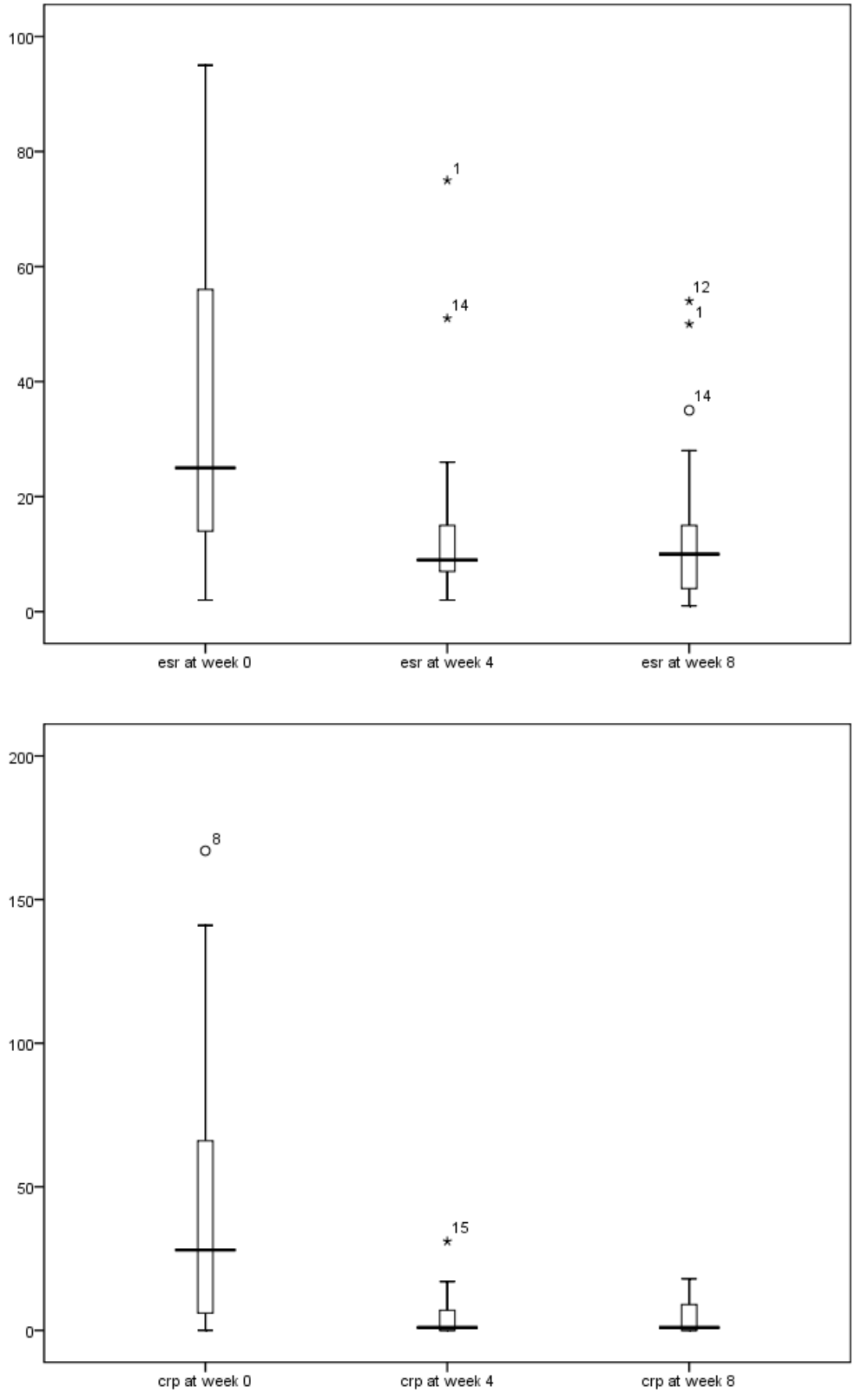


Figure 2.7.2.2 Significant drops in ESR and CRP in the first 4 weeks of treatment whith no further change in the subsequent 4 weeks through to week 8

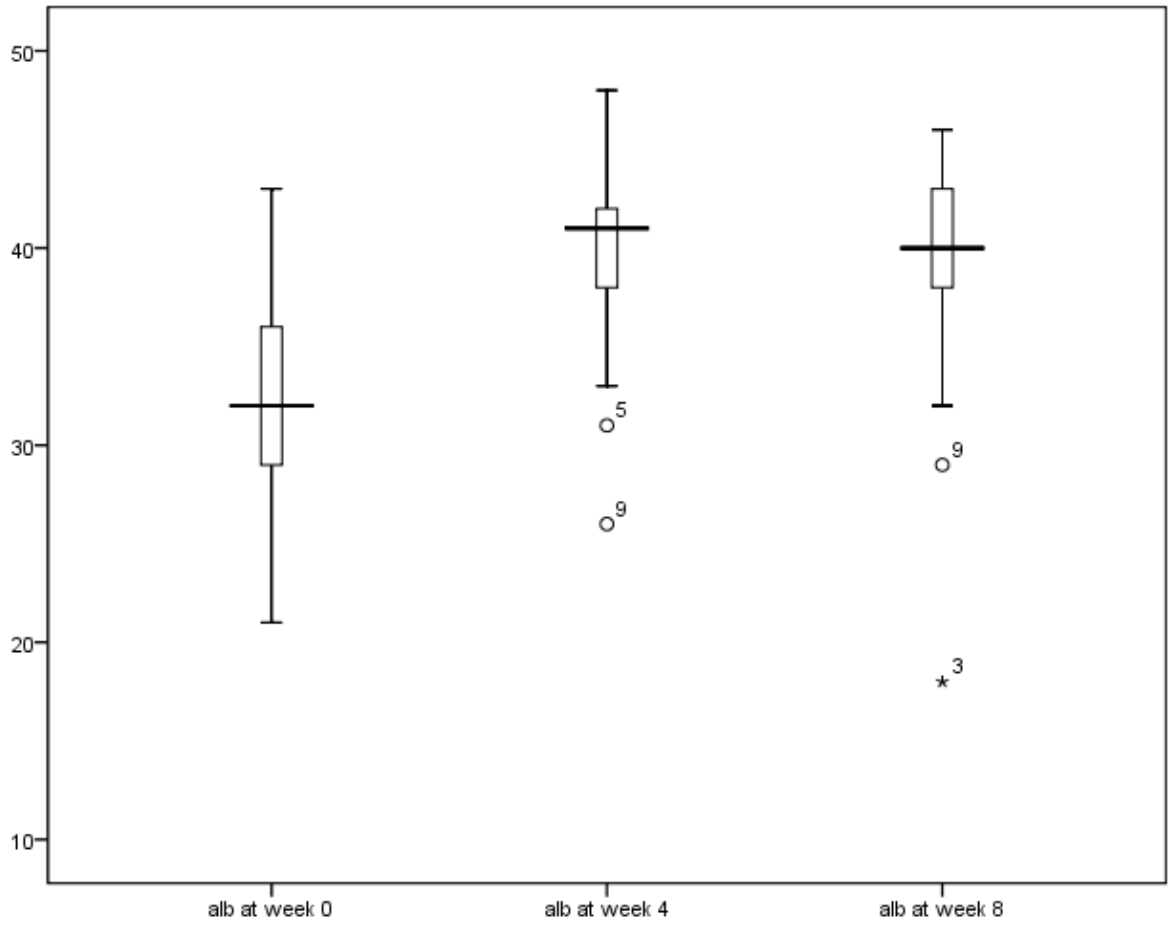


Figure 2.7.2.3 Significant increase in albumin in the first 4 weeks of treatment which then remains constant till completion of treatment

2.7.3 Response according to disease phenotype

2.7.3.1 Clinical response

The majority of the children had ileocolonic Crohn's disease (n=22, 52.4%). Of the remainder, 11 had ileal (26.2%) and 9 colonic disease (21.4%). The disease subclassification is based on the Vienna classification discussed in detail in subsection 1.2.2 and table 1.2.2.1.

There was no significant difference between PCDAI, ESR, CRP, WAZ and albumin at presentation in the three groups (Kruskall Wallis, p=ns). Colonic Crohn's disease was signicantly commoner in boys (88.9%, p=0.02) with

54.5% boys in the ileal subgroup and 63.5% boys in the ileocolonic disease subgroup.

At completion of 8 weeks of treatment there was a significant difference between the remission rates of the colonic, ileal and ileo-colonic subgroups (see table 2.7.3.3). Only 44.1% children in the colonic group were in remission compared to 81.8% in the ileal and 90.9% in the ileocolonic sub-groups.

Table 2.7.3.2 shows change in PCDAI, blood and weight parameters in each Crohn's disease subgroup. Although only 44% of children with colonic Crohn's disease achieved remission, all had a significant drop in PCDAI although not low enough to qualify as remission. The change in ESR and albumin in this disease group was insignificant.

In comparison, the ileal and ileocolonic groups showed significant improvement in all disease parameters at completion of enteral nutrition.

Table 2.7.3.1 Demographics and disease severity in the three phenotypes, at diagnosis.

		Ileum	Ileo-colon	Colon	Test	p
1.	n	11(26.2%)	22 (52.4%)	9 (21.4%)		
2.	Age (median)	13.4 (9.9-14.6)	14 (11.8-15.4)	12.5 (8.8-16.8)	KW	0.40
3.	M:F	6:5	14:8	**8:1**	χ^2	0.02 (colon)
4.	Pubertal status				χ^2	0.72
	- Pre-pubertal	5	18	9		
	- Early puberty	3	9	3		
	- Late puberty	4	12	2		
5.	Weight (z score)	-1.6 (1.7)	-1.1 (1.1)	-1.4 (1.1)	KW	0.45
6.	CRP at dx	23.4 (23.5)	48.1 (48.3)	28.5 (28.8)	KW	0.14
7.	ESR at dx	26.3 (21.7)	41 (31)	40.6 (35.3)	KW	0.32
8.	Albumin at dx	38.1 (8.4)	33.6 (5.1)	35.5 (6.5)	KW	0.08
9.	PCDAI at week 0	34.2 (10.6)	40.5 (12.2)	40.7 (14)	KW	0.05
10	**Remission at end of treatment (%)**	**9 (81.8%)**	**20 (90.9%)**	**4 (44.4%)**	**χ^2**	**0.016**

KW – Kruskall Wallis test, χ^2 - Chi squared.

Table 2.7.3.2 Change in PCDAI, weight, albumin, ESR and CRP in ileal, colonic and ileocolonic Crohns treatment after treatment with ACD004

a. Ileal Crohns disease group

	Pre treatment	Post treatment	p
PCDAI	40 (25 - 50)	6.25 (1.9 – 11.3)	0.005
WAZ	-1.05 (-1.92 – 0.07)	-0.81 (-1.62 – 0.22)	0.04
Albumin	32 (27 – 39)	41.50 (38.3 – 44.5)	0.008
ESR	20 (12 – 42)	9 (5.8 – 12.3)	0.008
CRP	24 (3 – 75)	0 (0 – 1)	0.011

b. Ileo-colonic disease group

	Pre treatment	Post treatment	p
PCDAI	45 (32.5 – 52.5)	7.5 (5 – 10)	0.0
WAZ	-1.26 (-1.87 – 0.08)	-0.9 (-1.5 – 0.38)	0.0
Albumin	32 (29 – 35)	39.5 (37.8 – 42.3)	0.001
ESR	43 (21 – 85)	8 (2 – 22.5)	0.001
CRP	39.5 (20 – 85.3)	1 (0.3 – 13.5)	0.0

c. Colonic disease group

	Pre treatment	Post treatment	p
PCDAI	42.5 (34.4 – 45)	16.3 (5 – 23.8)	0.012
WAZ	-1.02 (-1.7 - -0.31)	-0.64 (-1.4 - -0.22)	0.012
Albumin	31 (28.5 – 36.5)	40.5 (36.3 – 42.5)	0.161
ESR	31 (17.5 – 50)	17 (7.8 – 42.5)	0.612
CRP	23 (3 – 30)	2 (0 – 8.3)	0.018

WAZ = weight Z score

All values are 'medians with IQR (inter-quartile range) in brackets.

Table 2.7.3.3 Remission rates of three phenotypes at completion of treatment

		Ileum	Ileo-colon	Colon	Test	p
1.	n	11(26.2%)	22 (52.4%)	9 (21.4%)		
2.	PCDAI at week 0	40 (25-50)	45 (32.5-52.5)	42.5 (33.8-43.8)	KW	0.05
3.	PCDAI at week 8	6.3 (1.9-11.3)	7.5 (5-10)	12.5 (5-25)	KW	0.16
4.	**Remission at end of treatment (%)**	**9 (81.8%)**	**20 (90.9%)**	**4 (44.4%)**	χ^2	**0.016**

2.7.3.2 Mucosal response

There was no histologic improvement in colonic inflammation in the colonic Crohns disease subgroup. However, an improvement was noted in the endoscopic scores. See table 2.7.3.4.
The ileo-colonic Crohns' disease group showed a significant improvement in the colonic healing, at both endoscopic and histologic levels in response to treatment with enteral feeding. See table 2.7.3.4.

Table 2.7.3.4 Comparison of the colonic histologic and endoscopic scores in the ileocolon and colon groups. * A comparison of the endoscopic and histologic mean scores of the colonic and ileocolonic groups show no significant difference at commencement of treatment. (p=0.51 and p=0.67 respectively)

	Median scores at enrolment*	Median scores at end of treatment	p	Test
Ileocolon group (Endoscopic score)	2 (2 - 3)	1 (0 - 1)	**0.000**	WR
Colonic group (Endoscopic score)	2 (2 – 2.5)	1 (1 - 2)	**0.023**	WR
Ileocolon group (Histologic score)	2 (2 - 3)	1 (0 - 1)	**0.000**	WR
Colonic group (Histologic score)	3 (3 – 3)	1 (1 - 2)	0.083	WR

WR- Wilcoxon Rank Sum test

2.7.4 Compliance, tolerance, treatment failures and adverse effects

2.7.4.1 Compliance

Compliance was monitored by dieticians at recruitment and intitaiting enteral nutrition. Children stayed were inpatients admitted to paediatric gastroenterology ward for a median 3 days and discharged only when they were making full volumes with parental training for making feeds. Compliance during the trial was monitored by the tins/feeds used by

patients and by phone calls in between appointments. There were no compliance issues reported in the study.

2.7.4.2 Use of nasogastric tube

Three children (3/42) required nasogastric tube feeding during the eight week treatment period. Another required nasogastric tube only for the first week of treatment, which was removed at discharge from hospital.

2.7.4.3 Details of study failures/early dropouts

4 treatment failures dropped out early and did not complete the 8 weeks therapy, due to worsening of their disease. These children additionally commenced on corticosteroids for their treatment and as a result were excluded from the study. One of the four treatment failures developed refeeding syndrome; this is discussed below (sub-section 2.7.4.4).

2.7.4.4 Refeeding syndrome

A 14-year-old girl (Case number 20, Phase A – see table 2.7.1.1) with Crohn's disease developed refeeding syndrome. She, since onset of symptoms, before commencing treatment, over a period of eight weeks had lost 7 kg in weight 41.6 kg (weight for age = 14.8th centile, z = -1.05). At recruitment, she was 168.2 cms tall (height for age = 88.6 centile, z = +1.2) and her BMI was 14.70 (BMI SDS = -1.58). She was pale, afebrile but had no oral ulcers. By the time enteral nutrition was commenced 7 days later (patient's/parental choice in delay in treatment), the patient had lost a further 2.7 kg. She had a pulse rate of 120/min. She was prescribed 2500 kcal/day of ACD004. Within 72 hours the patient had lost a further 1.8 kg. As the patient was unable to take the prescribed amount (RDA), full enteral feeds were administered by a nasogastric tube. With the increase

of feeds there was a precipitous drop in phosphate levels to 0.23 mmol/l, despite a standard daily phosphate supplementation of 1.25 mmol/kg/day in the feed (Nestlé, Clinical Nutrition). A diagnosis of refeeding syndrome was made. Her weight had increased by 2.9 kg to 41 kg. An ECG was done with a normal corrected QT interval of 0.44 seconds (normal range: 0.35 - 0.45s). An echocardiogram showed normal cardiac function. Her enteral intake was reduced by 25% to 1800 ml (1800 calories/day), and phosphate supplements were increased to 5 mmol/kg/day. Within 48 hours her phosphate rose to 1.19 mmol/l followed by gradual improvement and recovery over the subsequent week.

Figure 2.7.4.1 Flow chart of investigations from the day of admission through to final follow up. Refeeding syndrome was diagnosed on day 5

	Admission	**D2**	**D4**	**D5**	**D7**	**D12**	**D21(F Up)**
Hb	**8.3**	7.4	10.3	**9.0**		10.1	**11.8**
Plat	**646**	579	404	**351**		788	**331**
CRP	**193**	156	145	**166**	43	10	**1**
ESR				**9**		12	**7**
Albumin	**21**	21	18	**16**	18	22	**41**
Phosphate	**0.98**	0.84	0.63	**0.23**	1.19	1.48	**1.36**
Ca	**2.43**	2.34	2.3	**2.28**	2.33	2.49	**2.48**
Na	**134**		132	**125**	133	137	
K	**3.6**		3.9	**5.0**	4.1	4.7	
Mg	**0.81**					0.93	**0.85**
Urea	**3.0**		3.5	**2.5**		3.1	
Selenium	**28.8**					46.4	
Zinc	**5.8**					11.3	

2.7.5 Food reintroduction – After phase A

4 children left the study (described in section 2.7.4.1) before completion of phase A. 5 more children dropped at completion of phase A due to disease relapse, 1 required surgery for persistent right sided disease. All 33 children in remission entered the food re-introduction phase.

During this phase, food was gradually introduced whilst the enteral feed was reduced to 30% of RDA at the end of this phase. Unfortunately, there was a high drop out during the food re-introduction stage (24.2%). Children in this group have been termed as 'early relapsers'.

3/8 dropped out of the study although still being in remission. This was because one was lost to follow up, one moved area and the last once in remission did not return for any further follow ups until two years late for treatment of another relapse.

Of the remaining 5, two relapsed in the 3rd and another two in the 4th week of food re-introduction. The paediatric gastroenterology team chose to use Azathioprine in one child with a PCDAI < 20 as she had marginally raised inflammatory markers following food re-introduction and was seen to be following her brother's disease pattern. In the drop-out group, 5 children had ileocolonic, 2 ileal and 1 colonic Crohn's disease.

2.8 Discussion

ACD004 is an effective enteral feed and its remission rate is comparable to Modulen IBD® (CT3211), a similar whole protein based polymeric enteral feed. Results of the CT3211 study have been previously published and reported [24]. Comparing disease severity in children recruited in both studies, those treated with ACD004 had relatively more severe (81% vs. 41.4%) disease (as defined by PCDAI > 30).

These remission rates (both ACD004 and CT3211 studies) are also comparable to a previously published Canadian trial of a comparative study of corticosteroids and enteral nutrition [356]. In this study children with colonic Crohn's disease were excluded and they achieved a remission rate of 75% for enteral nutrition and 89% for corticosteroids.

ACD004 is a palatable polymeric feed and nasogastric tube feeding was only required in 3 children (7%) and in a 4th for a very short while. Previous

studies using elemental and semi-elemental diets have used nasogastric tube feeding in all children [304].

ACD004 was used for a period of 8 weeks for treatment of acute Crohn's disease. This study demonstrates resolution of symptoms and fall in inflammatory markers by week 4 (see table 2.7.2.1 and 2.7.2.2). Bannerjee [357] has recently shown a drop in IL-6 and ESR within 3 days of starting treatment. There is no definitive period of ideal duration of treatment, as the practice is very variable in gastroenterology units with shorter periods of 4-6 weeks, also reported. A decision of using enteral nutrition for 8 weeks was based on current policy and practice of our unit.

ACD004 has a higher ratio of n-3: n-6 fats (the constituents and ratios in these feeds have been discussed in section 2.2). Several clinical studies have suggested a beneficial role of use of fatty acids in the pathophysiology of intestinal inflammation. High dietary intake of n-6 polyunsaturated fatty acids (PUFA) with low intake of n-3 PUFAs has been associated with development of Crohn's disease [358]. This was a retrospective and correlational study in a genetically stable homogenous Japanese population. Andoh and co-workers have recently demonstrated that n-6 fatty acid-rich diet in comparison to n-3 fatty acid rich diet enhanced initial mucosal damage in TBNS enteritis [359]. It is suggested that intake of n-3 fatty acids leads to PGE3 and LTB5 production which have 1/30 potency of PGE2 and LTB4 [360]. The latter is a chemotatic factor that facilitates accumulation of neutrophils in the mucosa. Ingestion of n-6 fats in the TBNS enteritis mouse model also results in a significant increase in serum IL-6 levels [359]. IL-6 is derived from several sources including macrophages/monocytes and endothelial cells which may possibly be modulated by intake of n-3 fats through less understood mechanisms. Belluzi et al assessed the role of a fish oil preparation for maintenance of remission in Crohn's disease. 11/39 compared to 27/39 relapsed in the fish oil group when compared to placebo [27].

In this study we used PCDAI to assess clinical disease score. PCDAI was developed by Hyams and involves scoring for questions about symptoms,

signs and blood tests (see table 1.4.4.1). At completion, the scores are totalled and net value gives an indication of the severity of disease. In the original article Hyams et al defined a score of greater than 10 to be representative of active disease, 11-30 as mild disease and 31 or more representative of severe disease. In this thesis a cut off score of 20 was used to define active disease out of a possible allowable score of 110. This was determined by peers developing the study trial. One of the main concerns regarding a cut off value of 10, in a study conducted over more than 2 years was to have inappropriate dropouts. We have often observed, in clinical practice, that a PCDAI score of 10 or 15 may inappropriately include children who are in clinical remission. An illustrative example would be of a child presenting with abdominal pain secondary to viral infection which results in a raised ESR. This child would score at least 10 on the PCDAI scale and hence by definition would fall in the category of active disease. Viral infections are common in children and inappropriate diagnoses may compromise this long term study as relapse is the end point of this prospective trial. Hyams and co-workers in a PCDAI re-evaluation study debated the point of remission/mild disease cut off at considerable length (this study/report was not available at the time of study trial). They raised the same concerns as discussed above. They demonstrated a lower PCDAI cut off value (for remission/mild disease) had greater specificity but lower sensitivity in relation to physician's global assessment of mild disease vs inactive disease. Although the group stayed on the original definition of disease cut off it was accepted that with a lower cut off, it would be impossible for a child with slow linear growth to acheive remission even with the most effective therapy (poor growth scores 10 on PCDAI scale).

I used a new endoscopic mucosal scoring system for inflammation. This system although described and used before remains unvalidated. An alternative is, the Crohn's disease endoscopic index of severity (CDEIS) which is a validated research tool used in adults developed by French group GETAID (Groupe d'Etude Therapeutique des Affections

Inflammatories Digestive) [361]. It is the gold standard for adult research studies and has been used in many trials. There are however, no reported trials of its use in paediatrics as it is not validated for paediatric usage. CDEIS contains four questions; two of them are about length of colon affected by disease. A 4 year old's colon will be shorter than that of a 16 year old adolescent and as children of varying ages are recruited in this study, such a scoring system would be difficult to use. I, in agreement with co-investigators, therefore, did not adopt this system.

Whilst using the endoscopy scoring system described by Williams CB, the greater difficulty was to devise a meaningful formula which would give a figure representing the best global score for bowel inflammation in the ileum and colon. There were three possible ways to do so, each with its pros and cons, discussed as follows:

One is to add up all the numbers (0-3 in each individual colon segment). This will make the ileocolonic 'total' scores falsely high when compared to 'ileal' or 'colonic' disease sub-groups. This is easily explained. The colon will score '0' in the ileal disease group and the ileum '0' in the colonic disease group. Different totals in different disease phenotypes would make it impossible to analyse, quantify and compare degree of inflammation amongst the phenotypes of Crohn's disease.

A second option is to take a mean of all the colonic and ileal scores from the three disease phenotype groups. This technique would give ileum a very small representation in the total. In a child with severe ileal disease the ileum will underscore as its score will dilute when averaged amongst several 'normal' (each segment scoring zero) colonic biopsies. Mild widespread disease would score the same or even more compared to severe localized disease.

The third way is to take the worst possible inflammation score as representative of the bowel. This technique would result in a child with severe localized colonic disease scoring the same as another with severe widespread disease. However, severe disease would be correctly represented in addition severe ileal disease would also be correctly

represented and could be compared to colonic score if it were necessary. I adopted this technique for these reasons (least compromise) and was uniformly agreed by all co-investigators before commencement of study. This study also looks at the response of different Crohn's disease subgroups (as per Vienna classification) to treatment with enteral nutrition. The results are interesting. Although there is a clear overall improvement in disease after treatment with enteral nutrition, isolated colonic Crohn's disease in children responds poorly (systemic and mucosal) to treatment with exclusive enteral nutrition. It is important to emphasize that the colonic disease subgroup did not have associated ileal or small bowel involvement. Previously, Furukuwa and colleagues have shown severe colonic cobblestoning to be poorly responsive to treatment with enteral nutrition in adults [362]. Interestingly, this was not significant when patients were treated with total parenteral nutrition.

The understanding of mechanisms of effects of enteral nutrition is limited and why this should work less well in colonic disease is difficult to explain. There is now increasing evidence that inflammation in Crohn's disease is propagated due to contribution of both genetic and environmental factors [363-367].

NOD2/CARD15 is associated with ileal disease [368] and is composed of two caspase recruitment domains; a nucleotide-binding domain (NBD) and a leucin-rich-repeat (LRR) region. Truncation of the LRR domain of NOD2/CARD15 impairs recognition and binding activity for bacterial peptidoglycans therefore stimulating the pro-inflammatory NFκB pathway [369-371]. In addition increased populations of both E Coli and B Fragilis have been demonstrated in Crohn's disease [372] and particularly bacteroides have been shown to induce colitis in HLA B27 transgenic mice [373]. In this regard, increased bacterial contact in the ileum, caecum and rectum, due to relative stasis of food in these areas, may be significant, particularly in ileo-colonic Crohn's disease. Analyses of faecal flora shows that enteral nutrition (fibre free) results in an increase in total aerobes in the gut flora in humans [374]. Thus it may be that enteral nutrition is effective in off setting this

balance therefore making it effective in ileo-colonic Crohn's disease. It is also possible that differing genetic mechanisms may be operable in colonic disease responsible for the differential response. This is a speculation and remains unproven to date.

Last, a child developed refeeding syndrome at commencement of enteral feeding. Refeeding syndrome may develop on feeding malnourished children and is defined as "the occurrence of severe fluid and electrolyte shifts (especially, but not exclusively, of phosphate) and their associated complications in malnourished patients undergoing enteral / parenteral refeeding" [375]. Marik defined refeeding syndrome as a fall in phosphate levels by more than 0.16 mmol/l, to below 0.65 mmol/l [376]. Refeeding syndrome is not uncommon and severe hypophosphataemia (< 0.35 mmol/l) has been reported in 0.8% of all hospitalised adult patients [377]. Starvation for as little as 48 hours may predispose to refeeding syndrome, with a low serum pre-albumin level (<110 g/l) predicting hypophosphataemia [376]. Marik showed that 81% (17/21) of patients developing refeeding syndrome had a pre-albumin level of less than 110 g/l; yet similar levels were also found in 30% of patients who did not develop refeeding syndrome. Not all malnourished patients without mineral supplementation develop the classic electrolyte and fluid shifts, or their consequences, during refeeding [375]. The reasons for this are not clear. The child who developed refeeding syndrome had dramatic weight loss, although not unusual per se at first presentation, which, had occurred over a matter of weeks, and not months. As a result of this severe disease, nutritional stores had been depleted more rapidly than normal. The constellation of active inflammation, malabsorption and profound anorexia thus led to this episode of refeeding syndrome during conventional treatment with enteral nutrition. She had a persistent tachycardia during the early stages of her refeeding. While this may partly have been due to active inflammation and/or bacteraemia, several other factors may have contributed. The patient may have mounted a compensatory tachycardia in view of early fluid overload, and this may

have been exacerbated by her low serum albumin. Despite this fluid overload, clinical oedema was not documented. Significant hypophosphataemia may also have had a direct effect on cardiac contractility and output, although a normal cardiac echo was performed after the diagnosis was made. There have been very few reports of children with refeeding syndrome, and no reports of it occurring during the management of Crohn's disease with enteral nutrition. This case highlights the need for continued caution especially whilst using enteral nutrition in malnourished children. This instance of refeeding syndrome is very unlikely to be related to the type of formula or directly related to underlying Crohn's disease.

In summary, this pilot study demonstrates that ACD004 is not only effective in treatment of active paediatric Crohn's disease but is comparable to its predecessor enteral feed CT3211 (Remission rates: 78.6% vs. 79%).

Chapter 3. Randomised controlled trial for use of supplemental enteral nutrition to maintain remission – Phase B

3.1 Background

There is a constant search for an ideal maintenance agent in paediatric Crohn's disease; one which is effective and has the least side effect profile. Enteral nutrition is a recommended standard first line treatment for acute active paediatric Crohn's disease in many centres across the world. It is only logical that, with its excellent safety profile, paediatric gastroenterologists have considered it for maintenance treatment as well. Therefore, despite little evidence, paediatric gastroenterologists have also advised patients to use enteral feeds as a regular supplement alongside with their food intake in the hope this will help maintain remission. Retrospective studies [26] suggest a possible beneficial role of supplemental enteral nutrition, however to date there are no prospective studies. As a result this prospective trial was designed, looking at use of enteral supplementation for maintenance of remission in children with Crohn's disease. This is the phase B of the study.

3.2 Aims

The primary objective of this study is to assess reduction in relapse rate in Crohn's disease in children on long-term continuous enteral nutrition supplementation using it as part of their total daily requirements compared to a control unsupplemented group, over a period of 104 weeks (2 years).

3.3 Methods

All subjects recruited in phase A (newly diagnosed Crohn's disease or relapsed subjects) were treated for an 8-week period of exclusive enteral nutrition (chapter 2, see table 2.2.1 for feed composition). Those failing to respond to treatment, deteriorating or relapsing at any stage dropped out

of the study at that point and were counted as a relapse. All analyses were done on intention to treat basis.

Children in remission at eight weeks (end of phase A, chapter 2) entered a 4 to 6 week food reintroduction phase. Food items were re-introduced at the rate of one food item every two days over a period of 4 to 6 weeks (See sub-section 2.7.5). During this transition period the enteral feeds were reduced to 30% of the children's recommended daily allowance under guidance by the dieticians. All subjects in full remission (defined by PCDAI < 20) at completion of food re-introduction were enrolled in Phase B, which marked the start of the randomized controlled trial.

Once subjects reduced their enteral feeds to 30% of the daily requirement allowance (500-750 mls/day), they were randomized into two groups highlighting start of Phase B, the randomised controlled trial. One group continued to supplement their diet with 30% of recommended daily allowance with the enteral feed while the other group continued decreasing the oral enteral feed until a full ad libitum diet was taken. Their enteral nutrition was then stopped and a normal diet continued. The summary of these two groups is given as follows (see study design flow chart - figure 3.3.1):

Group 1: Full diet supplemented with about 30% of total daily requirement of the enteral feed (500-750 mls/day) to start at the beginning of Week 13-15 (end of food reintroduction) to Week 112-114 (2 years).

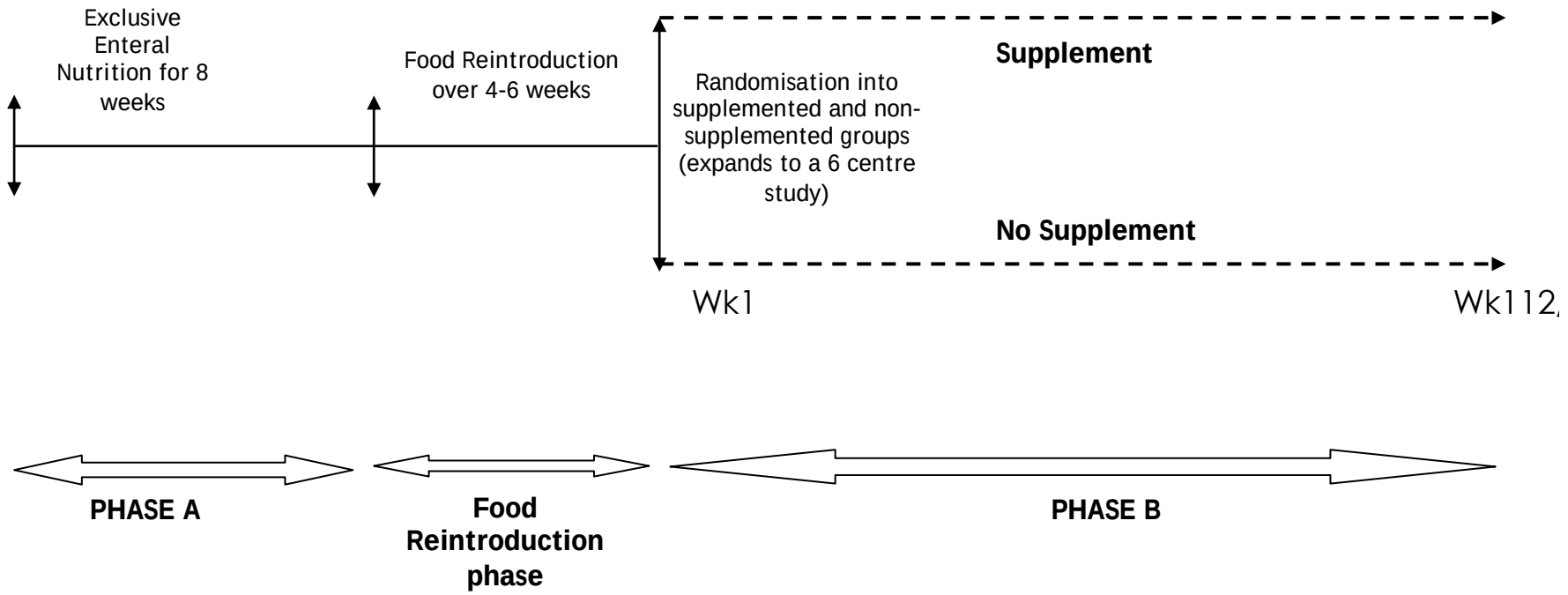
Group 2: This is the un-supplemented group. Normal diet to start at the beginning of Week 13-15 (end of food reintroduction) to Week 112-114.

The phase B was planned to be a multi-centre study involving 6 paediatric gastroenterology units (3 centres from UK, and 1 each from France, Netherlands and Switzerland). This was to be carried over a 2 year period till adequate numbers were recruited to meet the desired power of the study (n=72) determined at priori.

Children are followed 4 monthly after recruitment into phase B. Families were given access to the investigators phones so that an earlier appointment could be made if necessary eg; developing symptoms of Crohn's disease or discuss any dietary issues. On each visit the children had a clinical assessment which included a history of symptoms, a clinical examination and blood tests. Following this, children had a PCDAI score, and were asked to complete the quality of life questionnaire. The study design flow chart is given in table 3.3.1and the flow chart for clinical assessments and investigations is given in table 3.3.1.

All children filled a consecutive 3 days food diary for dietary assessment by the dietician at month 2 of recruitment into phase B. This involved documentation of all fluids and food taken by the child over three days. This information was completed on forms given to parents by the dietician and then posted or dropped by the parents to the hospital. The information was then fed into a software programme (Caveat V 5.0) for calorific as well as macro- and micro-nutrient assessment. The purpose is to check intake of children participating in the study. This was completed by children participating in both arms of the study, the supplemented as well as the non-supplemented groups. The supplemented groups took dietary supplements (ACD004) orally (nasogastric tubes were not used in phase B).

Figure 3.3.1 Study design flow chart



PHASE B (randomized controlled study)								
	0 month	**2 months**	**4 months**	**8 months**	**12 months**	**16 months**	**20 months**	**24 months**
Randomisation	X							
Hb	X		X	X	X	X	X	X
Hct	X		X	X	X	X	X	X
Platelet count	X		X	X	X	X	X	X
ESR	X		X	X	X	X	X	X
CRP	X		X	X	X	X	X	X
Albumin	X		X	X	X	X	X	X
Urea	X		X	X	X	X	X	X
Height (cm)	X		X	X	X	X	X	X
Weight (kg)	X		X	X	X	X	X	X
PCDAI	X		X	X	X	X	X	X
Quality of Life	X		X	X	X	X	X	X
Dietetic Assessment			X	X	X	X	X	X
Weighed food intake		X						

Table 3.3.1 Flow chart for clinical assessment and investigations at 4 monthly follow up from the time of recruitment.

3.4 Randomisation and Statistics

3.4.1 Randomisation sequence generation and randomisation allocation concealment & randomisation implementation

A computer programme was used to produce the randomization list based on computer-generated sequence of random numbers. This person was blinded to the details of the study. The list was transferred to a sequence of sealed envelopes each containing the name of the next treatment on a card. The person placing the cards in the envelope was also blinded and unaware of details of this particular study. This was conducted in Nestle, Switzerland. The envelopes were delivered by the Nestle study monitor to me in London. At recruitment, I opened the next envelope in the sequence and assigned treatment.

3.4.2 Blinding (masking)

This is a dietary intervention study. Due to its nature it was not possible to blind the investigators or the patients regarding supplementation.

3.4.3 Power calculation

Since no equivalent long-term follow study of nutritional intervention in Crohn's disease has been performed, historical relapse data was used by the investigators for power calculation. The estimate of the proportion of subjects who relapse without nutritional supplement is 0.65 and 0.40 for those on supplement [26]. The number of subjects needed in a one proportion power analysis (alpha = 5%, power = 90%) was 36 per group.

3.4.4 Description of statistics analyses

All analyses were done on an intention to treat basis. Statistical software, SPSS v 11.01 was used for all statistical tests. The data was rechecked with SPSS v 16.0.0 for the repeat submission after the MD thesis examination interview (viva).
All power calculations were done by statisticians based at Nestec, Luassane. Statistcal analyses were carried out by me as guided by Dr Corrine Hager (statistician in Nestec) and Dr Richard Morris, Reader in Medical Statistics and Epidemiology, based at University College of London.
Databases were maintained in Microsoft® Excel 2000 and 2003 and SPSS v 11.0.0 and 16.0.0. All statistical analyses were performed in SPSS v 11.0.0, Standard Version. Normally distributed continuous data has been described using mean and standard deviation whereas non-normally distributed continuous data as median (range or interquartile range-IQR). All categorical results are a number (%). 't test' and 'ANOVA' were used to assess parametric data; 'Kruskall Wallis' and 'Wilcoxon Rank' test to analyse non parametric data. The relapse time was graphically demonstrated using Kaplan Meier Survival Curves. Regression analysis was used to assess factors predicting relapse.
Significance was defined as $p < 0.05$.

3.5 Funding, study site/dates and ethics

3.5.1 Funding sources

The phase B (as phase A) was funded by Nestle, Switzerland. However, no further moneys were provided to continue the study, once phase A (n=42) was completed through to phase B (see details in the results section – subsection 3.6). Continuation of the trial with expansion of phase B involving multicentre recruitment depended upon approval of further moneys by Nestle, Switzerland.

3.5.2 Dates and site of the study

The study for Phase B was conducted between, March 2000 to September 2002.
The study was carried out at Royal Free and Chelsea Westminster Hospitals, London. I managed all appointments at the two centres and conducted these studies in person.

3.5.3 Data collection

Data was collected in CRFs (case report forms provided by Nestle). The data was cross checked by the supervisor, in relation to clinical notes and laboratory results on the computer systems. Carbon copies of these records were retrived after cross checking. I retained the original CRFs in the hospital and transferred information to patient secured database to Excel and SPSS for analyses.

3.5.4 Ethics

Patient information sheet and patient consent forms given in appendix A and B, were devised using previously described guidelines used in the hospital. These along with the complete study protocol, were reviewed and approved by the ethical committee. The phase A and B studies were approved by the local research ethics and research committees (LREC) of the Royal Free and Chelsea and Westminster hospitals.

3.6 Results (see figure 3.6.2)

3.6.1 Phase A

See chapter 2 for details. In summary at completion of 8 weeks of enteral nutrition treatment, 33/42 children were in remission (78.6%)

3.6.2 Food re-introduction

Food re-introduction has been discussed in section 2.7.5 in detail. To re-summarize, all 33 children in remission at completion of phase A entered the food re-introduction phase. 8 children dropped out of the study during this phase. In the drop-out group, 5 children had ileocolonic, 2 ileal and 1 colonic Crohn's disease.

3.6.3 Phase B (Randomised controlled study of supplemental enteral nutrition)

3.6.3.1 Demographics

25 children proceeded on to be recruited in phase B of the study (randomized controlled supplemental study). Unfortunately, this RCT came to a premature end due to withdrawal of funding and failed to progress into a multi-centre trial. 34.7% of the study power was achieved (25/72). Of the total 25 children recruited in phase B, 2 had ileal disease, 20 ileocolonic and 3 colonic disease. 15/25 (60%) were males.

3.6.3.2 Comparison of the supplemented with unsupplemented group

The process of randomization has been previously described in the statistics section. There were 12 children in the supplemented and 13 in the unsupplemented group with no baseline differences between the two groups (age, Wt SDS, CRP, ESR, albumin, puberty, disease phenotype, sex and PCDAI). See table 3.6.1.
The supplemented group received 30% of their recommended daily allowance as a daily supplement of enteral feed.

3.6.3.3 Phase B results

At 6 months into phase B, 12 had relapsed which accounts for 48% of the group. 6 of them received supplemental nutrition and the other 6 were non-supplemented. One girl had a right hemicolectomy for stenosing ileal disease. A further 6 relapsed by one year (remaining 7); and at completion of the 2 year study 6/25 (24%) were in remission. 4 of these children were originally randomized to be supplemented and 2 non-supplemented. One teenage girl admitted patchy compliance with the supplement as she was

self conscious of her image and was keen to remain slim. 2 of them had colonic inflammation and 4 ileocolonic disease.

There was no significant difference in the remission period between the supplemented and non-supplemented groups (Supplemented (median 0.5 yrs, IQR 0.27–2 yrs) vs. non-supplemented (median 0.67 years, IQR 0.17-0.92 yrs) p = ns, MWU test (p=0.650). See figure and table 3.6.1.

A six centre meeting was held one year after commencement of Phase B at the two UK centres. Although plans were made for continuation of the study, funding was withdrawn by the company at the last moment which resulted in collapse of the randomised controlled trial. The 6 centre recruitment failed and I continued to monitor the original recruitees through to completion of their phase B.
The local research and ethics committee were informed re: collapse of trial. The subjects were informed verbally but not in writing.

3.6.4 Differences in food intake between the supplemented and non-supplemented groups

10 children (5 supplemented and 5 non-supplemented) completed a three day food diary under supervision of the dieticians; the information was processed using software, Caveat v 5. This assessment took place at month 2 into phase B (see flow chart – table 3.3.1). 15 children failed to complete the food intake diary. 7/15 relapsed during the 2-3 month period and dropped out of the study. A total of 8 children/families (4 from the supplemented arm and the other 4 from the non-supplemented arm) failed to hand in the forms despite several reminders.
No difference was found in the calorific (total calories/kg), macro (carbohydrates, protein and fats) and micro-nutrient (calcium, iron, zinc,

phosphate, selenium, folate, thiamine, riboflavin, vitamin B6 and nicotinic acid) intake of the two groups (WR, p=ns).

3.6.5 Predictors of relapse

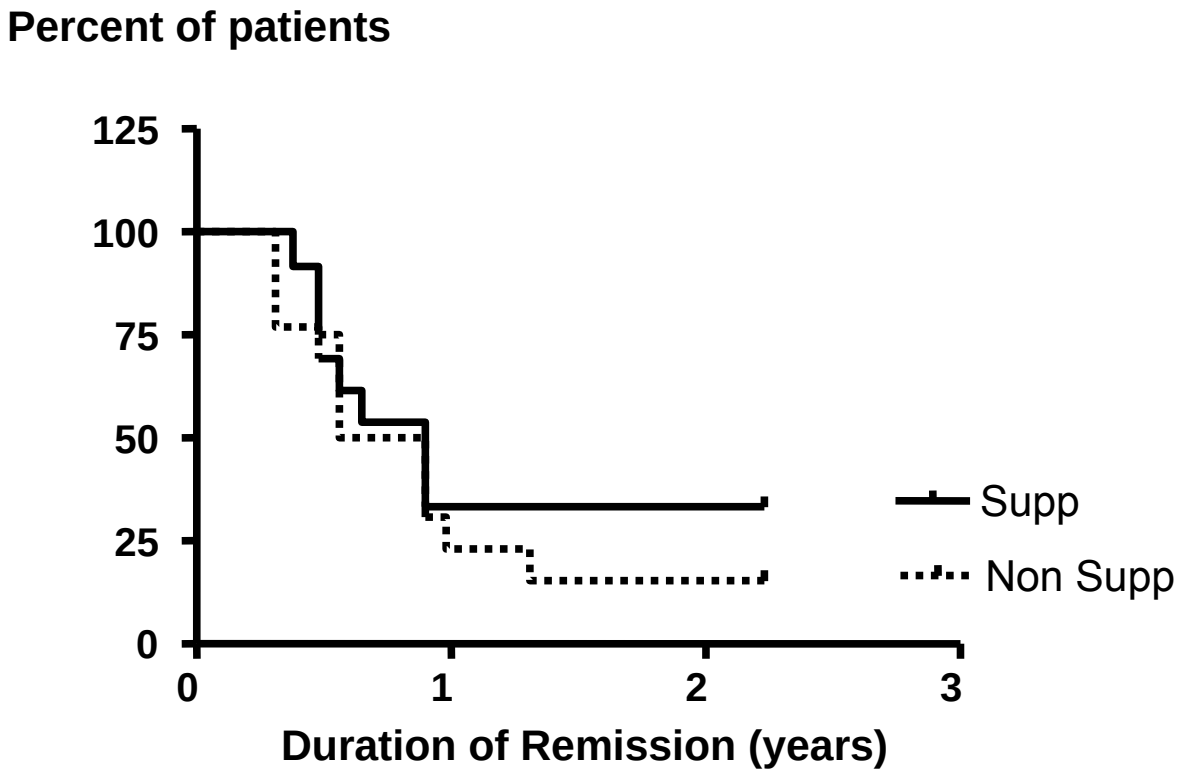
On univariate regaression analysis of children in phase B high PCDAI at first presentation was found to be predictive of early relapse (r = 0.416, p = 0.039). However no variables were found to be significant on multivariate regression analysis (p=ns). The other plotted factors alongside PCDAI were supplement status, age at presentation, sex, disease phenotype, weight SDS, PCDAI, Albumin, ESR and CRP at presentation.
Interestingly, only one child relapsed between year 1 (n=7 in remission) and year 2 (n=6 in remission).

3.6.6 Adverse events

No adverse events were reported in this RCT.

Figure 3.6.1 Kaplain Meier Survival curve reflecting maintenance of remission in the supplemented and non supplemented sub-groups, for the full duration of the study (2.23 years).

There was no difference in duration of remission achieved in between the two groups (Mann Whitney U test, p=ns)



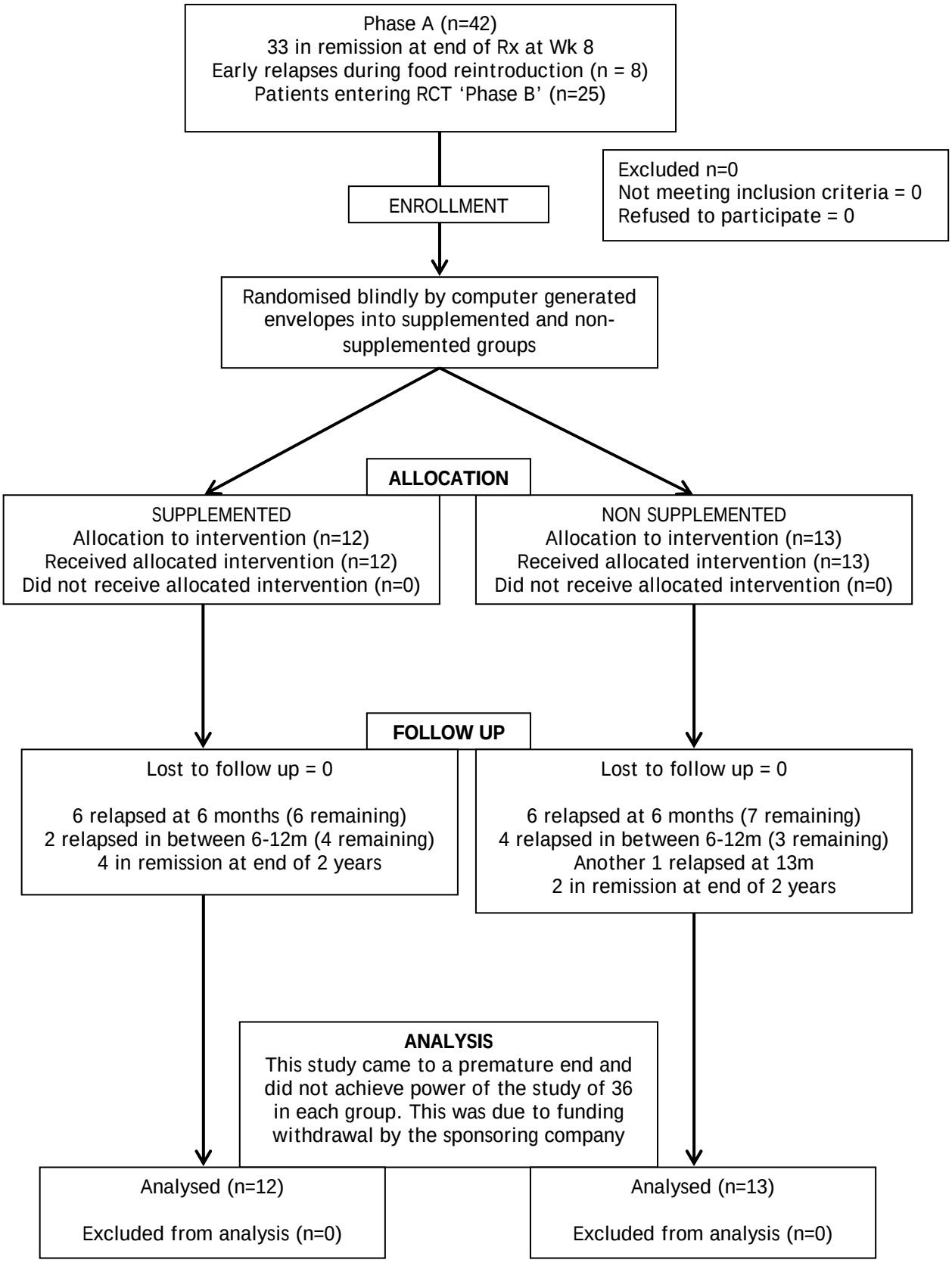


Figure 3.6.2 Flowchart for the randomised controlled study of supplemental enteral nutrition (Phase B)

	Supplemented	Non-supplemented	Test	p
Demographics				
n	12	13		
Sex (males)	7	8	MWU	0.894
PCDAI	5 (0-7.5)	10 (1.25-10)	MWU	0.207
WAZ	-0.48 (-1.4-0.36)	-0.89 (-1.5–0.26)	MWU	0.611
Albumin	42 (38-44)	41 (34-45)	MWU	0.797
ESR	12.5 (7.3-19.3)	12.5 (6.5-34)	MWU	0.912
CRP	4 (2-9)	7 (1-21)	MWU	0.365
Outcome				
Remission at 2 years (n)	4	2	$\chi 2$	0.294
Median time to relapse from enrolm. (IQR)	0.5 years (0.27-2)	0.67 years (0.17-0.92)	MWU	0.650

Table 3.6.1 A comparison of supplemented and non-supplemented groups

3.7 Discussion

Supplemental enteral nutrition is an attractive option as it is without side effects and is believed to maintain remission and promote growth an important issue in paediatric IBD management. Belli has demonstrated significant height and weight gain in a small prospective study of 8 children with growth failure. The elemental feed was administered for one month out of four via continuous nasogastric infusion at home [320]. Aiges used a year long nocturnal supplemental nutrition via nasogastric tube, and demonstrated significant growth (weight and height) in 8 children who were feeding less than normal daily intake [321]. Israel reported growth spurt in a group of 16 children receiving enteral nutrition via gastrostomy [378]. Cautious interpretation is needed, as these methods administer

much more than 1/3rd or 1/4th of total daily requirement, as aimed or described in this study.

In this limited RCT, no difference has been demonstrated in the remission rates of the two groups (with or without supplementation). Previously, Wilschanski retrospectively reported a 43% relapse rate within 6 months of presentation after first treatment with exclusive enteral nutrition [26]. 60% of them had relapsed by completion of 1 year. In this study 32 children were in remission at end of Phase A. At end of food reintroduction 7 had early relapse and a further 12 in the first 6 months. This accounts for about 60% of the children relapsing within 6 months and more than 80% by year one; these results are not comparable to Wilschanski's study. This may be due to biased randomisation in Wilchanski's report, always a pitfall in retrospective studies.

On the contrary, Hirakawa has reported a better remission prognosis in adults when treated with 30 Kcal/kg IBW/day of enteral feed at home [379]. They achieved a remission rate of 94%, 63% and 63% after 1, 2 and 4 years. This was significantly higher than adults not receiving any maintenance treatment who had a remission of 50%, 33% and 0%. There is however a major reservations about this study. From all practical purposes daily use of 30 Kcal/kg is extremely hard. This regimen of nutrition usage continuously over 1-4 years is impractical and cumbersome; difficult for children to follow. In another study, Teahon reported a retrospective study on a cohort of 113 adult patients (mean=32 years (1SD=15)) treated with elemental diet. 85% of the patients (n=96) achieved remission after 4 weeks (average figure, range 2-12 weeks) of acute treatment with an elemental feed, Vivonex®. 22% patients relapsed within 6 months of treatment with an annual relapse rate of 8-10%. Patients with disease complicated by fistula or perianal involvement had early relapse, approaching 100% for the latter [380]. There is however,

considerable patient selection bias using enteral nutrition in this study. Most recently, in 2007 Akobeng has reported a Cochrane review of role of supplemental enteral nutrition for maintaing remission [322]. The review includes two adult trials using enteral nutrition as a supplement positively supporting its role in maintaining remission. In one study [319], patients who received half of their total daily calorie requirements as elemental diet and the remaining half by normal diet had a significantly lower relapse rate compared to patients who received unrestricted normal diet (9 of 26 versus 16 of 25; OR 0.3, 95% CI 0.09 to 0.94). In the other study [318], elemental and polymeric feeds (providing between 35 and 50% of patients' pretrial calorie intake in addition to unrestricted normal food) were equally effective for maintenance of remission and allowing withdrawal of steroid therapy (8 of 19 versus 6 of 14; OR 0.97, 95% CI 0.24 to 3.92).

A review of the long term follow up reveals interesting information. Children doing well at the end of 1st year of diagnosis, regardless of receiving/not receiving supplemental nutrition; seem to do well by 2 years as well. In this study 7/42 (16.7%) were in remission by end of year 1 and only 1 relapsed between years 1 and 2; 6/42 children (14.3%) in remission at end of second year. Early relapse is predicted by high PCDAI at first presentation. Children with mild disease (defined by PCDAI) seem to fare better.

The mechanism, by which supplemental enteral nutrition may work, if it were to work, is unclear. Johnson [296] has recently reported a prospective randomized controlled trial of using partial enteral nutrition (enteral nutrition + diet) compared to sole enteral nutrition in children with active acute Crohn's disease. Although by principle this study is different from the idea of using supplemental enteral nutrition, some features of it are certainly relevant to the discussion here. First the response to enteral feeds is much worse than

previously reported literature. Based on intention to treat analysis, remission (PCDAI <10) was achieved in only 15% (4/26) of the partial enteral nutrition group compared with 42% (10/24) of the total enteral nutrition group (p = 0.035). Withdrawal from the allocated treatment before completion of the intended six week period was necessary in 10/26 (39%) in the partial enteral nutrition group and 8/24 (33%) in the total nutrition group. Importantly, there is no mention of compliance in this study. Poor compliance always results in failure of enteral nutrition; a common problem encountered in its usage in the adult population (chapter 1.6). Despite these faults partial enteral nutrition does not seem to work as well as total enteral nutrition, to achieve remission in children with active Crohn's disease. Applying the same argument to supplemental nutrition, if a child on supplemental enteral nutrition were to have a relapse, it perhaps will fail to treat it.

In view of the currently available data, there seems to be little evidence to support a case in favour of supplemental enteral nutrition being an effective treatment; a larger study may be needed to answer the question. In light of availability of a wide range of immunosuppressants and monoclonal antibodies, some would recommend use of 6MP or azathioprine early at disease onset. Markowitz has demonstrated a lower remission rate at 18 month follow up using 6MP as maintenance treatment when compared to placebo in a multicentre placebo controlled prospective study of 55 children [232]. It is however, hard to justify a blanket use of immunosuppressants particularly in children who may not need it. In view that severe disease (high PCDAI) at presentation predicts early relapse, it may be that immunosuppressants should be considered in this group of children. The "step-up *vs* top-down" study, by D'Haens and colleagues [381] suggests that introducing the

most efficacious IBD drugs early in disease course has a significant impact on outcome in adults with Crohn's disease. This randomized study compared the conventional therapeutic approach ("step-up") with a newer, more aggressive strategy ("top-down"). In the "step-up group" patients were treated first with steroids and, in case of steroid dependency or resistance, immunosuppressants and infliximab were used. In the "top-down group" patients received upfront a combined treatment of immunossupressants and infliximab. This study demonstrate the superiority of the "top-down" over the "step-up" approach, as demonstrated by a significantly higher proportion of patients in remission and showing MH in the "top-down", as compared to the "step-up" group. Markowitz [232] reported in children on 6-MP group (compared to immunosuppressive maintenance treatment), the duration of steroid use on first relapse was shorter (observed-to-expected ratio of days with prednisone of 0.73 ***versus*** 1.34 in the control group, $P < 0.001$). Kugathasan [215] has suggested early use of Infliximab in children with Crohn's disease. Further studies are needed regarding these options. Such decisions are not easy as one always has to weigh the side effects of these treatments. Please see discussion on side effects of monoclonal anitbodes such as T cell lymphoma in section 1.5.1.4. This RCT came to a premature end due to withdrawal of funding and failure to progress into a six centre multi-centre trial. The total recruited number for the study is under-powered (34.7% recruitment). The study was originally funded for a period of two years, with a verbal promise of extending it to a 6 centre study in future; the money accounted for payment was for the project, a research fellow (myself selected in an interview, following advertisement of the post in the BMJ) and the overhead university fees (100%). Research contract income (overhead university fees) is important in all drug company funded trials [382]. If a university

researcher seeks financial support for research from industry (for example a pharmaceutical company), the university requires that the industry source pays them an additional overhead charge, which ranges from 50 to 150% of the research support. Income from industry is classed as research contract income, and universities are penalised if they fail fully to recover research contract overhead money.

The two year project involved a phase A of the study which was use of ACD004 a new enteral feed, the recruitment to continue with launching of phase B as each child finished phase A. This was to develop into a multicentre study after two years with recruitment by centres in Europe. As the payment for the two years had been made, the ethics committee accepted this proposal. In hindsight it was an error and a full contract down to the last detail and penny should have been negotiated and agreed before commencement of study. The initial agreement also involved recruitment of a research fellow for a period of two years. Though it was agreed that a further research fellow will be recruited, if necessary, this never happened.

Research sponsored by pharmaceutical companies may be fraught with problems. People may have differing agendas and the control group selection may be poor. Moreover, there is little doubt that long term studies are difficult to conduct and maintain. It needs continued motivation of the investor and the investee. Personnel in either group may change after a year or two; the new personnel may not be as interested in the project. In the study described in this thesis, Professor John Walker-Smith retired after a year of starting the project. He was the principal investigator in this project and had negotiated the original funding. In addition it is also likely to be related to the company's disappointment in finding the results comparable to Modulen IBD ®, the already used feed. ACD004 did

not prove to be vastly superior (comparing remission percents/numbers) feed. In addition, there were problems in manufacture and supply of the product closer to the end of the study. I suspect the company did not wish to invest further in this and pulled out at the earliest opportunity.

There are several lessons to be learnt from this study. Randomized controlled trials should not be over-ambitious, be realistic, involve a strict legal contract and binding for both the investor and the investee encompassed in a well defined time frame. Any deviation should be penalised. The current research governance practice has changed and it would have strengthened this study if input had been made at the start. Recently the Department of Health (England) has commissioned a research network on medicines for children. This is based at University of Liverpool in partnership with Alder Hey children's hospital. The collaborators include Imperial College, London, the Liverpool Women's Hospital, the National Perinatal Epidemiology Unit at the University of Oxford and the National Children's Bureau. The aims of this network are to facilitate the conduct of randomized controlled trials and other well designed studies of medicines for children including those for prevention, diagnosis and treatment. This should enable to maintain uniform quality in paediatric medical trials and particularly foresee and prevent mishaps like these. The ACD004 study was well designed and uniform quality not being an issue in this case, but may be drug companies would be perhaps less likely to pull out of studies, as they will have a strict binding and the worry of developing bad publicity when a central organisation is involved. Another advantage is that these organisations can contribution towards the trial costs as well. In summary, this was the first ever randomized controlled on use of supplemental enteral nutrition in paediatric Crohn's disease and

despite its early end, it illustrates some important management points. Children with mild disease sustain a longer remission; this has not been shown before. Children well (in remission) at the end of the first year are likely to continue doing so at end of second year. Further studies are required to assess benefits of treating the severe disease group early with immunosuppressants such as azathioprine. Though limited recruitment, this prospective study fails to duplicate the results of Wilschanski's biased retrospective study. Also, contrary to common belief, enteral feed supplementation does not increase the calorific intake, macro or micro nutrient intake of the child.

Chapter 4. Prospective assessment of quality of life (QOL) in children with Crohn's disease after treatment with exclusive enteral nutrition

4.1 Introduction

Over the last decade, increasing emphasis has been placed on formal documentation of improvement in quality of life during and after any medical intervention. Quality of life is a complex term referred to as 'the perception of life with respect to physical, social and psychological functioning' [350] (chapter 1.7). Crohn's disease is characterised by gastrointestinal symptoms, malnutrition & anorexia, growth and pubertal delay, and the adverse effects of treatments such as corticosteroids and surgery. These factors result in low mood and stress, which in turn affects physical, social and psychological functioning ultimately resulting in a poor quality of life [383-385] (chapter 1.4 & 1.7).

IMPACT II is a recently validated questionnaire used in assessment of quality of life in children with Crohn's disease; discussed in chapter 1.7 [25,350]. Cross sectional studies show association of active Crohn's disease with a poor quality of life [19]. However it remains undocumented and unproven whether an individual's successful treatment with exclusive enteral nutrition will result in an improved quality of life. Despite the often excellent compliance as demonstrated in chapter 2 (subsection - 2.7.4.1) [24,305], enteral nutrition is historically considered difficult to administer and use; thought by many to adversely effect quality of life in children. We undertook this prospective study to document changes in quality of life for children with active Crohn's disease, and assess if they were associated with mucosal healing after treatment with exclusive enteral nutrition.

4.2 Aims

This study addresses the secondary aim of the phase A and B studies, which is to assess quality of life in children using ACD004.

4.3 Methods

4.3.1 Description and use of IMPACT II questionnaire

I consecutively enrolled children (age 8-17 years) over a period of 2 years. Children recruited in this study are a selection from the cohort described in chapter 2 (Table 4.7.1.1 shows all the children in the ACD004 study with the last column, highlighting the cases able to participate in this study. Selection was made on ability of the children to self-complete the IMPACT II, quality of life questionnaire without any parental assistance. This was to avoid advertant/inadvertant parental transference and bias introduced by their help.

At enrolment, children completed the IMPACT II questionnaire following standard instructions [25,350]. Details of the quality of life instruments with history and evolution of IMPACT II questionnaires is detailed in sub-chapter 1.7. To recap, the IMPACT questionnaire, originally devised and validated in Canada was modified for use in the UK. It consists of 35 questions answered using a 7 cm visual analogue scale. These questions are organised into six domains: IBD symptoms, systemic symptoms, emotional functioning, social functioning, body image and feelings towards treatments and interventions. The total score can be converted linearly to range from 0-100, with higher scores representing a better quality of life. The questionnaire takes 5-10 minutes to complete. In this study all

questions were completed in the outpatient department by children without help from either parents or the investigator. Children unable to understand the questions or scoring system were excluded from the study.
The IMPACT II questionnaire was used for assessment of quality of life in this thesis. Details of the questionnaire have been discussed in sub-chapter 1.7.8. The quality of life concepts and background are detailed in chapter 1.7.

In the prospective quality of life study in this thesis, the questionnaire was filled in by the children, in the presence of the same investigator (Dr N Afzal). This was to ensure that the patients' feelings were represented accurately. If the child could not understand a question, they were encouraged to ask the interpretation from myself but not their parents. This was because at the start of study, when younger children asked their parents for assistance, transference of parents' feelings and answers was obvious resulting in a biased answer.
Children unable to understand the questionnaire or the scoring system at all, despite repeated explanations, were excluded to avoid bias (from the person explaining the questions) in the study.
At completion of phase A as children progressed through the food reintroduction phase into phase B they continued to have their quality of life assessment (See flow chart for investigations and quality of life – figure 2.4.1.2). Exclusion from the study also marked the end of 'quality of life assessment' part of the study.

4.3.2 Clinical and mucosal disease scoring

As already described in chapter 4, ACD004 was used for a period of 8 weeks. Endoscopic investigations, quality of life assessment and

PCDAI scoring at recruitment were repeated at week 8. Remission was defined as a fall in PCDAI to less than 20. The inclusion and exclusion criteria for this study are the same as stated in table 2.4.1.2 with addition of another essential criterion, regarding children ability to fill the form themselves. As mentioned, those unable to self complete the IMPACT II questionnaire, were excluded from this particular study.

The terminal ileum and each segment of the colon received an endoscopic and histologic score ranging from 0-3 as previously described [355] – see Table 2.4.4.1 and sections 2.4.3 and 2.4.4 for detailed description. The discussion for using the system is detailed in section 2.8. The biopsies were scored in a blinded fashion by a histopathologist familiar with paediatric gastrointestinal diseases. The worst endoscopic and histological score from each ileocolonoscopy was then recorded and used to calculate means for comparison of pre- and post-treatment values.

4.5 Statistics

4.5.1 Description of statistics analyses

Statistical software, SPSS v 11.01 was used for all statistical tests. The data was rechecked with SPSS v 16.0.0 for the repeat submission after the MD thesis examination interview (viva).

The quality of life scores (inclusive of individual domains scores) were calculated by Dr. Hester Loonen, who designed the original IMPACT II. Further statistical analyses were carried out by as guided by Dr Loonen and Dr Richard Morris, Reader in Medical Statistics and Epidemiology, based at University College of London.

Databases were maintained in Microsoft® Excel 2000 and 2003 and SPSS v 11.0.0 and 16.0.0. All statistical analyses were performed in SPSS v 11.0.0, Standard Version. Normally distributed continuous data has been described using mean and standard deviation whereas non-normally distributed continuous data as median (range or interquartile range-IQR). All categorical results are a number (%). 't test' and 'ANOVA' were used to assess parametric data; 'Kruskall Wallis' and 'Wilcoxon Rank' test to analyse non parametric data. Median and interquartile ranges were used for non-parametric data.
Significance was defined as $p < 0.05$.

4.6 Funding, study site/dates and ethics

4.6.1 Funding sources, data collection, ethics and dates/site of study

The funding sources, data collection/recording and ethics have been described in chapters 2 and 3. The dates are the same as for phase A and B of the study (March 2000 to September 2002).

4.7 Results

4.7.1 Demographics

42 children were recruited in the pilot study (described in chapter 2). Of the 42, 26 children were recruited in the QOL part of the study (62% recruitment from the pilot study cohort). The analyses in this study are based on results from these 26 children and therefore disease assessment figures (for disease remission and deomgraphics) given here differ from those in chapter 2 (where analyses is based on 42 children).

Regarding details of the 16 dropouts, 2/16 children did not wish to take part in the QOL study. 3/16 children in the excluded group, although able to complete the IMPACT questionnaire, had additional treatment due to worsening of disease and were therefore excluded. The remainder 11 were unable to complete the IMPACT questionnaire on their own, with median age being significantly lower for those who couldn't complete it (median = 10.6 years) when compared to the recruited group (median 14.02 years)($p < 0.01$).

See table 4.6.1.1 for demographic details of subjects from the main study included in the quality of life study (tickbox in column 5).

16 males (67%) and 10 females were recruited in this study. Eight children (30.8%) were pre-pubertal, 5 (19.2%) in early puberty (Tanner stage 2-3) and 13 (50%) in late puberty (Tanner stage 4-5). The majority of children had ileocolonic disease (n=20) and of the remaining, 2 had only ileal, and 4 only colonic involvement. 21/26 (81%) children had moderate to severe disease (PCDAI > 30).

Serial	DOB	Sex	Decimal age at presentation (yrs)	QOL study enrolment
SJ 01	3/7/89	m	10.866	
BK 02	26/9/86	f	13.644	☑
MB 03	7/9/84	m	15.707	
LR 04	25/7/90	m	9.901	☑
SM 05	17/10/86	m	13.879	☑
CO 06	10/9/84	m	15.819	☑
CO 07	17/12/85	m	14.660	☑
PB 08	10/12/84	m	15.693	☑
DT 09	1/9/86	f	13.986	☑
AW 10	2/9/89	m	10.986	☑
CM 11	22/9/86	m	13.934	☑
AW 12	18/12/91	m	8.764	
SH 13	19/8/85	m	15.115	☑
KC 14	11/3/86	f	14.597	☑
LH 15	5/3/87	m	13.647	☑
VS 16	9/3/92	f	8.655	
WS 17	26/12/90	m	9.890	
GD 18	29/4/90	f	10.592	
KH 19	28/1/85	f	15.890	
VR 20	31/1/87	f	13.934	
AE 21	23/10/90	m	10.211	
GK 22	2/2/88	m	12.948	☑
PD 23	25/8/87	m	13.403	☑
LS 24	28/1/85	f	15.997	☑
AH 25	9/1/87	m	14.066	☑
SO 26	4/7/88	m	12.581	
SN 27	22/3/91	f	9.871	
GL 28	23/12/86	f	14.173	☑
JR 29	24/8/88	m	12.510	☑
EE 30	24/1/89	m	12.110	
JW 31	10/1/89	f	12.178	☑
DC 32	26/2/88	m	13.060	☑
OS 33	7/12/85	m	15.359	☑
MY 34	23/2/87	m	14.290	
SW 35	16/12/89	m	11.482	☑
LH 36	2/4/86	f	15.225	☑
RK 37	29/6/85	f	16.005	☑
BH 38	5/1/86	m	15.518	☑
BB 39	14/6/89	f	12.077	
PG 40	5/10/84	m	16.805	☑
AE 41	22/02/90	m	11.970	
FS 42	18/12/87	m	14.112	

Table 4.7.1.1 Children were recruited in the quality of life study (marked ☑ in last column) on the basis of their ability to independently fill and complete the QOL questionnaires. The children recruited in this study were significantly older (p=0.008) with

a median age = 14.02 years (IQR – 13.02 – 15.4 yrs) compared to those excluded from the study (n = 16) – median age 12.07 years (IQR – 10.04 – 14.01). In the excluded sub-group, the median age of children who were excluded as they did not understand the QOL questionnaire (11/16) was significantly younger at 10.6 years.

4.7.2 QOL in phase A during response to exclusive enteral nutrition

All children received exclusive enteral nutrition for eight weeks. The feeds were well tolerated orally, with only 3 children needing overnight nasogastric feeds to meet their daily requirements. These children were taught to themselves pass the nasogastric tube, check its placement and administer feeds (with parental help) overnight via a pump [304].

Of the total children who could complete the questionnaire enrolled in this study, 23/26 children (88.5%) achieved clinical remission (PCDAI < 20) after 8 weeks of treatment with exclusive enteral nutrition. Of the non-responders in the study, 1 had colonic, 1 ileocolonic, and one severe ileocaecal disease. Additional 3 patients who could also complete the questionnaire but dropped out of the study due to worsening of disease and commencement of additional treatment; 2 had ileocolonic and one ileal involvement.

There was a significant fall in the PCDAI scores (Median = 35, IQR 25 – 40.6) at completion of treatment ($p<0.01$). See table 4.7.2.1.

Table 4.7.2.1 Comparative scores before and after treatment with enteral nutrition

A. Clinical parameters (Wt, PCDAI, CRP, ESR, Albumin)

Parameter	Pre Treatment	Post Treatment	Test	P
PCDAI	43.8(31.9-50.6)	7.5(0-10)	WR	<0.0001
WAZ	-1.3(-2 - -0.2)	-0.98(-1.6 –0.21)	WR	<0.0001
Albumin	32 (29-37.3)	41(37.3 - 43)	WR	<0.0001
ESR	35 (14-61)	8 (2.5 – 19.8)	WR	<0.0001
CRP	27(15.5 - 56)	1(0-8.3)	WR	<0.0001

WAZ = weight for age Z scores

B. the 6 individual domains comprising the IMPACT QOL questionnaire

	Pre treatment	Post treatment	p (WR)
IBD symptoms	0.49 (0.37 – 0.74)	0.79 (0.55 – 0.85)	< 0.01
Systemic symptoms	0.29 (0.13 – 0.49)	0.90 (0.63 – 0.98)	< 0.01
Emotional functioning	0.47 (0.35 – 0.68)	0.79 (0.53 – 0.87)	< 0.01
Social functioning	0.65 (0.53 – 0.84)	0.87 (0.74 – 0.92)	< 0.01
Body image	0.52 (0.30 – 0.84)	0.74 (0.58 – 0.91)	< 0.01
Treatment/ interventions	0.53 (0.22 – 0.74)	0.66 (0.41 – 0.87)	0.04
Total QOL scores	0.58 (0.44 – 0.72)	0.81 (0.61 – 0.84)	< 0.01

Numericals in the table represent median quality of life scores (The figures in brackets represent IQR – interquartile range). Higher QOL scores represent better quality of life.

WR = Wilcoxon Rank

Figure 4.7.2.1 Relationship of QOL (IMPACT II) with the PCDAI scores (x axis). There is a significant negative correlation between the two variables. (r=-0.67, p<0.05)

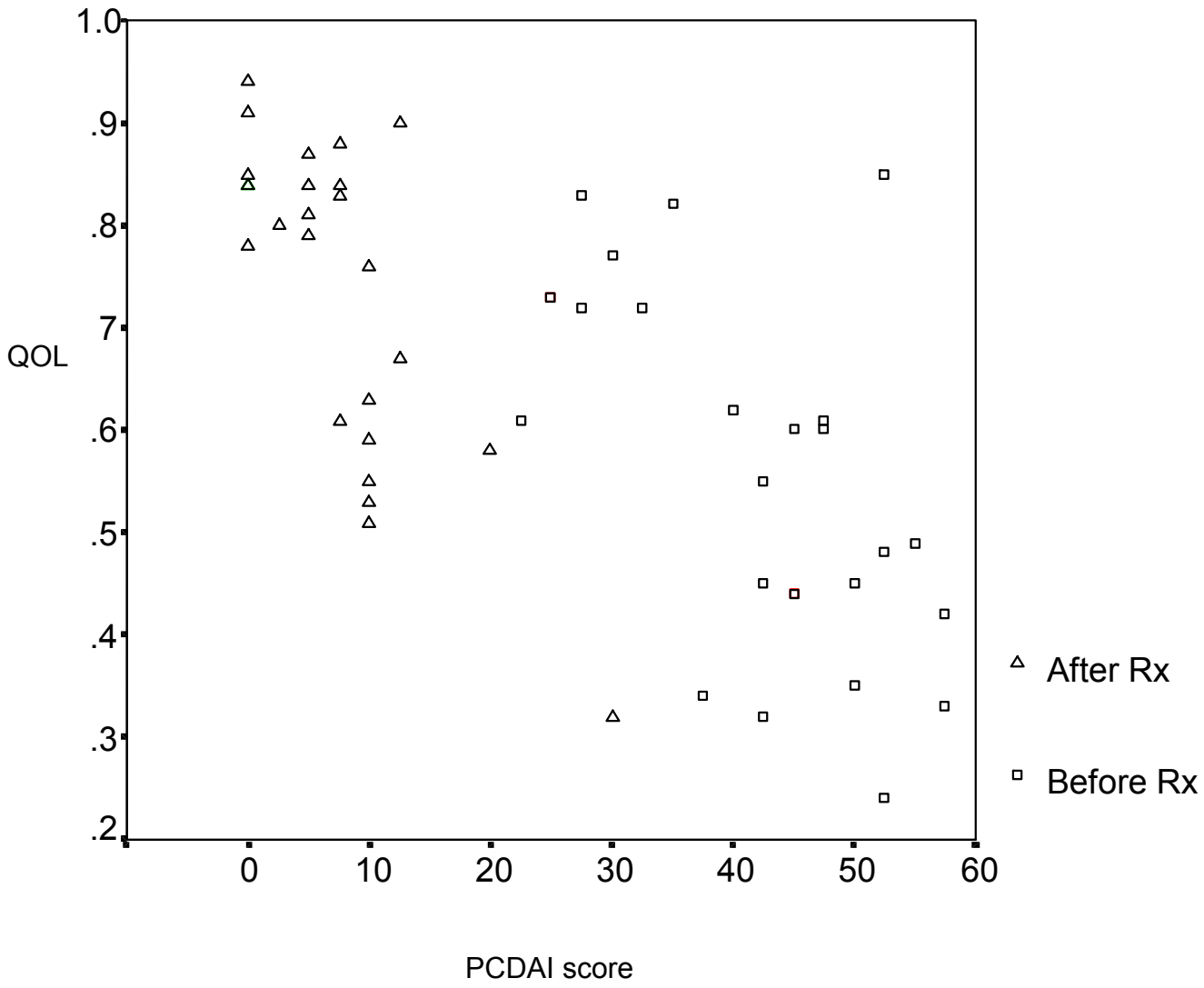
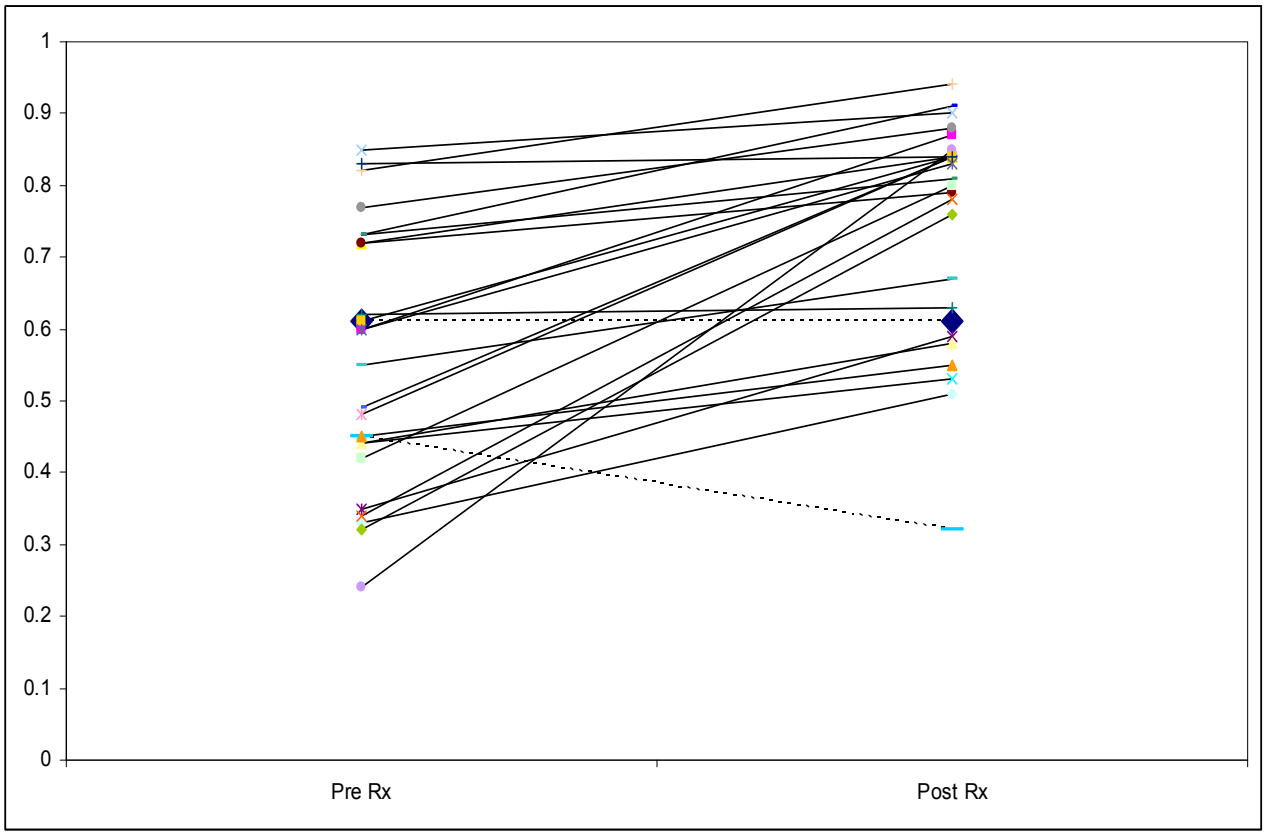


Figure 4.7.2.2. Change in total quality of life scores in each individual case before and after treatment with enteral nutrition. The two dotted lines represent two children one with the same quality of life score at completion of treatment and another showing considerable deterioriation in the QOL scores (see text section 4.7.3 for further details). Higher values represent better quality of life



4.7.3 Quality of life after 8 weeks of treatment

There was an overall improvement in QOL scores of children with Crohn's disease following treatment with exclusive enteral nutrition. Assessment of each of the six individual domains showed a significant improvement in all categories, including the domain "feelings towards treatments and interventions" (p=0.04). (See table 4.7.2.1)

One out of 26 showed deterioration in QOL. This child had isolated colonic disease and failed to achieve remission, eventually requiring bowel resection. Another child showed no change in QOL scores

before and after treatment, despite achieving a clinical and histological remission. Interestingly this patient underwent a small bowel resection 3 months later due to an ileal stricture. On the contrary, two children who failed to achieve a clinical remission, nonetheless showed an improvement in their quality of life after treatment.

4.7.4 Quality of life in children requiring nasogastric feeding

3/26 children (two girls and one boy) required nasogastric feeding to help them complete their 8 week course of enteral nutrition. Although the overall quality of life scores improved in all three of them, the individual domain scores for 'feelings towards treatments and interventions' deteriorated.

4.7.5 Mucosal healing

Endoscopic assessment of the terminal ileum (in 21/26 patients) and each colonic segment was carried out prospectively. Scoring was as previously reported, with the worst affected segment from each procedure being used for analysis, where 0=normal and 3=severe ulceration (see chapter 2, table 2.4.4.1 for scores and details in sections 2.4.3, 2.4.4 and 2.8). The median endoscopic score at diagnosis was 2 (IQR 2-3), and after treatment was 1 (IQR 0-1) ($p<0.01$).

Similar to macroscopic healing, there was a significant improvement in the mean histology scores before and after treatment with enteral nutrition (pretreatment: 2 (IQR 1-3), posttreatment: 1 (IQR 1-1) ($p < 0.01$). None of the 23 paired samples showed a histological deterioration after treatment. Six children showed no improvement

in histology, whilst the remaining 17 children had an improved score on blinded analysis.

I performed regression analysis to determine if changes in QOL scores predicted degree of change in mucosal histology scores. Items (questions in the questionnaires) assessed in both the PCDAI and the IMPACT II questionnaire overlap and this is demonstrated by their close correlation (r=-0.67) before and after treatment (Figure 4.3.1). Regression analysis failed to demonstrate a significant correlation between the change in IMPACT II score and histology scores (p=0.113). In addition there was no correlation between endoscopic improvement and change in either IMPACT II scores. Furthermore, none of the other predictors identified a priori as perhaps influencing mucosal healing were found to be statistically significant (data not shown). These included age at diagnosis, weight gain during treatment and change in ESR, CRP and albumin.

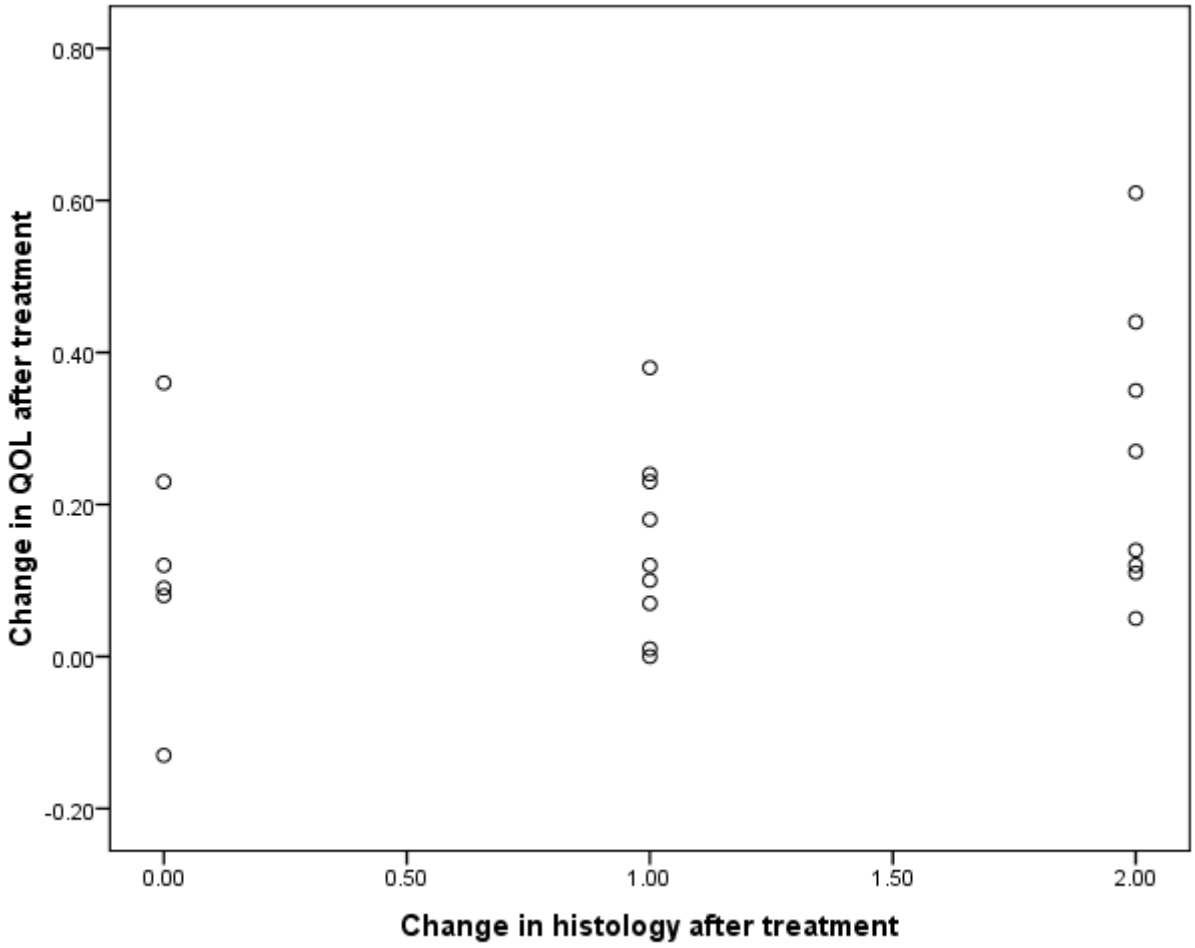


Figure 4.7.5 There is no correlation between change in quality of life and histology scores after treatment with enteral nutrition (r = 0.071, p = 0.113)

4.7.6 Quality of life assessment at completion of Phase A and commencement of phase B, during the 4-5 weeks food reintroduction stage

The food reintroduction took place over 4 weeks – see sections 2.8.5 and 3.6.2 for a detailed description. During this period, children underwent a gradual food reintroduction programme. At end of phase 'A' all children were on a complete enteral nutrition diet.
Of the total 26 children participating in the phase A QOL study, 9/26 children from end of Phase A dropped out. 6 of the children completing questionnaires relapsed before reaching Phase B and therefore had dropped from the study (see exclusion criteria – table 2.4.1.2). It was not possible to complete the questionnaire in the remaining 3, due to the strict rules of the author's presence during completion of these questionnaires. These children dropped out of the quality of life study and did not participate any further in this part of the study. QOL life questionnaire was completed by 17 children at commencement of Phase B post food reintroduction phase.

Although there was no change in the total quality of life scores at commencement of phase B, during the food reintroduction stage, significant improvement was seen in the social functioning domain and IBD symptoms. There was an insignificant change in the scores of the other domains.

	End of Phase A	Start of Phase B	p (WR)
IBD symptoms	0.79 (0.55 – 0.85)	0.93 (0.81-0.96)	**0.002**
Systemic symptoms	0.90 (0.63 – 0.98)	0.96 (0.87 - 0.98)	0.06
Emotional functioning	0.79 (0.53 – 0.87)	0.85 (0.73 – 0.97)	0.06
Social functioning	0.87 (0.74 – 0.92)	0.89 (0.81 – 0.93)	**0.008**
Body image	0.74 (0.58 – 0.91)	0.72 (0.50 – 0.87)	0.683
Treatment/ interventions	0.66 (0.41 – 0.87)	0.91 (0.72 – 0.95)	0.28
Total QOL scores	0.81 (0.61 – 0.84)	0.89 (0.65 – 0.91)	0.084

Table 4.7.6.1 Change in quality of life during food reintroduction phase. Higher scores mean better quality of life (values in medians and ranges in IQR)

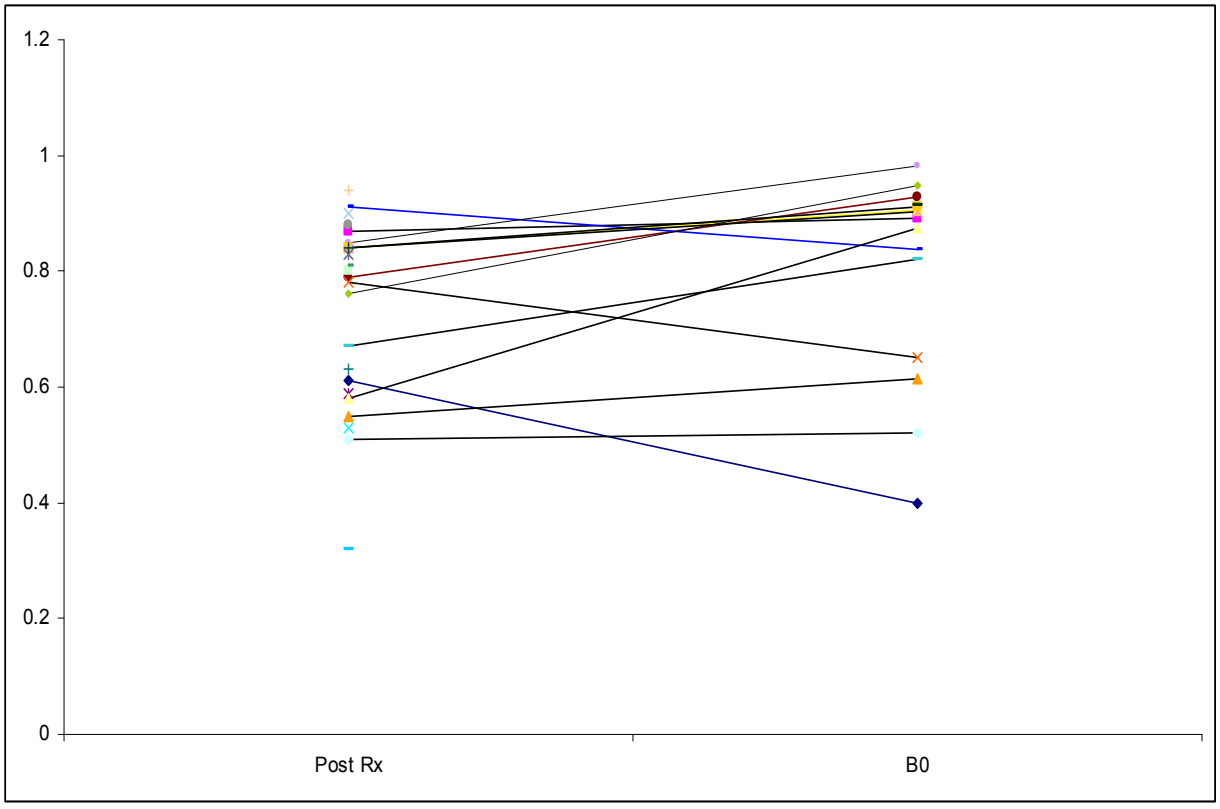


Figure 4.7.6.1 Change in quality of life scores during food re- introduction (End of phase A to start of Phase B). Higher values represent better quality of life

4.7.7 Quality of life in Phase B of the study

17 children had a quality of life assessment at the start of phase B (see section 4.7.6 and tables 4.7.6.1 & 4.7.7.1) following which were enrolled into randomised controlled trial (see details chapter 3).

8/17 were randomised to receive supplemental enteral nutrition (ACD004 – see chapter 3) whereas 9/17 children did not receive a supplement.

2 children each in the supplemented and non-supplemented group completed 2 years of the study in remission. The remaining 13/17 children relapsed before completion of 2 years. The median time to relapse was 0.67 years (IQR 0.25 – 1.54 years). There was no significant difference ($p = 0.696$) in the time to relapse between the supplemented (median 0.33 years, IQR = 0.25 – 1.34) and non-supplemented groups (median 0.67 years, IQR = 0.17 – 1.77).

Despite only 4 children in remission at termination of phase B (13/17 relapsing at end of study period), a comparison of quality of life scores shows no difference at completion of study (all children, including those in remission were included in this analysis). On comparison of individual quality of life domains deterioration is seen in the IBD and systemic systems QOL scores. However, there was neither an improvement nor deterioration in emotional functioning, social functioning, body image and attitudes towards to treatments and interventions.

	Start of Phase B	End of Phase B	p (WR)
IBD symptoms	0.93 (0.81-0.96)	0.69 (0.51-0.95)	**0.028**
Systemic symptoms	0.96 (0.87 - 0.98)	0.64 (0.26 - 0.94)	**0.015**
Emotional functioning	0.85 (0.73 – 0.97)	0.64 (0.30 – 0.91)	0.161
Social functioning	0.89 (0.81 – 0.93)	0.89 (0.81 – 0.93)	0.074
Body image	0.72 (0.50 – 0.87)	0.78 (0.67 – 0.91)	0.813
Treatment/ interventions	0.91 (0.72 – 0.95)	0.67 (0.51 – 0.83)	0.89
Total QOL scores	0.89 (0.65 – 0.91)	0.80 (0.53 – 0.92)	0.09

Table 4.7.7.1 Change in quality of life in Phase B follow up study. Higher values represent better quality of life. (values in medians and ranges in IQR)

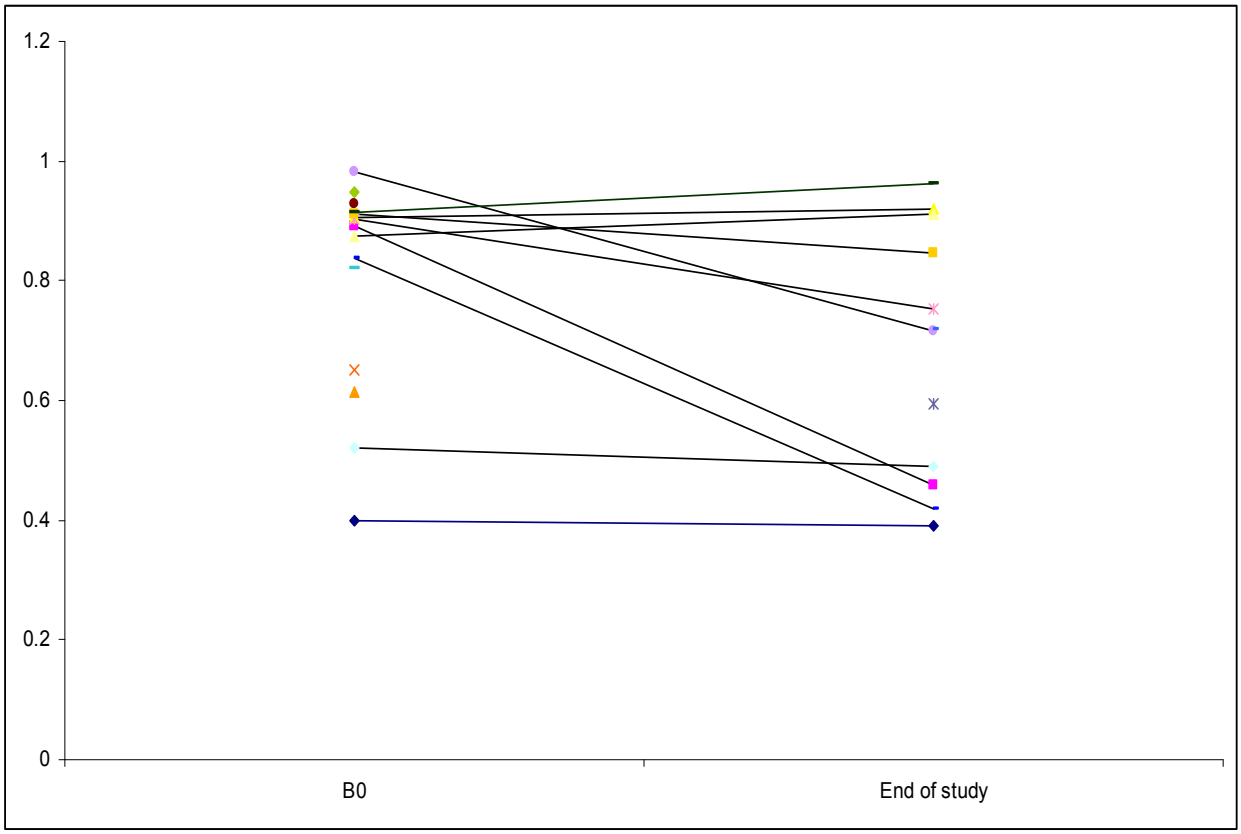


Figure 4.7.7.1 Change in quality of life scores of children during phase B follow up study. Higher values represent better quality of life

4.7.8 Comparison of quality of life between supplemented and non-supplemented group

There were no differences in the total quality of life scores or individual domain scores, between children receiving supplemental enteral nutrition and those not receiving any supplements at completion of phase B (p=ns).

4.7.9 Comparing quality of life from start of disease to time of first relapse

Finally, I have compared quality of life of children enrolled at start of phase A at the time of diagnosis with their quality of life at the end of the study. The median time to end of study is 0.92 years (IQR 0.50 – 0.90). Only 4/17 maintained remission by end of study.

There was an increasing acceptance to treatments and interventions with improvement of quality of life scores in this domain. In addition there was a significant improvement in the systemic symptoms domain. However the total quality of life scores and individual scores in the other domains remained unchanged.

	Start of Phase A	End of Phase B	p (WR)
IBD symptoms	0.49 (0.37 – 0.74)	0.69 (0.51-0.95)	0.131
Systemic symptoms	0.29 (0.13 – 0.49)	0.64 (0.26 - 0.94)	**0.05**
Emotional functioning	0.47 (0.35 – 0.68)	0.64 (0.30 – 0.91)	0.328
Social functioning	0.65 (0.53 – 0.84)	0.89 (0.81 – 0.93)	0.091
Body image	0.52 (0.30 – 0.84)	0.78 (0.67 – 0.91)	0.424
Treatment/ interventions	0.53 (0.22 – 0.74)	0.67 (0.51 – 0.83)	**0.037**
Total QOL scores	0.58 (0.44 – 0.72)	0.80 (0.53 – 0.92)	0.131

Table 4.7.9.1 Change in quality of life over the year from start of phase A to end of phase B – Median time = 0.92 years (IQR 0.50 – 0.90). Higher values represent better quality of life. (values in medians and IQR)

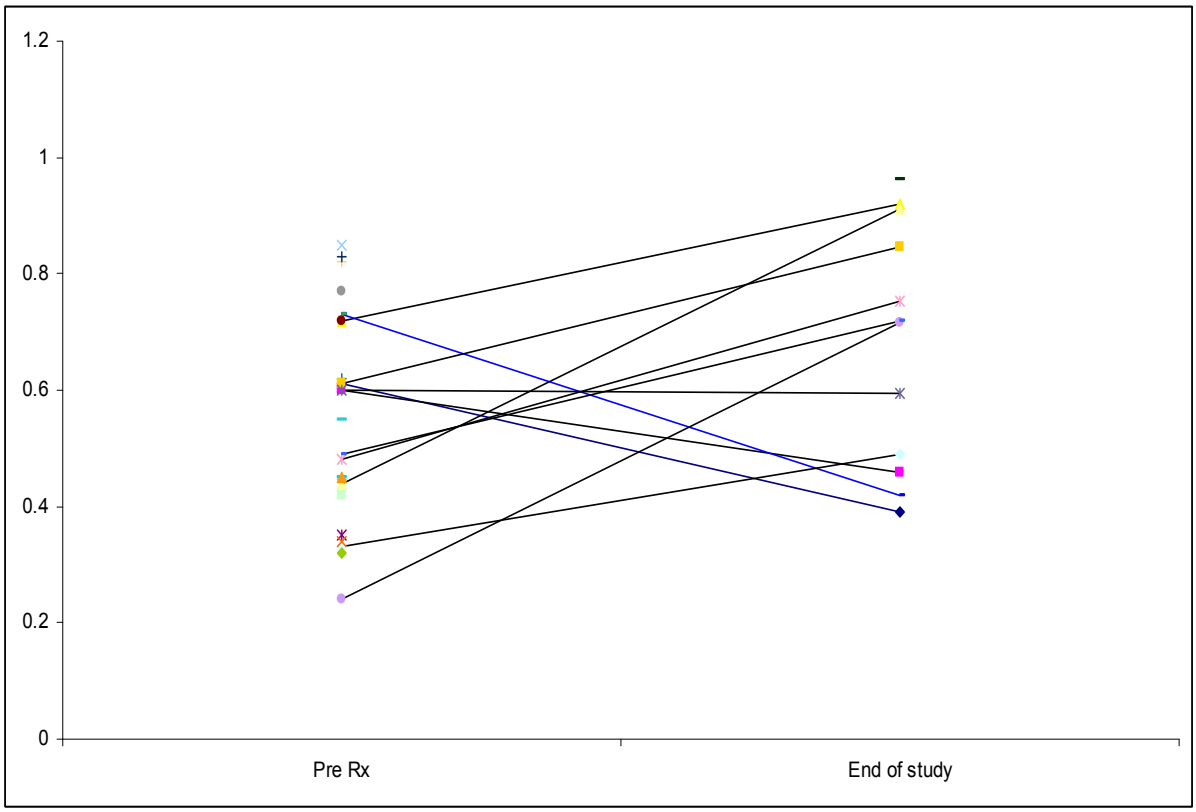


Figure 4.7.9.1 Change in quality of life scores from time of diagnosis (start Phase A) to time of first relapse

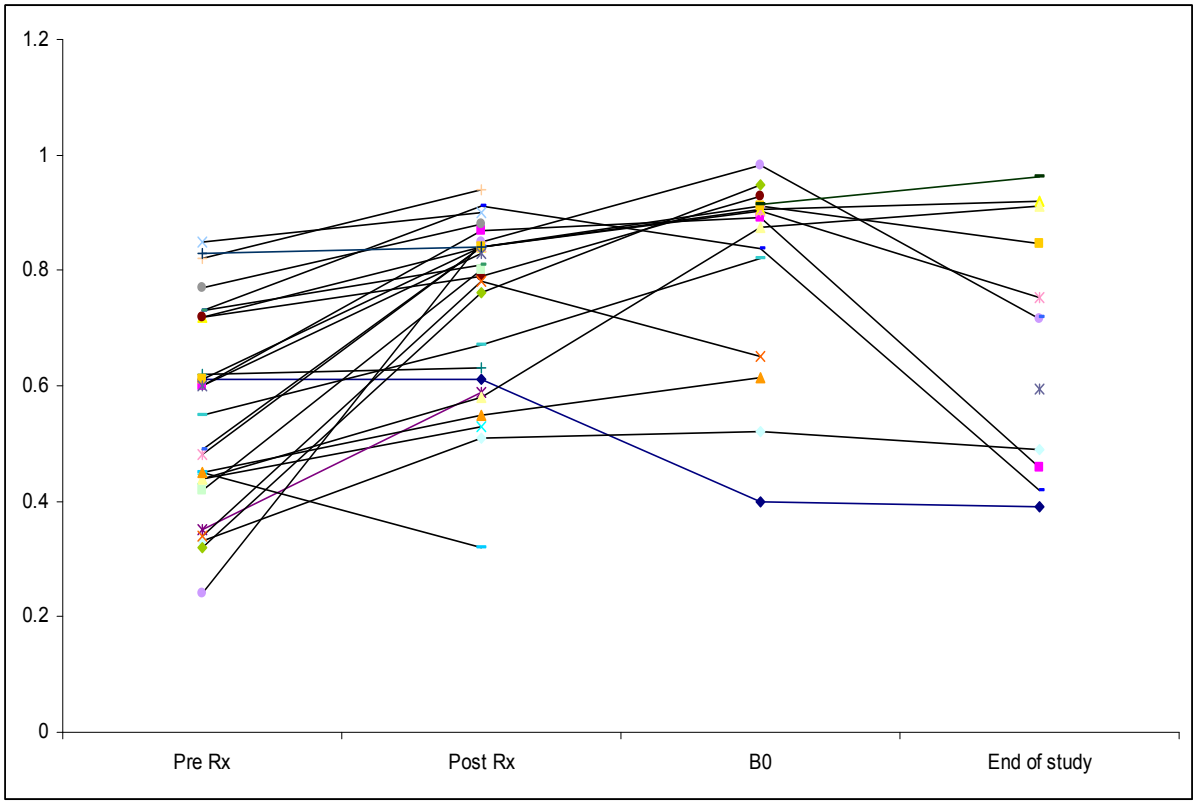


Figure 4.7.9.2 Changes in quality of life scores during different phases of the study trial. This is a breakdown of the same graph as shown in figure 4.7.9.1.

4.8 Discussion

This study shows successful use of exclusive enteral nutrition as treatment in a cohort of 26 children unwell with active Crohn's disease (part of the same cohort recruited in phase A). Despite complete food avoidance for a period of 8 weeks, children showed an improvement in their quality of life with clinical remission in 23/26 children (88.5%). More importantly this study illustrates the point that these clear improvements in quality of life and PCDAI scores are not mirrored by mucosal healing, as evidenced by using both histological and endoscopic criterions.

Physical measures of disease activity and degrees of mucosal inflammation, in isolation, are of limited interest to patients with inflammatory bowel disease. A successful therapy should ideally both improve a patient's quality of life and reduce the long-term consequences of the disease by modifying its course. One of the limitations of quality of life instruments such as the IMPACT II questionnaire is that they assess quality of life over a very short time frame (the last 14 days). It is well documented in children that both information recall and appreciation of long-term consequences are more limited than in adults. In addition the children coping mechanisms are different from adults [386-388]. As such, we must remain aware, of relying too heavily on short-term measures of quality of life when making management decisions in children with IBD. We assume that these decisions are perhaps also important in influencing their long-term well-being. Of course an ideal treatment is one that is efficacious and improves short- and long-term quality of life, yet data on the latter is simply not yet available, and information from single measures of quality of life should not be extrapolated to represent long-term quality of life outcomes.

Physical and psychological stressors have been shown to result in an increase in cytokine production in humans [387,388]. The same has been demonstrated in animal models where increased cytokine release occurs after injection of epinephrine [389]. Stress has also been shown to delay wound healing, which may in itself indirectly result in increased production of pro-inflammatory cytokines [390,391]. Similar mechanisms are likely to occur in children with inflammatory bowel disease. Therefore perhaps a reduction in anxiety and stress, with an improved perception of their quality of life may have a direct effect on their disease activity.

Quality of life is a complex concept (chapter 1.7). It is known that disease activity alone does not determine patient well-being and quality of life. QOL is also determined by personal characteristics, coping abilities, the environmental situation and social support [392]. This explains the fact as demonstrated in this study, two children with similar PCDAI scores may have very different quality of life scores. Generally instruments for measuring quality of life in children are scarce [393]. Use of adult instruments such as the generic SF36 are not appropriate as they measure health status (particularly physical functioning), rather than a patient's perception of their well-being, i.e., their health related quality of life (HRQOL) [350] (chapter 1.7). With the increasing need for such an instrument in paediatric IBD, 'IMPACT II' evolved from the original paediatric IBD specific instrument 'IMPACT I' developed in Canada by Griffiths et al [394] (chapter 1.7). Impact-II has been validated for use in children above 8 years of age. However, in this study I found it difficult for any child less than 11 years of age to understand and answer the questions independently. As the instrument is designed for self-administration, parental help in responding is likely to bias the results; echoing my experience from initial phase of this study.

While histological improvement was documented in 17/26 children after treatment, this did not appear to correlate with any QOL parameters. This could be due to several factors. The previously employed histological scoring system [314] uses a narrow range to quantify inflammation on biopsies. Together, the relatively small number of patients in the study and the lack of variability in histology score may be inadequate to conclude that there is no correlation. This may, also, not take into account children with mild disease who continue to have mild disease after treatment or those children with severe disease who continue to have severe disease. Children in

both scenarios will have a minimal difference in their histology scores. Quality of life is a complex concept, and disease treatment/healing is only one variable of many to affect it.

The good correlation between the PCDAI and IMPACT-II questionnaire is likely the result of common questions to both instruments, which makes it all the more surprising that improvements in histology scores correlate with changes in PCDAI, but not quality of life scores. Of course histological healing may in fact only be a minor determinant affecting quality of life. Histological healing may only be diagnosed by taking appropriate biopsies at an invasive procedure. Whilst some practitioners feel that mucosal healing is a vital goal in the long-term management of the disease, there is no evidence that this improves the long-term outlook for patients diagnosed with Crohn's disease in childhood.

Finally, it is particularly gratifying to see, in such a young population, that quality of life is improved with a therapy that has none of the side effects of corticosteroids, whilst having clear advantages in terms of growth and nutrition.

The phase B study in this chapter remains the only report looking at quality of life, prospectively over 2 years when children are treated with enteral nutrition. Interestingly the symptom scores improve by food reintroduction whilst 8 children drop out of the study. This improvement is perhaps likely to be related to presence of more well children at start of phase B compared to those at end of phase A (hence the high dropout). However the improvement in social functioning can be explained by the fact that enteral feeding over the day can result in a restrictive life style.

There is deterioration in the bowel and systemic symptoms domains at the end of phase B. This is likely to be related to the high number of relapsing children. Again, the total quality of life scores and those of the individual domains do not change. This may represent acceptance by the children regarding their chronic disease state resulting in a quality of life which is largely unaffected. In the same context quality of life scores, at the end of both phase A and B, when compared to scores at enrolment remain unchanged. It appears that though the disease process and its treatment do improve quality of life, children's first impressions and feelings about their disease tend to stay. Otley et al [395] have reported a quality of life study in a large cohort of children one year after diagnosis in which significant improvement in HRQOL was noted during the year from diagnosis. Mean IMPACT scores varied significantly depending on the disease severity and also decreased with increasing age. These results illustrate that quality of life is a much more complex concept which is in turn affected by many variables; disease state being only one of those variables in the equation.

In summary, this study demonstrates an improved quality of life after treatment with exclusive enteral nutrition in children with active Crohn's disease. Although some may raise the concern that quality of life measures may not reflect healing at mucosal level, it is extremely important to realize that QOL is integral to patient treatment. There is clearly a need for studies regarding long-term outcome of children diagnosed with Crohn's disease. This has to be the end point to effectiveness of treatments used in chronic disease. Perhaps, when we have good data on predictors of long-term quality of life, we may be able to focus even more effectively on short-term quality of life measures.

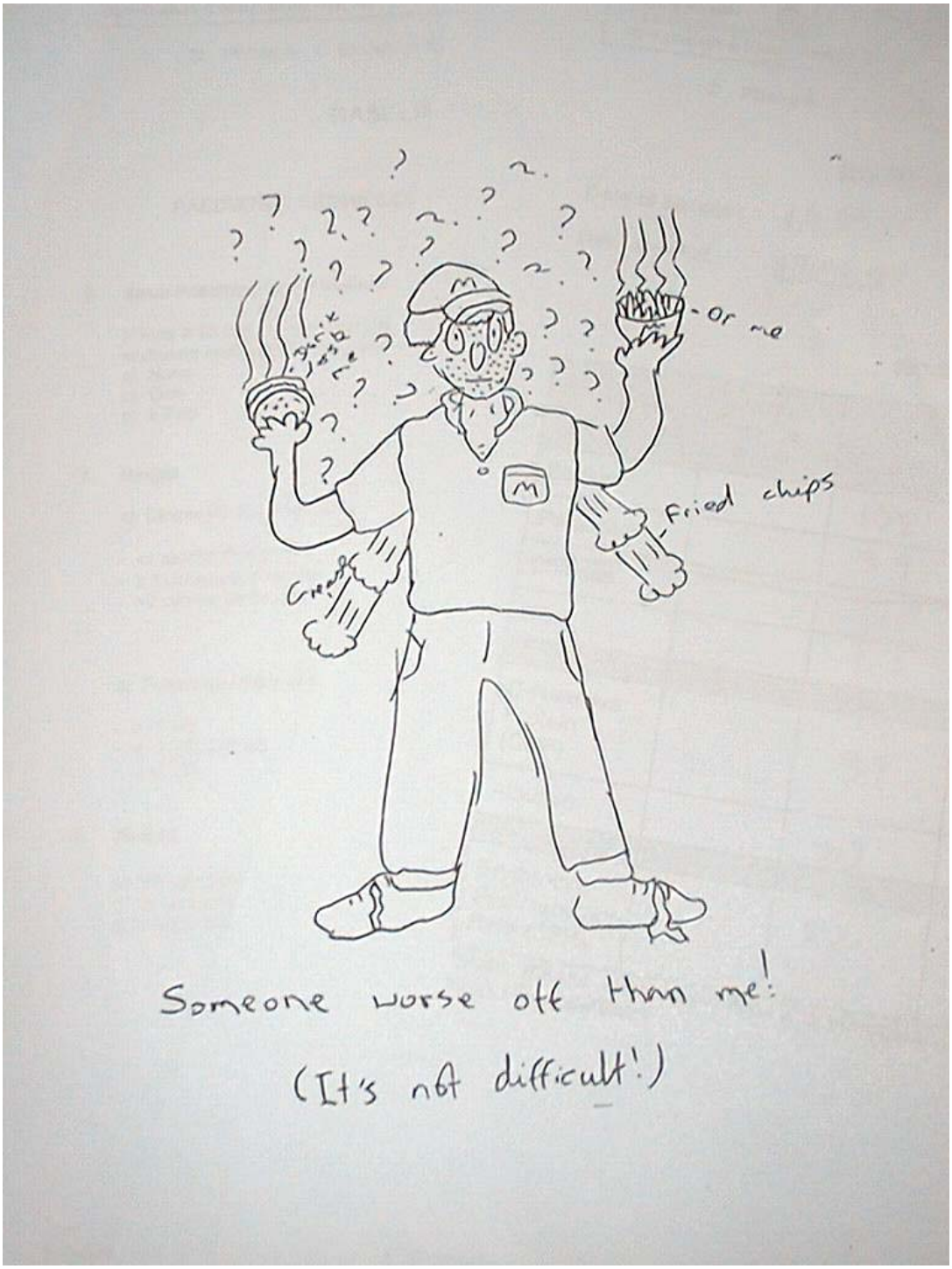


Figure 4.8 Cartoon illustration by a child (case SM05 - see table 2.8.1.1) in Phase A of the study, showing another child on exclusive enteral nutrition working in the MacDonald's serving chips and burgers but cannot eat them himself. The spotty face in the picture reflects Crohn's disease. This shows his view of restricted eating by enteral feeding and that there could be other children who are 'worse off' as they can't eat whilst working in food shops.

Chapter 5. Summary, critical discussion and conclusions

5.1 Summary

This thesis describes use of a new polymeric enteral feed ACD004, with a higher n-3 : n-6 ratio for treatment of paediatric Crohn's disease.

Chapter 2 describes effectiveness of the ACD004 feed in treatment of acute and active paediatric Crohn's disease. 78.6% of the children achieved complete remission. This was found to be similar to CT3211, the previous polymeric feed (with relatively lower n-3 : n-6 ratio). One child developed refeeding syndrome which is unlikely to be related to the feed itself. The colonic Crohn's sub-group responded less well to ACD004.

Chapter 3 decribes the randomised controlled trial, looking at role of ACD004 as a supplement compared to no supplement in maintenenace of remission. The trial collapsed with only 1/3rd of the calculated power being met due to withdrawal of funding. The limited study did not show any difference between the two groups.

Chapter 4 describes a longitudinal assessment of quality of life in children taking enteral nutrition for treatment and for maintaining remission. There is a significant improvement in quality of life scores at completion of acute treatment. Although disease and systemic symptoms deteriorate on relapse, there is no change in the emotional and social functioning domains of quality of life which is suggestive of disease acceptance in children. Taking supplements does not adversely affect quatliy of life in children. This highlights the complex concept of quality of life with disease state being only one of the variables amongst many, affecting quality of life.

5.2 Critical discussion

Enteral nutrition is an effective treatment for Crohn's disease. To date two paediatric meta-analyses shows it to be as effective as corticosteroids [182,396]. The Cochranre reviews however, show the steroids to be superior to exclusive enteral nutrition in inducing remission [311,312]. The phase A of this study could have been designed as a randomised controlled trial to assess the two forms of treatment prospectively. In addition it could have been useful to compare a quality of life study in the two groups. This would have, however, required a greater number of children for recruitment. It would have perhaps made sense to involve the six centres at the outset embarking on the randomised controlled trial in phase A, rather than at phase B.

Phase B (RCT) came to a premature end due to withdrawal of funding and failure to progress into a six centre multi-centre trial. The study was originally funded for two years with a verbal promise to of extending it to 6 centre study in future. The ethics committee accepted the trial proposal with full payment made for research fellow, university overhead fees and the project itself. In hindsight it was an error and and a full contract down to the last detail and penny should have been negotiated and agreed before commencement of the study. Long-term projects always require continued motivation of the investor and investee. During phase B of this study Professor John Walker-Smith retired after a year of starting the project. He was the principal investigator and had negotiated the original funding. In addition it is also likely to be related to the company's disappointment in finding the results comparable to Modulen IBD. Additionally to the end of the study there were problems with manufacture and supply of the product adding to

frustration and lack of interest. I suspect the company did not wish to invest further in this and pulled out at the earliest opportunity. There are several lessons to be learnt from this. Randomised controlled trials should not be over-ambitious, be realistic and involve a strict binding contract for both the investor and investee in a well defined time frame. Any deviation should be penalised. The research network on medicines for children did not exist at that time and a trial gone through the MCRN could have been useful in not only contributing to the trial costs but also making it difficult for the investors to abandon the trial with a worry of bad publicity.

5.3 Conclusions and future

Enteral nutrition is an effective and safe remission inducing agent in paediatric Crohn's disease. Sanderson [304] and Thomas [397] have shown enteral nutrition to be superior over steroids in preserving growth with higher height standard deviation scores at 6 months after the induction treatment in children with Crohn's disease. Another study evaluated the final adult height in a group of 123 patients with CD diagnosed prior to 16 years of age. Their mean final height was found to be 2.4cms less than the parental or target height. Almost one fifth had a final height < 8cms below their target height. The two main factors causing reduction of final height were presence of jejunal disease and period of symptoms prior to diagnosis. Interestingly, corticosteroids and requirement for surgery weren't linked to final height acquisition [398]. More longitudinal comparable studies are needed to look at long-term growth with use of enteral nutrition. A therapeutic intervention in a child with inflammatory bowel disease cannot be judged successful unless growth is normal and proceeding satisfactorily. Future studies with

enteral nutrition and other treatments in children with IBD should also incorporate normal growth as a marker of success.

In addition to reducing inflammation, decreasing disease activity, and improving nutrition in children with newly diagnosed CD, exclusive enteral nutrition normalizes serum markers of bone turnover, suggesting an improvement in bone health with its use [399]. Infliximab has already been shown to have a positive effect on bone metabolism in the REACH study [400]. Further studies on short- and long-term effects of enteral nutrition on bone density and overall bone health in children with Crohn's disease are needed. Currently there is little evidence of using enteral nutrition with other treatments for induction of remission. One report from Japan, a study of 110 adults with Crohn's disease, showed a greater response with infliximab when used in conjunction with enteral nutrition [401]. Combination therapy may be particularly useful in moderate to severe cases where there may be treatment resistance present.

There is a wide variation in practice regarding use of enteral nutrition. Exclusive enteral nutrition is less commonly used in USA compared to Britian [402]. The reasons for these differences are unclear and could be related to lack of dietetic and nursing support, financial support or lack of understanding. Increased understanding should permit more considered decisions. In addition hard-boiled lollies [403] and flavouring agents [353,404] in conjunction with enteral nutrition is reported. Further studies are required into these practices with a view to improving compliance.

There are no prospective studies to show that supplement enteral nutrition is an effective form of treatment. Equally, the initial results (in the limited ACD004 trial) are discouraging. Although a better trial on

use of enteral feed as a supplement needs to be organised, equally, it is difficult to stay away from proven effective treatments like azathioprine and 6-mercaptopurine which have stood the test of time and have been around 1960s [230]. The health commissioners also see a cost benefit in such treatments. From a children's point of view tablets are easier to swallow in comparison with supplement enteral nutrition. A redesign and any re-attempts to conduct Phase B of this study, should incoroporate comparative or adjunctive usage of immunosuppressants such as thiopurines.

Supplementary enteral nutrition may also have benefits in preventing post-operative recurrence of Crohn's disease. In an adult study, those receiving at least 1200 Kcal of an enteral formula (polymeric or elemental) for the first 12 months following a resection had a lower risk of disease recurrence [405]. These benefits are particularly seen in patients with penetrating disease and in those without colonic disease. Further studies are required evaluating maintenance enteral nutrition post-operatively with accurate definition of disease phenotype.

Quality of life issues are important in all chronic conditions. In treatment of acute paediatric Crohn's disease, although, the overall quality of life scores generally improved there are reservations about difficulty in taking the enteral feed. Even though, polymeric feeds remain the best tasting feeds to date it still, is far from ideal. Children would prefer better tasting flavour options and feed manufacturers should incorporate this. A better tasting feed would perhaps make enteral feeding a preferable treatement of choice for the adults as well. In the same context more studies are needed regarding the duration of use of the enteral feed.

Crohn's disease is not a single disease but a heterogeneous group of disorders. There is a need for studies which incorporate studies taking the phenotype classifications such as the Montreal's classification into consideration. This should enable us to tailor the treatments more effectively for individual cases. Our understanding of the disease pathogenesis continues to improve. We are now beginning to understand that genetic predisoposition, dysregulated immune response and environmental influences contribute to pathogenesis of the disease [406].

Quality of life questionnaires continue to evolve and since the writing of this thesis, IMPACT III is available [271]. It uses the Likert scale making it easy to be used and measured. Despite this, there is still a dearth of quality of life assessment tools in the younger age group. Although the IMPACT II is validated to be used by children above 8 years of age, I failed to administer it successfully to children younger than 10 years of age, as they found it difficult to understand. Easily reproducible qualityof life assessment tools for young children with inflammatory bowel disease need to be developed in future research.

Quality of life issues in paediatric Crohn's disease are complex and certainly disease activity forms only one dimension of the assessment. We as doctors are good at addressing disease issues but poor at diagnosing and addressing other domains (emotional and social functioning, body image and attitudes to treatments) forming quality of life. We need to do more work to look at ways to improve quality of life other than improving it by treating the disease. Clearly, a simplistic psychological assessment is not the answer either. I have worked with children and families with Crohns disease for last many years and I feel that there needs to be a

parallel psychological assessment/input (in addition to disease assessment) during clinic visits with required tailored to each individual child and family. Further studies are required in this regard as development of these services would require use of resources and already stretched psychiatry services in the NHS, UK.

Last, randomized controlled trials should not be over-ambitious but should be realistic. RCTs should involve a strict legal contract and binding for both the investor and the investee encompassed in a well defined time frame. Any deviation should be penalised. The current research governance practice has changed and it would have strengthened this study if such steps had been taken at the start. Recently the Department of Health (England) has commissioned a research network on medicines for children. This is based at University of Liverpool in partnership with Alder Hey children's hospital. The collaborators include Imperial College, London, the Liverpool Women's Hospital, the National Perinatal Epidemiology Unit at the University of Oxford and the National Children's Bureau. The aims of this network are to facilitate the conduct of randomized controlled trials and other well designed studies of medicines for children including those for prevention, diagnosis and treatment. This should enable to maintain uniform quality in paediatric medical trials.

Chapter 6. Appendix

6.1 Consent Form

(Form to be on hospital headed paper)

Centre Number: 02-CWH

Study Number: 9916-CLI (final version dated 16.07.1999)

Subject Identification Number for this trial:

CONSENT FORM

Please initial box

1. I confirm that I have read and understand the information sheet dated…….(version……) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of my medical notes may be looked at by responsible individuals from NESTEC S.A or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

Name of patient/guardian	Date	Signature
Name of Person taking consent (if different from Researcher)	Date	Signature
Researcher	Date	Signature

1 copy for subject; 1 for Researcher (stored in the Study Master File); 1 to be kept in hospital notes.

6.2 The study information leaflet for children and parents consenting to participate – patient informed consent

You are being asked to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your relatives, friends and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.
Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.
Thank you for reading this.

What is the purpose of the study?
At the …… hospital most children with active Crohn's disease are now treated initially with a special milk based diet as their sole nutrition (only food) for 2 months. Most often this can be drunk by mouth, if not it is given intra-gastrically via a tube through the nose. Children are able to cope with this because usually after 48 hours they feel so much better. A new form of diet, ACD004, is being evaluated. It has a different fat composition which is believed may help further to reduce bowel inflammation. Otherwise it is very similar to other special feeds for the treatment of Crohn's disease. We think it may offer children a better chance of keeping well after its use (i.e., remission).

We would also like to test the idea that continuing supplementation with this diet for sometime after your child returns to an otherwise normal diet helps keep your child well. We would like your permission to include your child in a random allocation of supplement or no supplement. In this way we can find out if oral supplements are helpful. This study will last a total of 5 years.

Why has my child been chosen?
Your child has been chosen because we feel that with his/her Crohn's disease, nutrition along may heal his/her gut. Initially, 27 subjects will be studied from the Royal Free and Chelsea and Westminster Hospitals. From about April 2000, other patients from France and the Netherlands will also take part in the study, making it a total of 72.

What will happen if my child takes part?
If you and your child decide to take part in the study, during the first part, we will ask him/her to take nothing but the special milk diet for 8 weeks, followed by a gradual re-introduction of food items over a period of 4-6 weeks. During this time he/she will be weaned off the product until the amount of tested feed he/she is taking represents only 25-30% of daily nutritional needs. Having reached this amount, he/she will be entered into the second part of the study when he/she will receive a normal diet with or without ACD004 as a supplement for many months. This will be decided by randomization. Sometimes when we do not know which way of treating patients is best, we need to make comparisons. Children will be put into groups and then compared. A computer that has no information about the individual selects the group –i.e., by chance. Subjects in each group then have a different treatment and these are compared.

Before starting the test milk treatment your child will be investigated in exactly the same way as all children with Crohn's disease at the ….., are at the moment. The number of blood tests and special investigations to assess treatment response and colonoscopies or Barium meal X rays will be the same.

Your child will initially have to stay in the hospital for 3-5 days to get used to having only the tested product instead of food. This may also mean placing a tube through the nose into the stomach to feed him/her if she is too ill to take it by mouth.

Your child will be attending the paediatric inflammatory bowel disease clinic after treatment in the usual way. To assess how well the treatment is working we will ask your child to fill in a questionnaire after a few of the visits.

What does my child have to do? Are there lifestyle restrictions?
As mentioned above your child will not be allowed any food apart from the special milk drink for the first 8 weeks of your taking part in the study. If your child is selected to be in a group to receive long term supplementation he/she will need to carry on drinking a small amount of the feed (roughly 1-1½ pints a day) on a regular basis even if totally healthy.

What is the product being tested?
The product is a complete nutritional support feed based on specially treated cow's milk protein and vegetable oils. These vegetable oils are known to potentially reduce inflammation. Otherwise the feed is very like other special diets we use to treat children with Crohn's disease.

It looks like milk and fulfils all nutritional needs plus the extras due to the disease. Your child will be given a study card, the size of a credit card. Please make sure he/she carries the study card at all times.

What are the alternatives for diagnosis or treatment?
Alternatives to this treatment at this stage of Crohn's disease are other special feeds or corticosteroids, although at our hospital we try to avoid use corticosteroids.

What are the side effects of taking part?
Your child may experience a temporary worsening of any of the following: diarrhoea, nausea, vomiting and abdominal cramps. These are more likely to occur at beginning of treatment. That is why treatment is started in hospital. If your child suffers these or any other symptoms after discharge from your hospital, you should report them to the investigator Dr…… or any of his team either straight away or if mild, at the next scheduled meeting.

What are the possible disadvantages or risk of taking part?
The possible disadvantages will be not having any normal food during the first 8 weeks of the treatment. Secondly, and like all treatments, it might not work on your child.

What are the possible benefits of taking part?
We hope that the treatment will help your child. The inflammation of his/her gut can disappear and he/she may catch up on height and weight growth. However,

this cannot be guaranteed. The information we get from this study may help us treat children with Crohn's disease better.

Has any other study of this kind been done before?
A similar product was used in a previous study involving 29 Crohn's disease patients at the Royal Free Hospital, London between 1995 and 1997.

What if new information becomes available?
Sometimes during the course of the research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an update consent form.

What happens when the research study stops?
Sometimes, the sponsor might decide to stop the study. Should this be the case, a similar product is available on the market to help your child.

What if something goes wrong?
Compensation for any injury caused by taking part in this study will be in accordance with guidelines of the Association of British Pharmaceutical Industry (ABPI). Broadly speaking, the ABPI guidelines recommend that 'the sponsor' without legal commitment, should compensate you without you having to prove that it is at fault. This applies in cases where it is likely that such injury results from giving away any new drug/new treatment or any other new procedure carried out in accordance with the protocol for the study. 'The sponsor' will not compensate you where such injury results from any procedure carried out which is not in accordance with the protocol for the study. Your right at law to claim compensation for injury where you can prove negligence is not affected. Copies of these guidelines are available on request.

Will my taking part in this study be kept confidential?
Data from this study will be recorded on specially designed forms. Your name will not appear on any of those forms, in fact you will be given a number once enrolled in the trial. Access to your medical records may be available to doctors, the sponsor's monitors, clinical trials auditors, ethics committees and regulatory authorities if required. The study results may be published but your identity will not be disclosed.

6.3 Declaration of Helsinki

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, the 41st World Medical Assembly, Hong Kong, September 1989 and the 48th General Assembly, Somerset West, Republic of South Africa October 1996.

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In the current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a subject, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be

obtained by a physician who is not engaged in the investigation and who is completely independent of his official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with the national legislation.

Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every subject - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the subject to participate in a study must never interfere with the physician-subject relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the subject.

III Non-therapeutic Biomedical Research Involving Human Subjects (Non-clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or subjects for whom the experimental design is not related to the subject's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

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