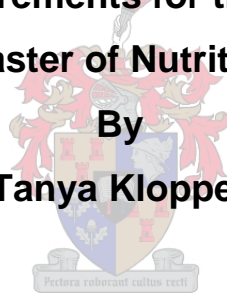


**SAFETY AND EFFICACY OF N-3 ENRICHED
NUTRITIONAL SUPPLEMENTS IN THE MANAGEMENT
OF CANCER CACHEXIA**

**Thesis presented to the Department of Human Nutrition
of the Stellenbosch University
in partial fulfilment
of the requirements for the degree of
Master of Nutrition**

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Degree of Confidentiality: A (unrestricted)

April 2006

DECLARATION OF AUTHENTICITY

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and that I have not previously, in its entirety or in its part, submitted it at any university for a degree.

Signature

February 2006

ABSTRACT

Background

At least 40 - 80% of all cancer patients develop some degree of clinical malnutrition and cachexia. The complex and multi-factorial nature of cancer cachexia and the inability of conventional nutrition intervention to reverse or attenuate the effects of this syndrome have driven investigators to consider new therapies and approaches to manage the syndrome of cancer cachexia including eicosapentaenoic acid (EPA), an *n*-3 fatty acid of fish oil origin.

Objectives

The aim of this study was to review Phase I, Phase II and Phase III (RCT) trials investigating the safety and efficacy of *n*-3 supplementation in the treatment of cancer cachexia in adult patients with unresectable solid tumours, with special reference to weight loss, body composition, appetite, dietary intake, energy expenditure, functional status, acute phase response and quality of life. Adverse effects associated with EPA supplementation were also reviewed.

Methodology and data collection

The major databases were systematically searched for studies that met the inclusion criteria using a structured keyword search strategy or various combinations of these keywords. Relevancy of studies was assessed by two independent reviewers according to pre-determined inclusion and exclusion criteria. Quality was assessed by two independent reviewers using the Jadad scale. Data extraction was performed by the principal reviewer and one of the independent reviewers, and investigators of the included studies were contacted where further information was required. Meta-analysis was not appropriate due to heterogeneity of the data. However, where possible, the paired t-test was used for analysis of the data. Descriptive or non-quantitative analysis of the tabulated data provided a summary of the characteristics of the included studies enabling comparisons to be made between interventions and outcomes within the specified population.

Results

The search resulted in a total of 1408 citations, of which only 16 studies met the inclusion and exclusion criteria. Of these, only 4 studies were of a good quality. Although the reported data was incomplete and variable, the combined analyses suggested that the effect of EPA supplementation on weight, fat mass, dietary intake, energy expenditure, and acute phase response was not significant. Interestingly there appeared to be a significant increase in lean body mass ($p < 0.05$). There was little or no data to draw any conclusions regarding the effect of supplementation on appetite and quality of life.

Conclusion

Despite several limitations in this review, the data collected and analysed are suggestive of the beneficial effects of EPA supplementation, but there remains a significant lack of substantial evidence and conclusive statistical analysis to confirm that EPA supplementation is a safe and effective method of intervention in the management of patients with cancer cachexia.

OPSOMMING

Agtergrond

Ten minste 40 – 80% van alle kanker pasiënte ontwikkel 'n mate van kliniese wanvoeding en kanker kageksie. Die komplekse en multifaktoriale aard van kanker kageksie en die onvermoë van konvensionele voedingintervensies om die effek van die sindroom om te keer of te vertraag, het navorsers aangespoor om nuwe behandelings en benaderings te oorweeg vir die behandeling van kanker kageksie. Een van dié benaderings sluit in eikosapentanoësuur (EPS), 'n *n*-3 vetsuur afkomstig van vis olie.

Doel van studie

Die doel van die studie was 'n oorsig van Fase I, II en III studies om die veiligheid en effektiwiteit van *n*-3 supplementasie in die behandeling van kanker kageksie in volwasse pasiënte met onverwyderbare, soliede gewasse te bepaal, met spesiale verwysing na gewigsverlies, liggaamsamestelling, eetlus, dieetinname, energieverbruik, funksionele toestand, akute fase respons en lewenskwaliteit. Nuwe-effekte geassosieer met EPS supplementasie is ook ondersoek.

Metodiek en data versameling

Die belangrikste databasisse is sistematies nagegaan vir studies volgens spesifieke insluitings kriteria deur van 'n gestruktureerde soektog volgens sleutelwoorde, of deur middel van 'n kombinasie van dié sleutelwoorde. Die toepaslikheid van studies is bepaal deur twee onafhanklike nasieners volgens voorafbepaalde insluitings en uitsluitings kriteria. Kwaliteit is met behulp van die Jadad skaal deur die twee onafhanklike nasieners bepaal. Die hoof nasiener en een van die onafhanklike nasieners was verantwoordelik vir data ekstrahering. Indien nodig, is die navorsers van die studies wat ingesluit was gekontak vir addisionele inligting. As gevolg van die heterogene aard van die studies was meta-analise nie moontlik nie. Waar moontlik is die gepaarde *t*-toets vir analise van die data gebruik. Beskrywende of nie-kwantitatiewe analise van die getabuleerde data het 'n opsomming van die eienskappe van die ingeslote studies verskaf. Dit het toegelaat dat daar vergelykings gemaak

kon word tussen die intervensie en die uitkomst, binne die spesifieke populasie groep.

Resultate

Die soektog het 1408 studies geïdentifiseer waarvan net 16 aan die insluitings en uitsluitings kriteria voldoen het. Slegs 4 van hierdie studies was egter van goeie kwaliteit. Alhoewel die gerapporteerde data onvolledig en uiteenlopend was, het die gekombineerde analise daarop gedui dat die effek van EPS suplementasie op gewig, vetmassa, dieet inname, energie verbruik, funksionele toestand en akute fase respons, nie beduidend is nie. 'n Interessante waarneming was dat daar 'n beduidende verhoging was in maer liggaamsgewig na suplementasie ($p < 0.05$). Daar was egter nie voldoende data om enige gevolgtrekkings te maak oor die effek van EPS suplementasie op eetlus of lewenskwaliteit nie.

Gevolgtrekking

Ten spyte van verskeie beperkings van hierdie oorsig, is die data wat ingesamel en geanaliseer was suggestief van 'n moontlike voordelige effek van EPS suplementasie. Daar is egter nog 'n groot tekort aan substansiële bewyse en konkrete statistiese data om te bewys dat EPS suplementasie 'n veilige en effektiewe metode van intervensie is in die behandeling van pasiënte met kanker kageksie.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

- CC – Cancer cachexia
- CINAHL – Cumulative Index to Nursing and Allied Health Literature
- CLL – Chronic lymphocytic leukaemia
- CNTF - Ciliary neurotrophic factor
- CORDIS - Community Research and Development Information Service
- CRP – C-reactive protein
- DARE – Database of Abstracts of Reviews of Effects
- EFAT – Edmonton Functional Assessment Tool
- EMBASE – Excerpta Medica
- ENS – Enriched nutritional supplement
- EPA – Eicosapentaenoic acid
- EORTC – European Organisation for Research and Treatment of Cancer
- FAACT – Functional Assessment of Anorexia / Cachexia Therapy
- FACT – G – Functional Assessment of Cancer Therapy General Well-being
- FM – fat mass
- IL-1 - Interleukin-1
- IL-6 - Interleukin-6
- INF- γ - Interferon gamma
- ISTP – Index to Scientific and Technical Proceedings
- KPS – Karnofsky performance status
- LBM – Lean body mass
- MEDLINE – Index Medicus
- MTD – Maximum tolerated dose
- NCI – National Cancer Institute
- NHS CRD – NHS Centre for Research and Development
- NHS EED – National Health Service Economic Evaluation Database
- NRR – National Research Register
- NS – Nutritional supplement
- NSAIDS – Non-steroidal anti-inflammatory drugs
- n*-3 fatty acids – omega-3 fatty acids
- PIF – Proteolysis Inducing Factor
- QOL – Quality of Life

RCT – Randomised Control Trial

SIGLE – System for Information on Grey Literature in Europe

TNF – Tumour Necrosis Factor

UK CCCR – United Kingdom Coordinating Committee on Cancer Research

WHO – World Health Organisation

Zetoc – British Library's electronic table of contents

LIST OF DEFINITIONS

EuroQol – This is a short self-report questionnaire to measure generic health-related quality of life in 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension is measured with one item and scored between 0 to 1 (0 equals death and 1 perfect health). It also includes a 0-100 graphic rating scale to measure overall health status. The EuroQol (EQ-5D) was developed by the EuroQol Group in 1990¹.

Heterogeneity – The variability or differences between studies in terms of key characteristics (clinical heterogeneity), quality (methodological heterogeneity) and effects (heterogeneity of results)².

Internal Validity - The degree to which the results of a study are likely to approximate to the 'truth'².

Meta search engine – A search engine that searches other individual search engines and then combines the results that are received from all³.

Phase I Trial – These are the initial studies used to establish the safety and effectiveness of new drugs in humans⁴.

Phase II Trial – These are controlled clinical trials to evaluate the effectiveness of a new drug in a small group of people with a specific condition. They are also used to determine the common short-term side effects and risks⁴.

Phase III Trial – Once a new drug has been established as reasonably effective and safe, Phase III trials are designed and conducted to compare the new drug with an existing drug or intervention known to be effective. Most Phase III trials are RCTs⁴.

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

Nutrition plays a significant role throughout the clinical course of the cancer disease process, with at least 40 - 80% of all cancer patients developing some degree of clinical malnutrition⁵. The association between malnutrition and weight loss and the increased risk of dying in patients with cancer has been a well established observation over the last 60 years. It is, however, only more recently that the role and challenge of nutrition intervention in this process of malnutrition has been investigated. In general terms, simple provision of nutrients does not help overcome the metabolic impact of malignancy⁶.

At least 50% of patients with cancer lose weight prior to their diagnosis. Following the results of an earlier study, it has become a well-documented and accepted concept that poor performance status and weight loss of more than 10 % is associated with a poor response to treatment and shortened survival⁷. This study also established that the occurrence of weight loss differed with the type of malignancy. Certain subtypes of lymphomas, sarcomas, leukaemia and breast cancer are associated with a low incidence of weight loss, with only 30-40% of these patients losing weight, whereas a weight loss of 48 – 61% is documented with other subtypes of lymphoma, colon, prostate and lung cancer. The group of patients known to have the highest incidence of weight loss are those with pancreatic and gastric cancer. At least 83 – 87% of such patients will lose weight, a third of whom will lose more than 10% of their body weight^{7, 8}. Furthermore, Dewys *et al*⁷ have shown that survival time within each tumour type was influenced by the percentage of weight loss that occurs. A 30 % loss of body weight is frequently fatal. Nevertheless, a few patients have been able to survive despite a loss of up to 50% of their body weight^{7, 9}.

The pattern of weight loss seen in cancer patients is very different from the pattern seen during simple starvation, and forms part of a syndrome known as cachexia. In addition to the weight loss, cancer cachexia is characterised by anorexia, taste changes, early satiety and weakness. Starvation primarily

produces losses of fat but also of muscle and visceral protein, while cancer patients may lose up to 75% of muscle protein and up to 80% fat with preservation of visceral protein. It therefore appears that there are different mechanisms inducing weight loss in patients with cancer compared with those suffering starvation^{10, 11}. It is these differences that complicate the nutritional management of a cancer patient.

1.1.1 Impact of cancer cachexia

Unintentional weight loss in patients with cancer is merely one of the clinical features of a syndrome known as cancer cachexia (CC), which combines physiologic, metabolic and psychological factors. This reflects the multifactorial nature of the syndrome, which ultimately leads to a reduction in food intake, an increase in energy expenditure, or a combination of the two. Although there are no strict criteria for the specific diagnosis of CC, clinical manifestations include progressive involuntary weight loss and wasting, anaemia, anorexia, fatigue, hypoalbuminaemia, impaired immune function and poor performance status, all of which have a profound effect on the progression of the disease and have an overall effect in reducing the quality and possibly the quantity of life.

CC can appear at any stage of the disease process and is present in at least 50-80% of patients with malignancies. Over 20% of cancer related deaths are as a result of malnutrition and host tissue wasting^{6, 8, 11-13}.

1.1.2 Clinical Manifestations

1.1.2.1 Anorexia

Anorexia is a prominent component of cancer cachexia. It is the most common and clinically significant symptom and is characterised by a spontaneous decrease in dietary intake and adversely influences nutritional status¹⁴. Anorexia can consist of appetite loss and / or satiety as well as altered food preferences¹⁵. The frequency of anorexia in cancer can vary from

15-40% at presentation and up to 80% in patients with advanced cancer. Pain, mechanical obstruction of the gastrointestinal tract and various side effects of chemotherapy are some of the causes of the anorexia. However, the frequent absence of these causes has led to speculation that there may be other factors, either produced by the tumour or by the host in response to the tumour, that contribute to the anorexia. Further research has shown that leptin, a molecule secreted by adipose tissue, can influence food intake and energy expenditure and thus contribute to the anorexia seen in patients with cancer. One of the important aspects of the anorexia is its impact on a patient's quality of life^{6, 12, 13}.

1.1.2.2 Weight loss

Weight loss is a major prognostic indicator of poor survival and also contributes to a poor response to therapy. The loss in weight may occur as a result of poor dietary intake, the position of the tumour in the gastrointestinal tract, side effects of radiotherapy and/or chemotherapy, pain and emotional distress. The weight loss impacts a patient's performance status which in turn will have a negative effect on quality of life¹³.

1.1.2.3 Gastrointestinal Complications

A variety of symptoms such as early satiety, taste changes, xerostomia, nausea, vomiting, diarrhoea and constipation can result from the tumour or be a consequence of treatment. Furthermore, direct involvement of the tumour can alter the digestion and absorption of nutrients which may directly or indirectly influence nutritional status.

1.1.2.4 Quality of life

The clinical manifestations of CC all have a negative effect on nutritional status and are closely associated with quality of life which in turn will have a direct impact on a patient's ability to maintain simple activities of daily living, result in changes in body image and contribute to depression and interfere

with family and social relationships. It is this significant impact on quality of life that very often initiates the process of investigations and consequent diagnosis of cancer^{13, 16, 17}.

1.1.3 Mechanisms and mediators of cancer cachexia

The altered dietary intake resulting from many of the factors already discussed, cannot adequately explain the inability of patients with cancer to maintain or gain weight. Other possibilities thought to be playing a role include hypermetabolism and altered metabolism of carbohydrate, protein, and fat. Furthermore, certain mediators have also been implicated in the development of cancer cachexia (Figure 1.1)¹³.

Hypermetabolism describes the raised resting energy expenditure, which is a feature in patients with cachexia but not in starvation¹⁸. Approximately 60% of patients with cancer have abnormal resting energy expenditure (REE) with studies showing that the REE can range from less than 60% to more than 150% of predicted values, with approximately 35% being hypometabolic and 25% being hypermetabolic.

A recent study has confirmed that REE is raised in patients with pancreatic cancer which may play a role in accelerating the wasting and further increase the energy deficit already present in these patients¹⁹.

Studies performed in animals have also shown that energy expenditure changes with disease progression. Initially, there is a period of hypermetabolism which then changes to a relatively normometabolic phase to a preterminal hypometabolic phase. Although such measurements have not been investigated in humans, this pattern could account for some of the observed variation in energy expenditure. In addition to this, the tumour type plays an important role in determining energy expenditure. Although there may be changes in REE, total energy expenditure may be unchanged due to a reduced level of physical activity, thus maintaining the overall energy balance^{13, 20-22}.

A variety of changes in nutrient metabolism in patients with cancer have been described, which emphasize that CC is more than a failure to meet nutritional requirements with dietary intake^{6, 21}. The changes in carbohydrate metabolism are characterised by a relative glucose intolerance and insulin resistance. There is an increased glucose production of up to 40% and a 2-5 fold increase in glucose recycling through the Cori cycle in response to tumour production of lactic acid. It appears that disease progression makes these changes more pronounced, and it has been suggested that the energy cost of these changes is approximately 260 kcal/d^{6, 10, 20, 21}.

The significant depletion of fat stores is one of the most obvious and characteristic features of CC and accounts for the wasted appearance of many patients with cancer. This depletion is associated with elevated fat oxidation rates; however, the abnormalities in fat metabolism can be attributed to reduced lipogenesis as opposed to increased lipolysis rates. This may be secondary to decreased levels of lipoprotein lipase (LPL), which can also result in a type IV hyperlipidaemia. The raised level of circulating lipids is thought to facilitate the provision of energy for the host, but as with carbohydrates, these lipids may be providing the tumour with additional nutrients to meet its metabolic requirements^{6, 10, 21}.

Similar to the loss of fat stores, muscle wasting is another prominent feature of CC and is a major factor responsible for reduced survival time in cancer patients. However, despite an increased whole-body protein turnover, which appears to increase with disease progression, protein breakdown rates in cancer patients have not been found to be very different from controls. Instead there appears to be a decrease in protein synthesis producing a net protein breakdown. There also appears to be reprioritisation of hepatic protein synthesis, also referred to as the acute phase response, which has been associated with the acceleration of weight loss seen in patients with cancers such as pancreas, lung and melanoma. It is also possible that the acute phase response contributes to shortened survival by accelerating the

development of muscle wasting as a result of greater demand for amino acids to support increased hepatic export protein synthesis^{6, 10, 18, 20, 21, 23}.

Although it has been established that a tumour could be regarded as a new organ, which contributes to an increased demand for nutrients and to weight loss if these requirements are not met, the presence and severity of the cachexia correlates poorly with the size of tumour and cannot provide an explanation for the early clinical manifestations such as a change in appetite and altered nutrient metabolism. It is therefore thought that the metabolic changes could be the result of mediators produced by the tumour or the host's response to the tumour. Such mediators include neurotransmitters, cytokines, neuroendocrine hormones and tumour-specific products^{10, 20, 21}.

Proinflammatory cytokines such as tumour necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), interferon gamma (INF- γ) and ciliary neurotrophic factor (CNTF) have been implicated in the development of CC. Administration of these cytokines in animals produces anorexia, weight loss, an acute phase protein response, protein and fat breakdown, raised levels of cortisol and glucagon, decreased insulin levels, insulin resistance, anaemia, fever and elevated energy expenditure. Identifying raised levels of these cytokines and the effects thereof in humans has been more difficult; however, the cachectic effects are thought to be the action of a combination of pro-inflammatory cytokines as opposed to individual cytokines acting alone^{20, 21, 24}.

Changes in hormone regulation and sensitivity, independent of the cytokine network, may also play a role in the pathogenesis of CC. The administration of the hormones cortisol, glucagon and adrenaline in humans produces features of CC. Furthermore, raised levels of cortisol and glucagon have been observed in people with cancer, which is thought to amplify the acute phase response. The raised levels of cortisol is also thought to alter the cortisol:insulin ratio which in turn may contribute to the catabolism of peripheral tissues. Therapeutic manipulation of these hormonal changes are, however, difficult to achieve and may interfere with what is thought to be an adaptive response^{6, 10, 21}.

The inability of cytokines to independently induce cachexia in an experimental model has led to the identification of additional potential mediators, which are thought to be tumour-derived. Proteolysis-inducing factor (PIF) and lipid mobilizing factor (LMF) have been identified in the urine and tumour cells of weight-losing cancer patients but not in weight stable patients. PIF is therefore thought to play a role in protein breakdown and non-fat weight loss whereas the LMF can account for the loss of body fat and possibly contribute to the increase in energy expenditure^{18, 20, 21, 24}.

Gaining greater understanding of the different mediators and their roles in the development of CC in humans may provide the opportunity and potential to better manage and improve the quality of life of patients with cancer cachexia.

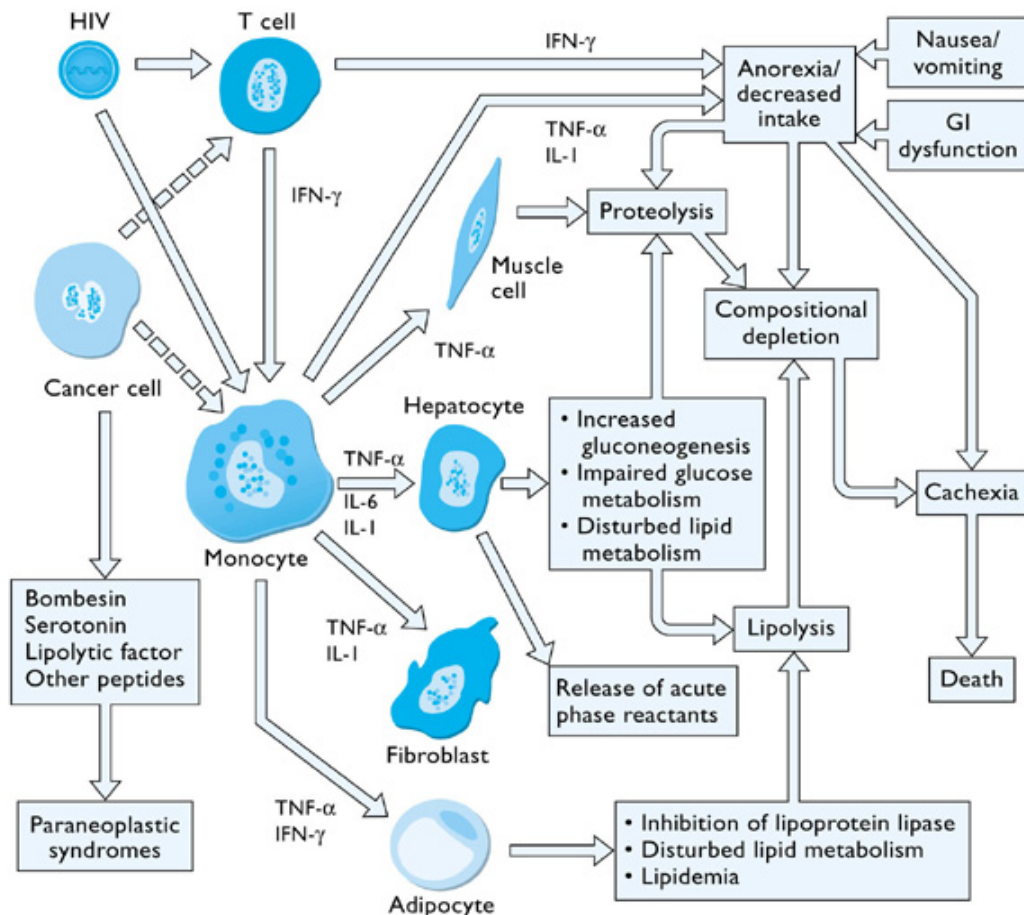


Figure 1.1 Metabolic effects of tumours²⁵

1.1.4 Intervention and management of cancer cachexia

Managing cancer cachexia is challenging. Curing the cancer would be the ideal intervention; unfortunately this remains a rare achievement in adults with solid tumours. The alternative approach is therefore to consider the role of nutrition intervention in order to increase nutritional intake^{13, 20, 24}.

The goal of nutrition support in the cancer patient should be to minimise weight loss, prevent nutrient deficiencies, support immune function, aid tissue repair and wound healing and ultimately contribute towards maintaining and / or improving quality of life²⁶.

Options to achieve such goals can vary from dietary counselling and oral supplementation to the use of enteral and parenteral nutrition. It was hoped that these options would be adequate to help overcome anorexia and alleviate malnutrition. Unfortunately, such interventions have repeatedly shown that despite an increase in total energy intake, there is little change in terms of weight, anthropometric measurements, response rate, survival or quality of life. Parenteral nutrition has also been associated with its own complications, difficulties with long-term use thereof, and it has failed to show any significant survival benefit or decrease in chemotherapy-induced toxicity. Although there is a lack of clinical evidence, there still remains a certain amount of controversy regarding the effect that nutrition support has on tumour growth and development^{13, 18, 21, 27}.

Despite the inability of nutrition support to influence or reverse the effects of cancer cachexia, it remains an important means of intervention for a certain subset of patients. More careful consideration regarding appropriate patient selection and route of administration needs to be given to ensure that the intervention is going to be effective.

The limitations of conventional nutrition support to effectively manage cancer cachexia have led to the use of a number of pharmacologic agents to try to modulate the underlying metabolic problems, thus improving the effectiveness

of the nutrition intervention, and to treat or provide symptomatic relief for patients with CC^{6, 21}.

The most widely used pharmacologic agents for cancer cachexia are corticosteroids and progestational agents. Corticosteroids are frequently used for their appetite stimulating effects and to increase well being. They have a significant anti-nausea effect and help control asthenia and pain. The effects are, however, short-lived, and any change in weight is usually an accumulation of fluid as opposed to body weight gain. In addition to this, the use of corticosteroids is associated with other adverse effects such as oedema, muscle weakness, dysphoria, hypokalaemia, hyperglycaemia and immune suppression, that limit their use to the preterminal phase of disease (Table 1.1). Similarly the use of anabolic steroids has also been suggested as an appetite stimulant but the associated adverse effects also limit their use^{13, 18, 20, 21}.

Progestational agents such as megestrol acetate (MA) and medroxyprogesterone acetate (MPA) were initially used in the treatment of metastatic breast cancer. The unwanted weight gain and appetite enhancement seen in these patients using these agents led to them being used in patients with CC (Table 1.1). Further trials using these agents have found that they are well tolerated at high doses and have few adverse effects. The mechanism of action remains unknown but following the finding that serum levels of cytokines decreased with the use of MA and MPA, it has been suggested they have steroid-like effects. Unfortunately, despite the appetite enhancement, the weight gain seen with MA is adipose and not lean body mass (LBM) and the use of MPA failed to show an improvement in weight, performance status, energy or mood. Of more concern is that a recent trial with MA showed that patients had a poor response to chemotherapy and a trend to poorer survival^{13, 18, 21}.

Prokinetic agents such as metoclopramide may be beneficial in the relief of nausea, anorexia and early satiety associated with gastric stasis (Table 1.1). The roles of other prokinetic agents still require further investigation^{13, 18}.

Hydrazine sulphate, tetrahydrocannabinol derivatives, cyproheptadine, pentoxifylline are further examples of other agents that have been used in the management of CC. The greatest impact is on appetite and nausea, but unfortunately they have failed to prevent further weight loss, and there remain uncertainties with regards to the safe use of some of them^{6, 13, 18, 21}.

There are other drugs now being considered for the management of CC. Limited evidence is available regarding their potential use. However, larger randomized studies are needed to assess the efficacy of these new options. These include melatonin, thalidomide, β 2-agonists and NSAIDs¹⁸.

A further future consideration with the management of CC is the role of combination therapy. In other words, maybe the combination of diet intervention with one or more of the pharmacological agents will be more effective than the current approach. Such options will, however, need to be investigated. Nevertheless, emerging evidence on the combination of MA (progestational agent) and Ibuprofen (NSAIDs); suggests that this combination may stabilize quality of life and weight in advanced gastrointestinal cancer^{20, 21}.

Table 1.1 The main pharmacological agents used in the management of cancer cachexia^{6, 13}

CLASSIFICATION	NAME OF AGENT	POTENTIAL BENEFITS IN MANAGING CANCER CACHEXIA	REASONS FOR LIMITED USE IN PATIENTS WITH CANCER
Steroids	Corticosteroids	Appetite stimulant Increased sense of well being Anti-nausea	Oedema Muscle weakness Dysphoria Hypokalaemia Hyperglycaemia Immunosuppressive
	Anabolic steroids	Appetite stimulant	
Progestational Agents	Megesterol Acetate	Appetite stimulant	Weight gain mainly adipose and not LBM Possible poorer response to chemotherapy Possible trend to poorer survival
	Medroxy-progesterone	Appetite stimulant	No improvement in weight, performance status or mood
Prokinetics	Metoclopramide	Anti-nausea Anti-anorexic Increases gastric motility	

1.2 *n*-3 Fatty acids and cancer cachexia

In evaluating new therapies to treat cancer cachexia, the role of omega-3 (*n*-3) fatty acids in cancer has only recently been considered. Initial interest in *n*-3 fatty acids stems from the association of the high *n*-3 diet of Greenland Eskimos and their low incidence of cancer and coronary heart disease.

Omega-3 fatty acids are long-chain, polyunsaturated fatty acids which cannot be synthesised by the human body, they are thus an essential part of the diet²⁸. They are derived from plant and marine origin and are found in the diet as a component of oily fish, flaxseed, hemp, canola and walnut oils. The *n*-3 fatty acids are involved in the synthesis of eicosanoids (prostaglandins, leukotrienes, and thromboxanes) and in membrane, receptor and enzyme function. The major metabolically active *n*-3 fatty acid component of oily fish is eicosapentanoic acid (EPA). Similarly, the metabolically active *n*-3 fatty acid component of plant sources is alpha linoleic acid which is metabolised in the liver to EPA²⁸.

Omega-3 fatty acids and its role and actions in cancer cachexia are multifaceted. It would appear that EPA is able to affect the production and end organ effects of a number of potential mediators of cachexia^{20, 29-31}.

The eicosanoids and prostanoids, such as PGE₂, produced by the malignant tumour are thought to encourage angiogenesis and metastasis. However, results from several animal studies are indicating that by enriching the diet with fish oil, the EPA is able to alter the metabolism and production of the prostaglandins and leukotrienes and thus play a role in growth of tumour cells. Although complete tumour inhibition has not been observed, there is certainly tumour cell growth retardation, which warrants further research. Furthermore, a decrease in the formation of the immunosuppressive PGE₂ is also associated with a probable improvement in the host's immunologic defence against cancer^{29, 30, 32, 33}.

Further experimental studies have shown that the administration of EPA reduces the production of the cytokines IL-6, IL-1 and TNF in healthy subjects, and TNF and IL-6 in patients with pancreatic cancer, and the effect appears to be maintained for weeks following the supplementation. The mechanism of action occurs through the substitution of EPA for arachidonic acid (AA), which results in decreased cytokine and prostanoid production^{20, 30, 31, 33}.

Animal studies have also been able to show that EPA can inhibit fat and protein breakdown, and this is possibly attributable to EPA's inhibition of the end-organ effects of the tumour-derived lipolytic and proteolytic factors^{20, 29, 31, 34}. A clinical trial investigating the effects of EPA supplementation on the mediators of cachexia found that three weeks of supplementation produced a significant decrease in PIF levels excreted in the urine³⁴.

Completed clinical trials using EPA supplements have found that it promotes weight maintenance, improves food intake, inhibits tumour growth and may improve survival. It therefore appears that EPA has the potential to be an

effective non-toxic, anti-cachectic and anti-inflammatory agent. To enhance these effects, trials using an *n*-3 enriched nutritional supplement have been and continue to be carried out. The motivation to use such an enriched supplement is to modulate the process of cachexia with the EPA as well as supply additional energy and protein to encourage an improvement in weight and lean body mass and thus ultimately contribute to improved functional ability^{20, 30, 32, 35}.

1.3 Motivation of the study

The purpose of this study was to systematically review the available evidence on the safety and efficacy of EPA supplementation derived either from an *n*-3 enriched nutritional supplement or as fish oil capsules in patients with pancreatic malignancy, and to search for evidence of trials that have incorporated cancers other than pancreatic cancer.

Although the results are favourable and appear to be associated with few adverse effects, there is little data available with regards to achieving similar benefits with *n*-3 enriched nutritional supplements used in other cancers associated with cancer cachexia. Similarly there is little evidence considering the impact that the use of *n*-3 enriched nutritional supplements will have on a patient's quality of life.

The findings will facilitate the implementation of guidelines for medical professionals with regards to the use of *n*-3 enriched nutritional supplements in cancer.

CHAPTER 2: METHODOLOGY

2.1 AIM AND OBJECTIVES OF STUDY

2.1.1 Aim

The initial aim was to perform a systematic review of randomised controlled trials regarding the safety and efficacy of *n*-3 enriched nutritional supplements in the treatment of cancer cachexia in adult patients with unresectable solid tumours.

The search and selection of studies according to this criteria was, however, very disappointing because there were far fewer studies on the topic than anticipated; the scope of the study was therefore extended to include Phase I, Phase II and Phase III (RCT) trials investigating the safety and efficacy of *n*-3 supplements and *n*-3 enriched nutritional supplements in the treatment of cancer cachexia in adult patients with unresectable solid tumours. The latter criteria form the basis of this study.

2.1.2 Objectives

The primary objectives of the review were as follows:

- To establish if the use of an eicosapentaenoic acid (EPA) supplement can attenuate or reverse the weight loss experienced in patients with cancer cachexia
- To establish the effect that the use of an EPA supplement will have on body composition in patients with cancer cachexia
- To establish if appetite and dietary intake in patients with cancer cachexia is altered following the use of an EPA supplement
- To establish if the use of an EPA supplement can influence energy expenditure in patients with cancer cachexia
- To establish if the use of an EPA supplement can improve functional status in patients with cancer cachexia
- To establish the influence EPA supplements may have on the acute phase response in patients with cancer cachexia
- To establish if the use of EPA supplements can improve the quality of life of patients with cancer cachexia. Quality of life is usually assessed

by means of a questionnaire considering a combination of mental, emotional and physical aspects.

- To define any adverse effects associated with the use of EPA supplements

The secondary objective of the study is as follows:

- To determine if trials have considered the use of EPA supplements in cancers other than pancreatic cancer (majority of the studies used patients with pancreatic cancer)

2.2 STUDY PLAN

2.2.1 Study Design

A systematic review of Phase I, Phase II and Randomised controlled trials.

2.2.2 Scope of the study

The studies that were reviewed related to adult patients with an unequivocal diagnosis of cancer with symptoms of cancer cachexia, who received EPA supplementation either in the form of a fish oil capsule or as an enriched nutritional supplement.

2.3 LITERATURE SEARCH

A search of several sources of evidence was completed during May and June 2004. To establish the extent to which this topic has been researched, the search period was initially not restricted; however, for final inclusion in the review, studies must have been completed in the last ten years to ensure that this study's findings are based on the most recent evidence available. Search results were limited to English. Although this initial search used very broad search criteria (Table 2.1) and was not very specific, it did allow for the maximum number of potentially relevant studies to be identified. Once these were identified, stricter inclusion and exclusion criteria were applied to these studies for final inclusion (Table 2.7).

Table 2.1 Initial selection criteria used to identify potentially relevant studies

SELECTION CRITERIA	KEYWORDS AND RESTRICTIONS USED IN SEARCHES
Study Population	- Not restricted to adults at this stage - Cancer and related terms
Intervention	- Nutritional supplements - Fish oil supplements - <i>n</i> -3 fatty acids and related terms
Study Design	Not restricted at this stage
Language	Restricted to English
Search Period	Not restricted at this stage

2.3.1 Electronic Bibliographic Databases

The major databases, MEDLINE, CINAHL, EMBASE, Ovid, The Cochrane Library, Zetoc and NHS CRD databases (DARE & NHS EED) were searched to identify potential relevant citations.

The following search strategy was devised and entered into the databases that allowed a structured keyword search to be used:

1. exp. Cancer /
2. tumour.mp
3. 1 or 2
4. exp.eicosapentaenoic acid /
5. exp.fish oil /
6. exp. Omega-3 fatty acids /
7. nutritional supplement.mp
8. (fish oil adj2 supplement).mp
9. 4 or 5 or 6 or 7 or 8
10. 3 and 9

Various combinations of these keywords were used to search databases that did not allow for a structured keyword search to be used. A disadvantage of the unstructured keyword search was that it increased the likelihood of relevant information being overlooked. To minimise this effect, broader search terms were used.

On completion, this search produced 405 citations of which 85 were selected by the principal reviewer as potentially relevant citations (Table 2.2). They were selected according to the criteria specified in Table 2.1.

Table 2.2 Summary of the electronic databases searched and number of potentially useful citations identified

DATABASE	PERIOD SEARCHED IN DATABASE	TOTAL CITATIONS*	POTENTIALLY USEFUL CITATIONS
MEDLINE/EMBASE/CINAHL	1951-/1974-/1982-2004	140	41
OVID	1950-2004	55	6
ZETOC	Not specified	188	35
DARE/NHS EED	Not specified	20	1
COCHRANE LIBRARY	Not specified	2	2
Total		405	85

*Totals have been corrected for duplicate citations

2.3.2 Research Registers

Local, national and specialist research registers were searched for data regarding recently completed and ongoing research. Various combinations of the keywords produced a total of 64 citations (Table 2.3). According to the specified selection criteria (Table 2.1), the principal reviewer selected 15 potentially relevant citations.

Table 2.3 Summary of the research registers searched and the number of potential citations identified

RESEARCH REGISTER	TOTAL CITATIONS*	POTENTIALLY USEFUL CITATIONS
NRR	15	13
<i>meta</i> Register of clinical trials	49	2
UK CCCR	0	0
NCI	0	0
CORDIS	0	0
Total	64	15

*Totals have been corrected for duplicate citations

2.3.3 Internet

The Internet is another option to search for completed and ongoing research; it would however be an enormous task unless a structured approach is used. As per recommendation the following *meta* search engines were searched:^{2, 36}

www.copernic.comwww.dogpile.comwww.omni.ac.ukwww.mednets.com/

As with the databases and registers, the same combinations of keywords were entered into each search engine. The search produced a total of 929 sites, many of which were the same. Unfortunately, combining the results from each search to produce a more accurate total number of citations found would have been too complex and time consuming. After duplicates were eliminated, the principal reviewer selected potential citations from each search according to the specified selection criteria (Table 2.1). The search on the internet produced 20 potential citations, of which the findings are summarised in Table 2.4.

Table 2.4 Summary of the internet search and number of potential citations identified

META SEARCH ENGINE	TOTAL CITATIONS	POTENTIALLY USEFUL CITATIONS
www.copernic.com	478	20
www.dogpile.com	398	
www.omni.ac.uk	42	0
www.mednets.com/	11	0
Total	929	20

2.3.4 Investigators and manufacturers

Investigators who had completed trials on this topic were consulted via email to establish whether there was further information regarding ongoing research that could be considered for this review. The manufacturers of the *n*-3 enriched nutritional supplement were approached for any literature that could contribute to the comprehensiveness of this literature search.

The response received from investigators was varied. Prompt responses from some investigators facilitated the search process, but unfortunately, despite several attempts, some investigators failed to respond. Only 2 investigators were able to provide further information which facilitated the search.

2.3.5. Reference Lists, Conference Proceedings and Grey Literature

To ensure that relevant studies were not overlooked in the electronic searching, the reference lists of primary studies and reviews were scanned manually to identify further studies which could be considered for the systematic review. Any other format, which might have not been indexed in the major databases, was searched for on SIGLE (System for Information on Grey Literature). Similarly, the following databases on conference proceedings were searched for information regarding ongoing research: ISTP (Index to Scientific and Technical Proceedings), Dissertation Abstracts, Index of Conference Proceedings, and Conference Papers Index (Table 2.5).

Table 2.5 Summary of the search for grey literature

DATABASE SEARCHED	RESULTS
Research findings register	None
NHS Research and development health technology assessments	None
National Technical Information Service	None
SIGLE	None

2.4 INCLUSION AND EXCLUSION OF STUDIES

Upon completion of the literature search, 96 potentially relevant studies had been identified. Animal studies, language, and studies on other topics were the main reasons for exclusion.

The search strategy was more sensitive than specific, but this did ensure that more primary studies could be identified and used to review reference lists. Many of the studies considered to be relevant were review articles as opposed to clinical trials, but were included in this part of the search to facilitate the search of reference lists, thereby ensuring that no trials were overlooked.

During July 2004 – August / September 2004 the full reference of the 96 relevant studies were requested, of which only 76 were available for further review (Table 2.6)

Table 2.6 Initial exclusion of studies

REASON FOR EXCLUSION	NUMBER OF STUDIES EXCLUDED
Failed requests	7
Language	1
Study not requested	1
Current trial with no available results	2
Completed trial with no available results yet	9*
TOTAL EXCLUDED STUDIES	20

* Although the initial search identified them as 9 individual trials, they are part of the same multicentre trial

Table 2.7 Inclusion and exclusion criteria for the final selection of studies

Inclusion Criteria	Exclusion Criteria
Adult patients with solid tumours	Adult patients with other cancers (E.g. leukaemia)
Patients receiving only EPA supplements or EPA enriched nutritional supplements	EPA supplements or EPA enriched nutritional supplement in combination with other nutritional supplements
1 or more of the following outcomes <ul style="list-style-type: none"> - Attenuation or reversal of weight loss - Change in body composition - Change in energy expenditure - Change in appetite or dietary intake - Change in functional status - Alteration in tumour growth or acute phase response - Improvement of quality of life - Adverse affects associated with the EPA supplementation 	Outcomes not considered in the objectives
Phase I, II, III (RCT) controlled trials	Other study designs
Studies completed between 1994-2004	Studies completed prior to 1994

Two independent reviewers applied the inclusion and exclusion criteria to the 76 studies and identified 16 studies that could be included in this study. A third reviewer was required to settle a disagreement regarding the inclusion of two of the studies, both of which were finally included (Figure 2.1). The reviewers that assisted in the selection process were both allied health professionals and despite their experience, neither was expert in this particular topic. The risk of selection bias was therefore minimised.

There were a variety of reasons (Table 2.8) for studies being excluded. A more detailed list of the characteristics of excluded studies has been appended (Appendix 6.4) for reference purposes.

Table 2.8 Summary of the reasons which excluded studies after the final selection process

REASON FOR EXCLUSION	NUMBER EXCLUDED
Animal studies	10
Review articles	29
Abstracts / Protocols	10
Commentaries / Letters	5
Not meeting inclusion criteria	5
Other	1
TOTAL NUMBER OF STUDIES EXCLUDED	60

To maintain anonymity and reduce the risk of publication bias, all the studies were allocated a study identification number (Appendix 6.4-6.5). The included studies' identification numbers (Appendix 6.5) were used throughout this study in the data extraction forms, tables and figures. The full references and their corresponding identification number are listed in the appendix.

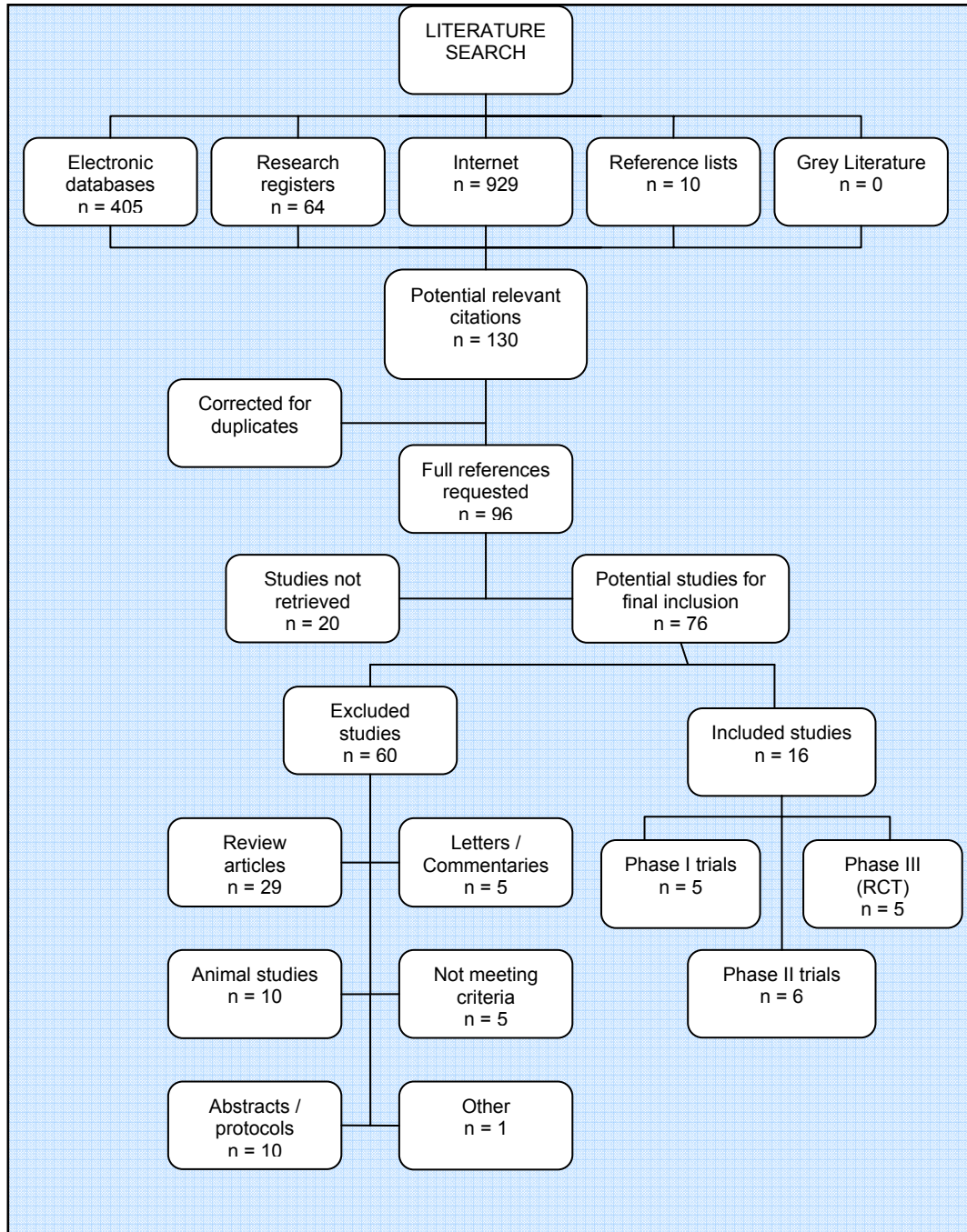


Figure 2.1 Diagrammatic representation of the process followed in the selection of studies

2.5 QUALITY ASSESSMENT OF INCLUDED STUDIES

Randomised controlled trials are generally regarded as the best means of assessing medical interventions. However, variation in internal validity could influence the results of trials and thus influence the effect size of the review. As bias can affect internal validity,² it is essential to utilise a means to assess

the quality of primary studies. To assess the quality of studies included in this study, a scale developed by Jadad *et al*³⁷ was used.

This particular scale considers the four main sources of bias in trials, namely selection, performance, measurement and attrition bias, and has been selected for its simplicity and validity (Appendices 6.6- 6.7). An additional benefit of this scale is that reviewers do not need to be familiar with the topic or have research experience³⁷.

Using the quality assessment tool (Appendix 6.7), two independent reviewers scored each of the included studies. Table 2.9 and 2.10 summarises the scores and associated quality of these studies as well as differentiating between the quality of the different study designs. Appendix 6.8 provides a detailed description of each study's quality assessment.

The quality of the studies was incorporated in the analysis of data as a means of establishing the extent of heterogeneity and to assist decision-making regarding the suitability of the included studies for meta-analysis².

Table 2.9 Study quality and scores of included trials

STUDY SCORE	STUDY QUALITY	NO. OF STUDIES (n)
Less than 3	Poor	12
3 and above	Good	4

n represents the number of studies

Table 2.10 – Study quality according to study design

TRIAL TYPE	STUDY QUALITY (n)	
	Good	Poor
Phase I	0	5
Phase II	0	6
Phase III (RCT)	4	1
TOTAL	4	12

n represents the number of studies

2.6 DATA EXTRACTION

The principal reviewer collected the data. To ensure that the data collection was thorough and standardised, tables were designed for each of the outcomes being investigated (Appendices 6.9.1 – 6.9.11).

One of the independent reviewers assisted with the data collection in situations where the required data was not clearly reported in the studies included in the review. To enable and ensure that the objectives of this review were met, investigators of the included studies were contacted for data that had been measured but not reported, and in some situations, for clarification on data that was reported. Unfortunately, there was a very poor response from the investigators who were contacted. Only one investigator provided the additional information that was requested.

2.7 STATISTICAL ANALYSIS

The Faculty of Health Science, University of Stellenbosch allocated a statistician to assist with the analysis of the data.

Descriptive or non-quantitative analysis of the tabulated data provided a summary of the characteristics of the included studies enabling comparisons to be made between interventions and outcomes within the specified population. The descriptive analysis also provided the basis whereby a decision could be made as to the suitability and appropriateness of the data for quantitative analysis (meta-analysis).

Ideally being able to perform a meta-analysis would have allowed a measure of effect of the intervention to be calculated between outcomes of the experimental group and the control group of individual studies. This would have enabled the direction and magnitude of the treatment effect to be determined.

The data that was collected was unfortunately too sparse and the different methods of intervention, trial designs and quality have made the data too heterogeneous to perform quantitative analysis.

Although meta-analysis could not be performed and despite the data being inconsistent and incomplete, statistical analyses on the baseline and end of treatment data were performed using *Excel* and *Statistica 7* data analysis programmes. Ordinarily this data should have been tested for normal distribution, but given the lack of adequate data, it was assumed that there was a normal distribution to allow the opportunity to calculate if there is a difference following the period supplementation with EPA. The paired t-test was used for this calculation. In situations where the data was not normally distributed, the Wilcoxon test was used instead of the paired t-test. Although this test was used and reported in the results section, it must be noted that the analyses only incorporated very small study numbers, which will have an influence on the strength of the results and should not be relied upon in the interpretation thereof.

2.8 ETHICS CONSIDERATIONS

The research protocol for the study was approved by the Ethics Committee, Faculty of Health Sciences, Tygerberg, University of Stellenbosch, South Africa (N04/03/051 Appendix 6.1). Approval was obtained to proceed with this review.

CHAPTER 3: RESULTS

3.1 CHARACTERISTICS OF STUDIES INCLUDED

This study comprised of the evaluation of 16 studies. Eleven of the studies were Phase I and II trials and 5 were Phase III trials/ RCT. Twelve of the studies were of poor quality (Table 2.10, Appendix 6.8).

3.2 CHARACTERISTICS OF THE REVIEW POPULATION

The studies included in this study engaged a total population of 640 patients at baseline, of whom the majority had been treated with EPA [Controls (n=227) versus Treated (n=413)]. There was a mean drop-out rate of 35% by the end of the treatment period, which reduced the treated population to a total of 269 patients [Control (n=160) versus Treated (n=269)] (Table 3.1). The drop-out rate of patients using capsules compared to an enriched nutritional supplement was 46% and 36% respectively (Table 3.2). The treated population comprised 184 men and 147 women with a mean age of 62.2 years; the median age was 63 years and the age range was 56 – 67 years. The median weight loss experienced among the patients at the pre-treatment stage was 16% (mean weight loss was 15.1%) over a median period of 6 months duration (mean 4.9 months) as opposed to the control patient group who lost a median of 11.8 – 14.6% (mean 12.3%) of their body weight over a period of 6 months duration (Table 3.1, Appendix 6.9.2).

It must be noted that not all 16 studies provided complete details. The discrepancies that exist in the total number of patients are as a result of calculations being made in this study with the available reported data, which were not necessarily consistent or accurate. The means and medians were also only based on the number of studies that had adequate details.

Table 3.1 Summary of study population characteristics

POPULATION CHARACTERISTIC	CONTROLLED STUDIES (n= 7)		UNCONTROLLED STUDIES (n=9)	TOTAL (n=16)
	TREATED	CONTROL	TREATED	TREATED ONLY
Size at baseline	223	227	190	413
Size at end of treatment**	154	160	115	269
Male:Female***	105:84	94:100	79:63	184:147
Median age	64	64	62 (n=7)*	63 (n=14)*
Median % weight loss (pre-treatment)	17.7 (n=7)*	11.8 - 14.6 (n=7)*	13.5 (n=6)*	16 (n=13)*
Mean period of time over which weight loss occurred (months)	6 (n=3)*	6 (n=3)*	4.1 (n=4)*	4.9 (n=7)*
SUPPLEMENT USED				
- EPA capsules	3	-	7	10
- ENS	4	-	2	6

* The number of studies providing details

** 4 Studies did not specify details regarding withdrawals, therefore an assumption has been made that the sample size at the end was the same size as at baseline – this may not therefore be an accurate representation of the sample sizes at the end of treatment

*** 3 studies did not specify the ratio of males to females and 1 study based their ratio on the number of people that completed the trial, compared to all the other studies that have based it on their baseline characteristics

EPA – Eicosapentaenoic acid

ENS – Enriched nutritional supplement

Table 3.2 Summary of the % drop-out calculated according to the type of supplement that was used

SUPPLEMENT USED	POPULATION AT BASELINE (n)	POPULATION AT END OF TRIAL (n)	% DROP-OUT
ENS	178	122	36%
Capsules	235	147	46%
Total	413	269	35%

n - Represents the number of patients in the study population

ENS – Enriched nutritional supplement

The majority of the patients [Controls (n=142) versus Treated (n=271)] included in the studies had cancer of the pancreas. Only 5 of the 16 trials included in this review considered other tumour sites. A total of 17 tumour sites were included in these studies (Table 3.3). Although the inclusion criteria specified that only studies with solid tumours were going to be included, there were three studies which included patients with solid tumours as well as other types of tumours. The total number of patients with tumours not classified as solid was 6 [Control (n=1) versus Treated (n=5), where n=number of patients],

which represented 0.9% of the total study population and 1.2% of the Treated population. These studies were included in the data analysis to avoid excluding 18.6% of the total study population and 22% of the Treated population who did have solid tumours, thereby potentially influencing the results of this review.

Table 3.3 A detailed representation of the tumour sites of the study population

TUMOUR SITE	CONTROLLED STUDIES (n= 7)		UNCONTROLLED STUDIES (n=9)	TOTAL (n=16)
	TREATED	CONTROL	TREATED	TREATED ONLY*
- pancreas	144	142	127	271
- genitourinary	7	5	2	9
- breast	9	12	3	12
- gastrointestinal	25	22	2	27
- lung	12	12	18	30
- liver	4	3	2	6
- colorectal/anal	1	0	10	11
- renal	1	0	3	4
- head and neck	1	0	1	2
- sarcoma	1	2	3	4
- neuroendocrine	0	0	3	3
- myelodysplastic syndrome	0	0	2	2
- myeloma	0	0	1	1
- carcinoid	0	1	0	0
- haematologic	0	1	2	2
- mesothelioma	0	1	0	0
- unknown	2	5	8	10

* These totals are only approximate totals as some studies classified tumour sites at baseline whereas other studies used the data collected at the end of the trial

A graphical representation (Figure 3.1) of the size of the study populations of the 16 studies shows the decrease in sample size in the Treated and Control groups from baseline to the end of the period of intervention. Interestingly, only 1 of the 16 studies had Treated and Control group sizes that exceeded 50 patients. Missing data from 2 of the 16 studies enabled only baseline sample sizes to be represented.

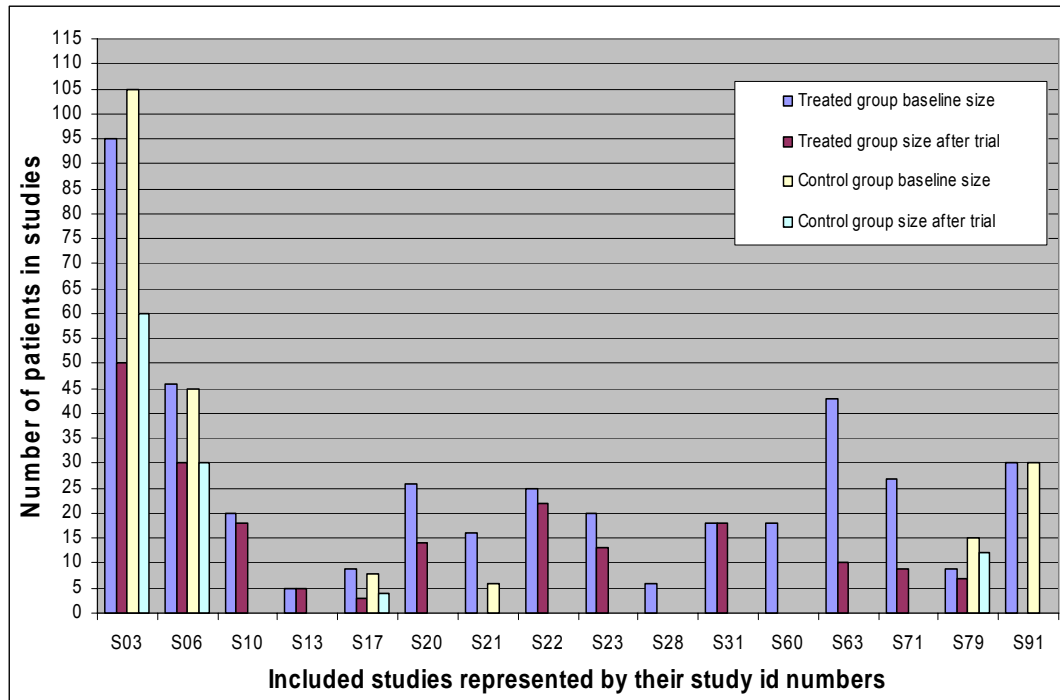


Figure 3.1 Study population sizes of the included studies at baseline and after intervention
Study ID – Study Identification number

3.3 CHARACTERISTICS OF THE SUPPLEMENTS USED AND TRIAL PERIOD

In studies (n=15) that specified the period of intervention, the duration ranged from 2 – 24 weeks (mean and median duration of the trials was 8.2 – 8.5 weeks and 8 weeks respectively).

The minimum duration that the enriched nutritional supplement (ENS) was used was 3 weeks and the maximum was 8 weeks. In comparison, the minimum duration that the capsules / emulsion were used was 2 weeks and the maximum was 24 weeks. Interestingly, in the latter study, Barber MD *et al* (S23)³⁴ there was 100% compliance of the prescribed regime.

Ten of the included studies used fish-oil capsules as their EPA supplement; the remaining 6 studies used a nutritional supplement enriched with *n*-3 fatty acids (Table 3.4).

Table 3.4 The type of supplement used according to study design

	ENRICHED NUTRITIONAL SUPPLEMENT (n=6)	CAPSULES / EMULSION* (n=10)
Phase I trials	2	2 + 1*
Phase II trials	2	4
Phase III trials (RCT)	2	3

* 1 study made use of an n-3 fatty acid emulsion

RCT – Randomised Controlled Trials

Of the 16 studies, the 6 studies that used the ENS appeared to have used the same product and prescribed the same volume of this supplement per day. The target intake was 2 x 237ml cans per day, providing 2.2g EPA per day. The average actual intake that was reported by 5 of the studies ranged from 1.4 – 1.9 x 237ml per day, which provided 1.25 – 2.0g EPA per day. One study did not report the actual intake of the supplement during the trial period (Table 3.5).

The remaining 10 studies used a variety of EPA supplements. They were introduced and administered either as fish oil capsules or as a liquid emulsion in varying doses that ranged from 0.34-36 g EPA per day and was increased at weekly intervals until a maintenance dose was achieved. Although the maximum dose tolerated was 36g/d (Barber MD *et al* (S23)³⁴), only 2 patients in this particular study managed to achieve this dose and they were only able to tolerate it for 1 week (specific reasons for this dose not being tolerated for longer were not reported). Compliance with the prescribed trial amount ranged from 50 – 100% (Figure 3.2). In the two studies of Burns CP *et al* (S22,S63)^{38,39}, patients managed to consume more than the prescribed dose; the actual intake was therefore 127% and 300% of the target intake respectively (Table 3.5).

Although both types of supplementation had good compliance during the study periods, it appeared that a higher dose of EPA was tolerated with the capsules than with an ENS drink.

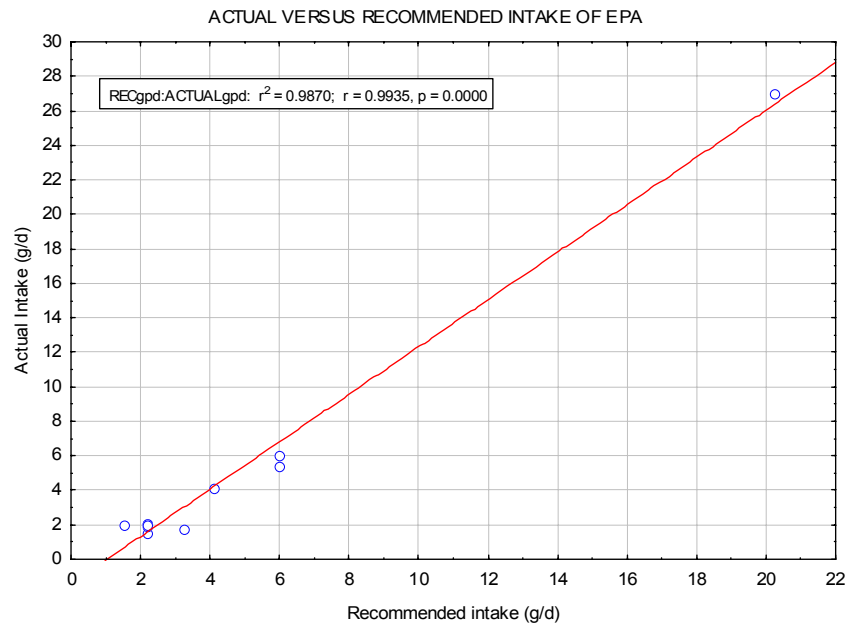


Figure 3.2 The actual intake of EPA versus the target intake of EPA

Table 3.5 The target intake compared to the actual intake of the EPA supplements

STUDY ID / TRIAL	RECOMMENDED INTAKE OF EPA / d (g)	ACTUAL INTAKE OF EPA / d (g)	COMPLIANCE (%)
ENS			
S3 / RCT	2.2g	1.54g	70%
S79 / RCT	2.2g	2.0g	91%
S21 / PI	2.2g	1.4 – 2.2g	63 – 100% (median 95%)
S23 / PI	2.2g	1.32 – 2.2g	60 – 100%
S10 / PII	2.2g	1.4 – 2.2g	63 – 100% (median 95%)
S60 / PII	2.18g	Not reported	-
CAPSULES			
S6 / RCT	3.24g	1.76g	54%
S17 / RCT	6.0g	5.4 – 6.0g	90 – 100%
S91 / RCT	3.06g	Not reported	?100%
S13 / PI	4.5 – 36g	18 – 36g	50 – 100%
S22 / PI	0.0378g /kg/d ~ 2.34g /d*	0.0378 – 0.1134g/kg/d ~ 2.34g – 7.03g /d*	100 – 300%
S28 / PI	1 – 6g	1-6g	100%
S20 / PII	1.0 – 6.0g	Not reported	-
S63 / PII	0.067g/kg/d ~ 4.3g / d*	0.067 – 0.086g/kg/d ~ 4.3 – 5.5 g / d*	100 – 127%
S31 / PII	0.34 – 2.72g	2g	74%
S71 / PII	2.2 – 2.9g & 6g	2.2 – 6g	100%

*To calculate the amount of EPA/day, the median weight of patients at entry to the study was used

Study ID – Study Identification number

EPA – Eicosapentaenoic acid

ENS – Enriched nutritional supplement

3.4 CLINICAL OUTCOMES

3.4.1 Weight change

Fourteen studies measured the change in weight following supplementation with either ENS or capsules (Appendix 6.9.4). There was baseline data for 11 of the 16 studies; unfortunately only 7 studies provided complete weight data for during or after intervention (Table 3.6).

Table 3.6 – Summary of weight data recorded by included studies

Study ID	INTERVENTION	WEIGHT (kg)						
		0 wks	3 wks	4 wks	7 wks	8wks	12wks	24wks
S3	ENS	60.3		60.05*		59.8*		
S21	ENS	55.2	56.2					
S23	ENS	55.2	56.2		57.2			
S60	ENS	55.0	**					
S6	Capsules	60.8				60.83		
S17	Capsules	67					**	
S20	Capsules	66.8		66.0		65.2	65	
S22	Capsules	62				**		
S31	Capsules	62		63			62	
S63	Capsules	64		**				
S71	Capsules	68.8		66.0		65.2	64.5	62.2

* Significant change in weight reported by investigators of that particular study

** Weight at the end of intervention not available

Study ID – Study Identification number

ENS – Enriched nutritional supplement

The mean weight at baseline of the Treated group was 61.6 kg (SD 4.92, n=11 of 16 studies) and that of the Control group was 61.0 kg (SD 1.87, n=4 of 16 studies). The mean weight of the Treated group after intervention was 61.7 kg (SD 2.75, n=8 of 16 studies) and that of the control group was 60.5 kg (SD 0.45, n=2 of 16 studies). The change in weight in the experimental group was 0.1kg and that of the control group was -0.5kg.

Figures 3.3 and 3.4 provide a graphical representation of the weight observed before and after supplementation with EPA. The weight has been represented using the reported baseline weight of the included study and the calculated mean of the weight measurements taken and reported during and after the period of intervention. The studies without graphical representation are those that did not report adequate data for any calculation to be made.

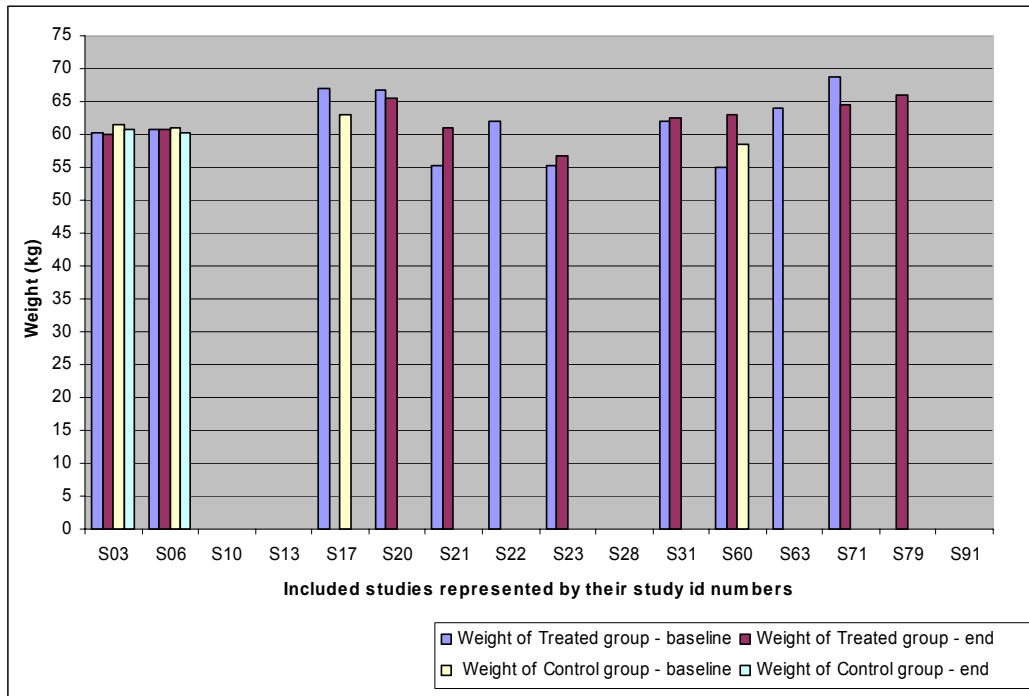


Figure 3.3 The weight in the Control and Treated groups before and after intervention
Study ID – Study Identification number

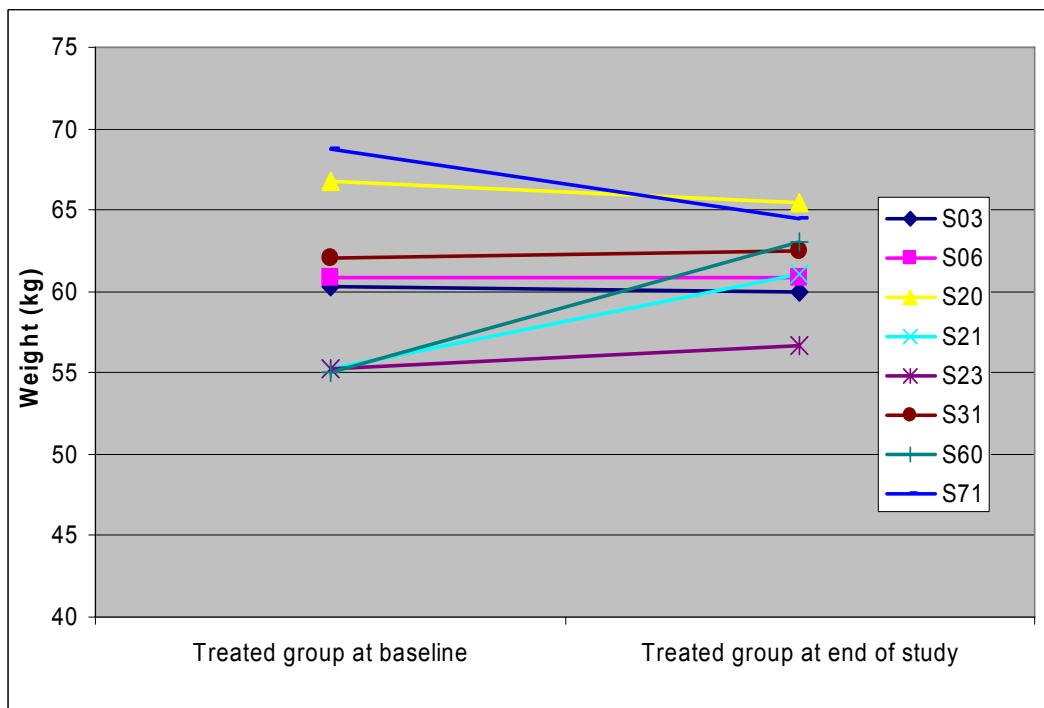


Figure 3.4 The weight in the EPA supplemented group before and after supplementation

Twelve of the 16 studies did, however, report the change in weight that occurred, although only 8 of the 16 studies had sufficient data to calculate the change in weight. Seven of the 16 studies reported the total weight change,

and 5 of the 16 studies reported the rate of weight change observed following supplementation with EPA (Tables 3.7.1 and 3.7.2 respectively)

Table 3.7.1 – Total weight change reported following supplementation with EPA

STUDY ID	INTERVENTION	DURATION OF INTERVENTION (weeks)	MEDIAN WEIGHT CHANGE (kg)
S10	ENS	3	+1.0
S21	ENS	3	+1.0*
S23	ENS	3	+1.0 *
		7	+2.0 *
S79	ENS	8	0.0
S6	Capsules	8	+0.03
S63	Capsules	*	- 0.8
S91	Capsules	6	0.0

*Significant change in weight reported by investigators of that particular study

Study ID – Study Identification number

ENS – Enriched nutritional supplement

Table 3.7.2 – The rate of weight change reported following supplementation with EPA

STUDY ID	INTERVENTION	DURATION OF INTERVENTION (weeks)	MEDIAN RATE OF WEIGHT CHANGE (kg / mo)
S3	ENS	8	-0.25*
S60	ENS	3	+1.0*
S20	Capsules	0	-2.0
		4	+0.5
		8	+0.2
		12	+0.3
S31	Capsules	12	+0.3
S71	Capsules	0	-2.2
		4	+0.75
		8	+0.2
		12	+0.3
		24	+0.1

*Significant change in weight reported by investigators of that particular study

Irrespective of how the weight change has been measured, the change following intervention with ENS and capsules was minimal, with only 5 of the 16 studies measuring a change that was statistically significant. Reflecting on the data in Tables 3.7.1 and 3.7.2, the greatest change in weight appeared to

occur within the first three to four weeks with both types of interventions. Similarly, the longer the period of intervention, the smaller the change in weight appeared to become.

The study of Burns *et al* (S63)³⁹ described the weight change in their study population in more detail. The majority of their sample maintained their weight over a median period of 1.2 months using capsules as the means of intervention. Table 3.8 is adapted from Burns *et al* (S63)³⁹ and summarises the change in weight that was observed in that study.

Table 3.8 – The results of the weight change observed in the study of Burns *et al* (S63)³⁹

WEIGHT CHANGE	DEFINITION OF WEIGHT CHANGE	NO. OF PATIENTS (%)
Gained weight	5% body weight gain / reached pre-morbidity weight	6 (17)
Lost weight	≥ 5% body weight	6 (17)
Stable weight	Weight gain ≤ 5% or weight loss < 5%	24 (66)
Unevaluable		7 (-)
Total Study Population		43 (-)

Source: Burns CP *et al*,2004³⁹

3.4.2 Body composition

3.4.2.1 Lean body mass (LBM)

Lean body mass was measured in 5 of the 16 studies. All 5 studies used bioelectrical impedance to measure body composition. LBM was calculated assuming lean tissue contains 73% water. Of the 5 studies, 2 were uncontrolled and 3 were controlled studies. The uncontrolled studies reported a change in LBM that was statistically significant ($p < 0.05$). The controlled studies, however, reported that there was no statistically significant change in LBM within either the treated group or the control group, or even between the two groups (Figure 3.5).

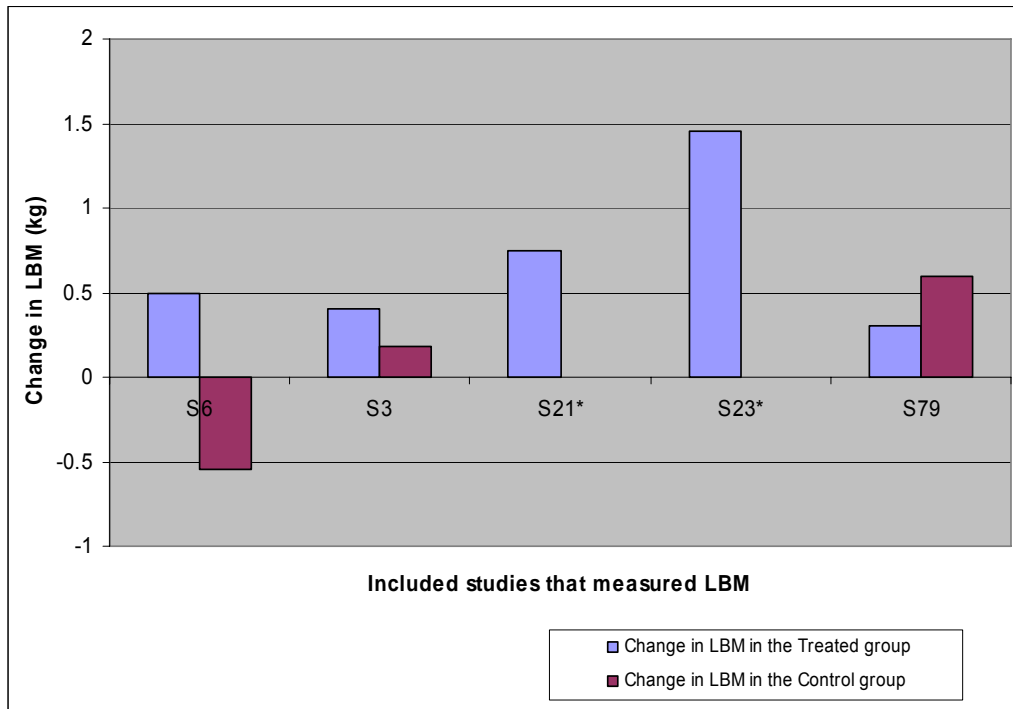


Figure 3.5 The change in LBM after a period of intervention

* Studies that reported a significant change in LBM in that particular study

The analysis performed in this study on the combined LBM data of 3 studies showed that there was no significant difference ($p=0.496$, $t=0.825$, $n=3$ studies) between the EPA supplemented group and the controls following supplementation.

Furthermore, this analysis has also shown that there was no significant difference ($p=0.841$, $t=0.228$, $n=3$ studies) in LBM in the control group following supplementation. However, the combined analysis of the EPA supplemented groups in these 5 studies showed that there appears to be a significant change ($p=0.03$, $t=3.286$, $n=5$ studies) in LBM following supplementation.

3.4.2.2 Fat mass (FM) and Body water (BW)

There was no significant change in fat mass in the two studies that did measure this outcome.

Both of these studies used ENS. The change that was measured and reported in these studies ranged from -0.2 - $+0.2$ kg over a period of 3 – 7 weeks.

Similarly, there was no significant change (p value not reported) in the percentage body water in the three studies that did measure this outcome. The change that did occur ranged from -1.8% - +1.0% over a period of 7-12 weeks. Two of the studies used capsules and one used ENS.

The lack of adequate data for the above mentioned outcomes prevented a combined analysis from being performed.

Only one⁴⁰ of the 16 studies measured all three of these outcomes. Interestingly, this study reported that there was a significant increase in body weight and lean body mass, whereas the change in fat mass and percentage body water was not statistically significant (p value not reported). Although fat mass appeared to increase in relation to the increase in body weight, the percentage fat mass actually decreased.

3.4.3 Appetite

Measuring the effect of n-3 supplements on appetite was not considered by many of the studies; only 2 of the 16 trials measured the change in appetite following EPA supplementation. Both studies reported a change in appetite that was not statistically significant (p value at end of trial not reported). The lack of adequate data prevented any analysis from being performed in this study.

3.4.4 Dietary intake

3.4.4.1 Energy Intake

Total energy intake per day (kcal/d) was measured by 6 of the 16 studies, 4 of which were RCTs, 1 Phase I trial and 1 Phase II trial. Within the 6 studies, 3 used ENS and 3 used capsules. Three of the studies had baseline and mid-study data and the remaining 3 studies had baseline and end of study data. Three-day food diaries were used by 4 of the 6 studies, 1 of the 6 studies used diet records, and 1 of the 6 studies did not specify the method that they used to record dietary intake.

With the exception of one study, there was an increase in energy intake following EPA supplementation, which ranged from 51 – 474 kcal/day. The mean change in intake was 139.3 kcal/d. In comparison, two of the control groups reported a decrease in energy intake and two reported an increase in energy intake per day. The mean change in intake was, however, -45 kcal/d. More specifically there was a mean 200 kcal/d increase in energy intake in the three studies that used ENS compared to a mean 79 kcal/d increase in energy intake in the studies that used the capsules. Despite these observations, it must also be noted that the trials vary in trial duration (Table 3.9).

Table 3.9 – A summary of the change in total energy intake per day after EPA supplementation

ID (DURATION OF TRIAL)	INTERVENTION	DIETARY INTAKE – KCAL/D						CHANGE IN INTAKE- KCAL/D	
		BEFORE		DURING		AFTER		E	C
		E	C	E	C	E	C		
S3 (8wks)*	ENS	1504	1613			1281	1237	-223	-376
S79 (8wks)	ENS	1574	1814			2048	1980	+474	+166
S6 (2wks)	Capsules	1386	1349			1437	1292	+51	-57
S17 (12wks)	Capsules	1964	1459	2098.6 (1wk)	1546.2			+134.6	+87.2
S23 (7wks)*	ENS	1450		1798 (3wks)				+348	
S20 (12wks)	Capsules	1777		1828 (4wks)				+51	
MEAN		1609	1558.8	1908.2	1546.2	1588.7	1503	139.3	-45

* Significant change in kcal/d intake reported by the investigators of the particular study

EPA – Eicosapentaenoic acid

Study ID – Study Identification number

ENS – Enriched nutritional supplement

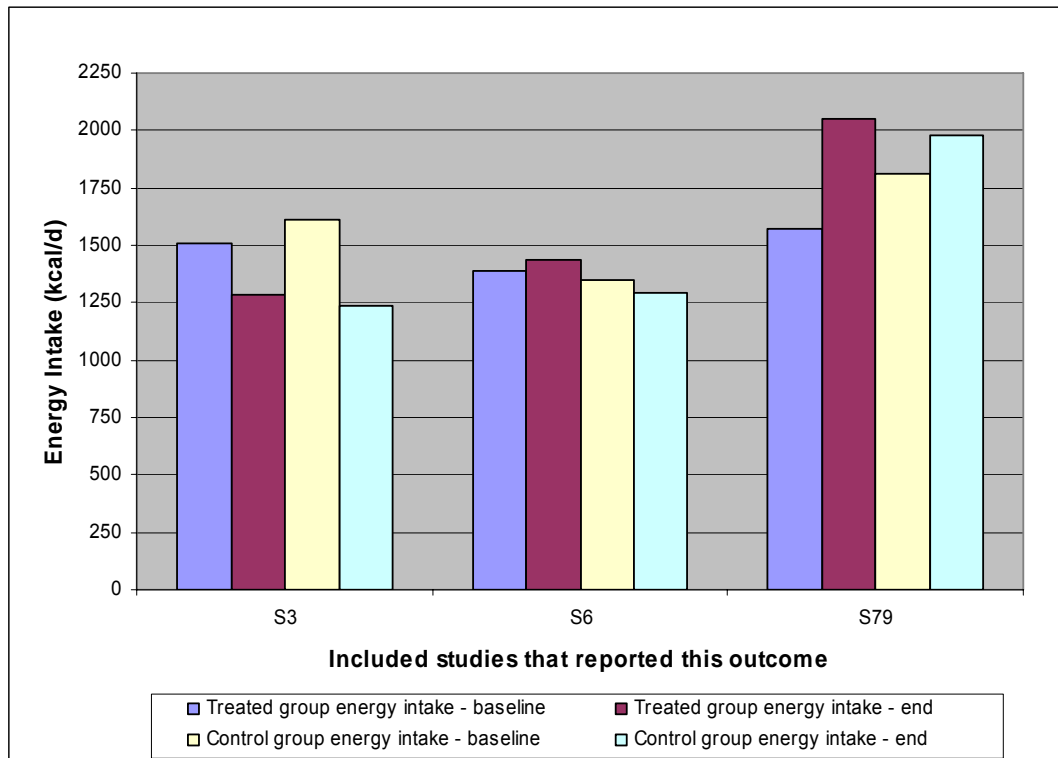


Figure 3.6 The energy intake of the Control and Treated group before and after the intervention

The analysis of the combined data available for the total energy intake per day showed that there was no statistical difference between the EPA supplemented group and the controls ($p=0.156$, $t= 2.239$, $n=3$ studies, paired t-test) and no significant difference between baseline and end of treatment total energy intake following supplementation with EPA ($p=0.261$, $t= 1.296$, $n=5$ studies, paired t-test). No further analysis was possible.

3.4.4.2 Protein Intake

Only 2 of the 16 studies measured protein intake per day. Both of the studies, namely Fearon *et al* (S3)³⁵ and Moses *et al* (S79)¹⁹, used ENS and reported that there was a significant change in protein intake per day; however, the study of Moses *et al* (S79)¹⁹ reported the change as an increase in intake, whereas the study of Fearon *et al* (S3)³⁵ reported the change as a decrease in protein intake (Table 3.10).

The combined analysis of this data showed that there was no significant difference ($p=0.263$, $t= 2.286$, $n=2$ studies, paired t-test) between the EPA

supplemented group and the controls; additionally, there was no significant change ($p=0.683$, $t=0.541$, $n=2$ studies, paired t-test) in protein intake from baseline to the end of supplementation with EPA. No further analysis was possible.

Table 3.10 – A summary of the change in protein intake per day after EPA supplementation

STUDY ID (duration of trial)	INTERVENTION	DIETARY INTAKE (grams protein / day)				CHANGE IN INTAKE- g/day	
		BEFORE		AFTER			
		E*	C**	E*	C**	E*	C**
S3 (8wks)	ENS	60	63	52	46	-8	-17
S79 (8wks)	ENS	57	73	84	77	27	4

* E represents the treated group that received the ENS

** C represents the control group that received a standard nutritional supplement

The studies of Fearon *et al* (S3)³⁵ and Moses *et al* (S79)¹⁹ recorded and reported energy and protein intake in more detail than as discussed above. These studies specified the protein and energy contribution the ENS made towards the total energy and protein intake.

By deducting the contribution made by the ENS and NS, the actual change in dietary intake can be assessed. Over a period of 8 weeks, there was a decrease in total dietary energy intake and protein per day in both the treated and control groups. The use of the supplements in both groups provided an additional 23 -28% energy/day and approximately 31 - 36% protein /day. This contribution therefore resulted in an overall increase in the total dietary intake per day (Tables 3.11-3.14).

Table 3.11 –Total energy intake at baseline and after 8 weeks of supplementation

STUDY ID	DIETARY INTAKE WITHOUT SUPPLEMENTS AT BASELINE (kcal/d)		AFTER 8 WEEKS OF SUPPLEMENTATION			
			DIETARY INTAKE WITHOUT SUPPLEMENTS (kcal/d)		DIETARY INTAKE WITH SUPPLEMENTS (kcal/d)	
	E (ENS)	C (NS)	E (ENS)	C (NS)	E (ENS)	C (NS)
S3	1504	1613	1280	1237	1728	1681
S79	1574	1814	1472	1519	2048	1980

Study ID – Study Identification number

ENS – Enriched nutritional supplement, NS – Nutritional Supplement

Table 3.12 – Protein intake at baseline and after 8 weeks of supplementation

STUDY ID	DIETARY INTAKE WITHOUT SUPPLEMENTS AT BASELINE (g/d)		AFTER 8 WEEKS OF SUPPLEMENTATION			
			DIETARY INTAKE WITHOUT SUPPLEMENTS (g/d)		DIETARY INTAKE WITH SUPPLEMENTS (g/d)	
	E (ENS)	C (NS)	E (ENS)	C (NS)	E (ENS)	C (NS)
S3	60	63	52	46	75	69
S79	57	73	54	53	84	77

Study ID – Study Identification number

ENS – Enriched nutritional supplement, NS – Nutritional Supplement

Table 3.13 – A summary of the change in dietary intake after 8 weeks of supplementation

STUDY ID	CHANGE IN DIETARY INTAKE WITHOUT SUPPLEMENTS				CHANGE IN DIETARY INTAKE WITH SUPPLEMENTS			
	Kcal/d		Protein g/d		Kcal/d		Protein g/d	
	E (ENS)	C (NS)	E (ENS)	C (NS)	E (ENS)	C (NS)	E (ENS)	C (NS)
S3	-223	-376	-8	-17	+224	+68	+15	+6
S79	-102	-295	-3	-20	+474	+166	+27	+4

Study ID – Study Identification number

ENS – Enriched nutritional supplement, NS – Nutritional Supplement

Table 3.14 – The % contribution the supplements made to the total dietary intake

STUDY ID	% ENERGY (kcal/d)		% PROTEIN – g/d	
	E (ENS)	C (NS)	E (ENS)	C (NS)
S3	25.9	26.4	30.7	33.4
S79	28	23.3	35.7	31.2

Study ID – Study Identification number

ENS – Enriched nutritional supplement, NS – Nutritional Supplement

3.4.5 Energy expenditure

Indirect calorimetry was used by 6 of the 16 studies to calculate resting energy expenditure (REE). Three of the studies used ENS and three used capsules. The measurements were expressed either as kilocalories per day (kcal/d) and / or as kilocalories per kilogram per day (kcal/kg/d).

From the data provided in the studies, there was no obvious pattern in the change in resting energy expenditure and no conclusions can be drawn from the statistical significance reported by the various studies. Two of the studies did not report REE as kilocalories per day; thus the mean baseline weight of these samples and the kilocalories per kilogram per day was used to calculate the kilocalories per day, thereby enabling better comparisons to be made between the studies. The results of such a calculation can only be used for descriptive purposes

From the data collected there does appear to be a decrease in the total energy expenditure following supplementation with EPA. There is only a 4kcal/d difference in the change in resting energy expenditure between ENS and capsules (Table 3.15). Figure 3.7 is a graphical representation of the resting energy expenditure following EPA supplementation. Only those studies that provided adequate data are represented on the graph.

The analysis performed on the combined data of the 6 studies showed that there was, however, no significant difference in resting energy expenditure expressed either as kcal / day ($p=0.216$, $t= -1.562$, $n=4$ studies) or as kcal/kg/day ($p=0.23$, $t= -1.414$, $n= 5$ studies, paired t-test, paired t-test) from

baseline to the end of the treatment period following supplementation with EPA. No further analysis was possible owing to the lack of data.

Table 3.15 – The change in resting energy expenditure per day after EPA supplementation

Study ID (study design)	Baseline Energy Expenditure kcal/day		End of treatment Energy Expenditure (kcal/day)		Change in energy expenditure (kcal/d)
	ENS	Capsules	ENS	Capsules	
S21 (P1)	1354		1295		-59
S23 (P1)**	1339		1303		-36
S79 (RCT)	1387		1386		-1
S17 (RCT)*		1494		Not reported	-
S31 (P2)*		1550		1612	118
S71 (P2)		1815		1570	-245
Mean kcal / day / supplement	1360	1619	1328	1591	
Mean kcal / day	1489.8		1433.2		

* The studies where the kcal/d was calculated from kcal/kg/d data using the baseline weight

** Significant change reported by investigators of this particular study

Study ID – Study Identification number, ENS – Enriched nutritional supplement

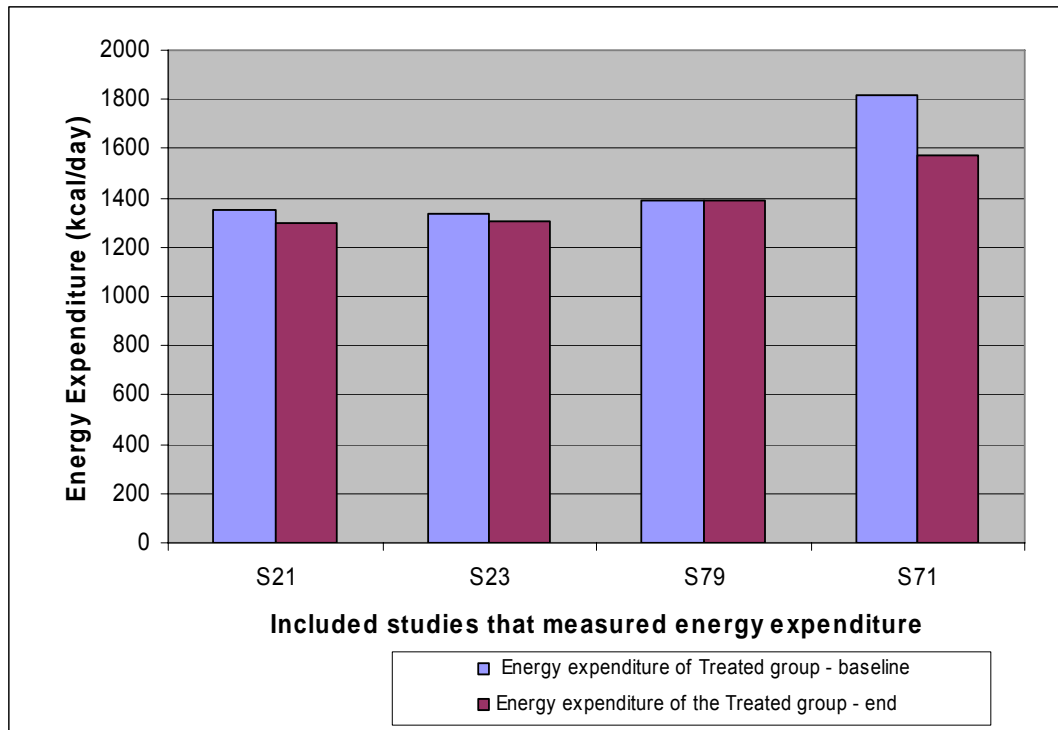


Figure 3.7 Energy expenditure in the Treated group after EPA supplement

3.4.6 Functional status

Functional status was measured in 8 of the 16 studies, and 5 of the studies used the Karnofsky assessment tool. The remaining three used the WHO performance status questionnaire, FAACT and FACT-G questionnaires and the physical activity level respectively. The Edmonton Functional Assessment Tool (EFAT) was used with the Karnofsky performance status in one of the trials.

Only 3 studies had complete data, 2 reported only the change in functional status, 1 reported only baseline data, 1 had incomplete data and 1 did not report any data on functional status.

Bruera *et al* (S6)⁴¹ measured functional status at baseline and at the end of the trial using KPS and EFAT. At baseline, the difference between the experimental group and the control group was significant ($p=0.05$) with the KPS but not with the EFAT. On completion of the trial, the changes in the KPS and EFAT in both groups were not statistically significant (p value was not reported).

Fearon *et al* (S3)³⁵ measured KPS at baseline and on completion of the trial. However, it was only reported that the change in functional status was not significant (p value was not reported).

Barber *et al*, 2001 (S13)⁴² used the KPS, but unfortunately no details were reported.

Barber *et al*, 1999 (S23)⁴⁰ measured functional status at baseline, at 3 weeks and at 7 weeks, using KPS. There was a statistically significant improvement in functional status at 3 ($p= 0.0047$) and 7 ($p=0.046$) weeks compared to baseline.

Burns *et al* (S63)³⁹ used FAACT/FACT-G to measure functional status. There was a positive change recorded in both questionnaires, but it was not reported if these changes were significant or not.

Wigmore *et al* (S20)⁴³ used the WHO performance status and measured functional status at baseline and monthly thereafter. The results showed that there was no statistically significant change in functional status (p value not reported).

Using total energy expenditure and resting energy expenditure, Moses *et al* (S79)¹⁹ were able to calculate the physical activity. The change in the Treated group was greater than the change in the Control group.

Gogos *et al* (S91)⁴⁴ also used the KPS to measure functional status. Within the experimental and control groups the researchers distinguished between malnourished and well-nourished patients. The only change that was reported was the significant improvement in the KPS score in the malnourished experimental group following 6 weeks of supplementation with capsules.

The only functional status data that could be used for the paired t-test in this study was for the KPS. The result of this analysis showed that there was no significant change ($p= 0.231$, $t= 1.704$, $n=3$ studies) in functional status using the KPS in the EPA supplemented group. In summary, irrespective of the assessment tool used, a change in functional status was reported by 7 of the 8 studies. Three of these studies reported the change as statistically not significant, 2 of the studies reported the change as statistically significant and 3 did not report on the significance of the change.

3.4.7 Acute phase response

Seven of the 16 studies⁴³ used C-reactive protein to assess the change in acute phase response. One study used other markers to measure the acute phase response whilst the remaining 8 studies did not measure the change in acute phase response (Appendix 6.9.9).

After four weeks of supplementation with fish oil capsules, a significant reduction in CRP levels was noticed in three of the trials (Figure 3.8). This

reduction was, however, not maintained and after 12 weeks of supplementation, the CRP levels had increased again. There was no change in CRP levels in the study using ENS.

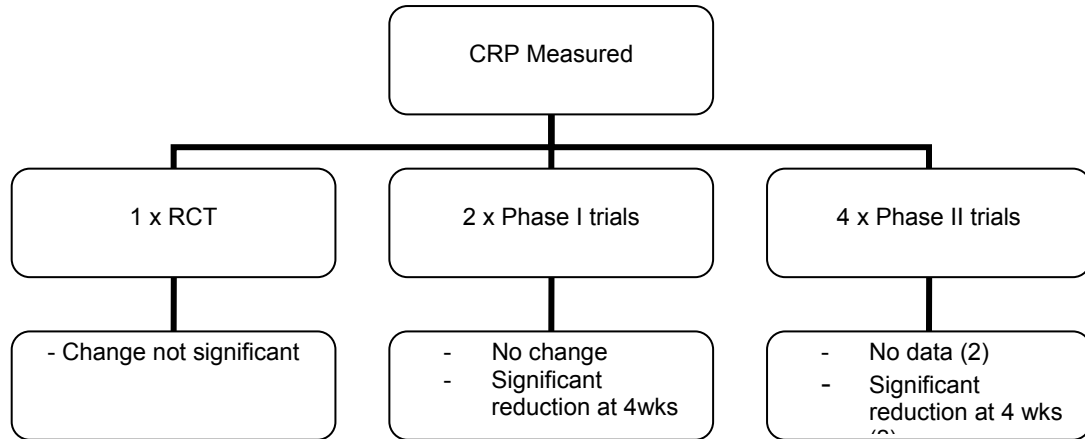


Figure 3.8 – Outcome of CRP Measurements

The combined analysis of the available data in this study showed that there was no significant change ($p= 0.542$, $t= -0.686$, $n=4$ studies, paired t-test) in CRP levels following supplementation with EPA.

3.4.8 Quality of life

With the exception one study, none of the studies investigated aspects regarding quality of life and the use of ENS and capsules (Appendix 6.9.11).

The study that did investigate quality of life measured this outcome using the EORTC and EuroQoL questionnaires and only reported that there was no significant differences between the baseline data and the data collected at the end of the study. Unfortunately, this data was not published. The investigators were contacted for these details but no response was received.

3.4.9 Safety

Details of the adverse effects noted following the consumption of the fish oil capsules and the ENS were reported by 7 of the 16 studies (Table 3.16). The remaining 9 studies either did not record this data or failed to report these

details. It is not necessarily an indication that no adverse effects were experienced (Appendix 6.9.11).

Patients in the studies using the EPA capsules experienced the majority of the adverse effects. Participants using ENS experienced fewer adverse effects

Table 3.16 A summary of the adverse effects reported following the use of EPA supplements

SYMPTOM	Adverse effects reported with the use of ENS (n)	Adverse effects reported with the use of CAPSULES (n)	TOTAL (n)
Taste changes		35 +*	35+*
Belching		26	26
Nausea		19	19
Flatulence		18	18
Body Odour		14	14
Diarrhoea		8+*	8+*
Emesis		8	8
Steatorrhea	3	4	7
Sensation of fullness		4	4
Vomiting		3	3
Constipation		3	3
Abdominal pain		3	3
Dyspepsia		2	2

* Symptoms specified but number not specified

n - represents the number of patients who experienced the adverse effect

ENS – Enriched nutritional supplement

CHAPTER 4: DISCUSSION

4. DISCUSSION

The complex and multi-factorial nature of cancer cachexia and the inability of conventional nutrition intervention to reverse or attenuate the effects of this syndrome have driven investigators to consider new therapies and approaches to manage the syndrome of cancer cachexia. One such approach is to utilise the apparent anti-cachectic and anti-tumour properties of eicosapentaenoic acid (EPA), an n-3 fatty acid of fish oil origin. The benefits of such actions suggest that EPA could have the potential to promote weight maintenance, improve dietary intake, inhibit tumour growth and ultimately have an influence on patient survival^{30 32}.

Initially, this study was only aiming to establish the safety and efficacy of a nutritional supplement enriched with EPA in patients with cancer cachexia. This was, however, changed to incorporate studies making use of fish oil capsules as a means of EPA supplementation. The objectives of this review considered those outcomes that have the greatest impact on a cancer patient's quality of life and potential survival. Interestingly, despite not restricting the search period, all relevant studies identified were within the specified period of 1994 – 2004. Date of publication therefore had little influence on the inclusion and exclusion of studies in this review.

4.1 The effect of eicosapentaenoic acid (EPA) on weight

The weight attenuation or reversal of weight loss seen with EPA supplementation is associated with EPA's ability to modulate PIF and LMF activity and prevent protein and fat breakdown.^{34, 35} Similarly, with these effects, there would be the expectation that EPA supplementation would also have beneficial effects on protecting lean body mass and fat reserves.

This study indicates, however, that the total weight change that does occur is minimal and although a few studies showed an initial significant change in the rate of weight loss, this appears to be short-lived. Disappointingly, despite providing additional calories, the use of an ENS only had the effect of weight stabilisation.³⁵

4.2 The effect of eicosapentaenoic acid (EPA) on body composition

Encouragingly, despite the small number of studies that measured changes in body composition, there is an indication that EPA supplementation significantly improves lean body mass. Although changes were observed in fat mass and body water, there is insufficient data to provide further insight or comment at present, although previous studies with enteral and parenteral nutrition in cancer patients have suggested that the change in weight can be attributed to a change in the percentage body water, Barber *et al* (S23)⁴⁰, however, have shown that there is no change in hydration status, and that the change in weight is the result of a significant increase in lean body mass, albeit a small increase. Further studies support these findings that the weight gain seen is not as a result of an increase in the percentage body water^{40, 45}.

4.3 The effect of eicosapentaenoic acid (EPA) on appetite

Given the lack of available data, establishing or commenting on the effect of EPA on appetite in this study is limited. Previous studies have had contrasting results. Appetite appears to increase soon after supplementation is initiated, which could contribute to the increase seen in dietary intake; however Bruera *et al* (S6)⁴¹ found no improvement in appetite following supplementation, although it has been questioned as to whether or not higher doses of EPA may be more effective to improve appetite, but this may have an implication on the tolerance thereof in cancer patients^{40, 41}.

4.3 The effect of eicosapentaenoic acid (EPA) on dietary intake

It remains a very difficult task for the dietician and clinician to encourage a cachectic cancer patient to drink a nutritional supplement as well as increase their dietary intake²⁰. In the studies that measured this outcome, there appeared to be a great variation in the change in dietary intake with regards to energy and protein intake. As this was not necessarily the main objective of many of the studies, the approach to recording intake may have varied greatly, which could have had an influence on the accuracy of the results reported. Interestingly, contradictory results of some studies raise the issue about how beneficial nutritional supplementation is. Barber *et al* (S23)⁴⁰ found that the significant increase in dietary intake in their study was not solely due

to the additional calories from the EPA enriched nutritional supplement. Patients managed to improve their total dietary intake following the use of the supplement⁴⁰. In comparison, the change in intake reported by Fearon *et al* (S3)³⁵ and Moses *et al* (S79)¹⁹ found that, although there is an overall increase in total intake per day with the supplements, the actual dietary intake decreases^{19, 35}. This could be attributed to disease progression and general deterioration of the cancer patient, in which case the additional calories of the supplements are beneficial. Alternatively, the increased intake of the supplements could be suppressing actual dietary intake, in which case their consumption may be of little value. The increase in total intake and changes seen in physical activity and lean body mass could be suggestive of the fact that with EPA supplementation there is greater utilisation of protein and energy for energy production, as opposed to energy storage, which could be related to the role of EPA on mediator pathways¹⁹.

4.4 The effect of eicosapentaenoic acid (EPA) on energy expenditure

Barber *et al* (S21)⁴⁶ have shown in their study that EPA supplementation is able to reduce resting energy expenditure in cancer patients, although Zuijdgheest- Van Leeuwen *et al* (S17)⁴⁵ were unable to repeat these results. Their study showed no change in REE^{45, 46}. Despite the fact that this study has shown no significant effect of supplementation on energy expenditure, it does appear that more studies than not have noticed a reduction in REE.

4.5 The effect of eicosapentaenoic acid (EPA) on functional status

The great variation of functional status assessment tools used by the included studies and lack of adequate data have also made it very difficult to accurately assess the effect of EPA supplementation on functional status. There does, however, appear to be a small but positive improvement in functional status following EPA supplementation.

4.6 The effect of eicosapentaenoic acid (EPA) on acute phase response

Wigmore *et al* (S20)⁴³ concluded that the data from their study could support the potential of EPA to modulate the acute phase response following the significant reduction in CRP after 1 month of EPA supplementation⁴³. Barber

et al have also observed that an EPA enriched nutritional supplement can help prevent progression of the acute phase response in patients with pancreatic cancer⁴³. This study has been unable to show any significant effect on CRP levels, although it does appear that there is an initial improvement, but it is not maintained beyond 4 weeks of supplementation.

4.7 The safety of eicosapentaenoic acid supplementation

Patients with advanced cancer are able to tolerate large doses of fish oil capsules with only minor side effects. Fearon *et al* have also demonstrated that large doses of EPA are well tolerated as an emulsion. The maximum tolerated dose could be influenced by several factors such as pancreatic insufficiency and by the types and amounts of other fats taken in the diet^{38, 42}. This data has little impact in this study as there hasn't been adequate information to relate these side effects to aspects such as compliance or drop-out rate from the studies. It would, however, have been of value to establish which method of supplementation is better tolerated and associated with the least amount and severity of side effects, as this will definitely have an impact on the efficacy of future intervention with EPA supplements.

It is well known that pancreatic cancer has the greatest impact on nutritional status and is associated with rapid disease progression. The severity of the cachexia and high drop-out rate could be seen as a limiting factor regarding the lack of effect of EPA supplementation seen in some of the studies using only patients with pancreatic cancer. Furthermore, it must not be overlooked that despite all the evidence supporting the beneficial effects of EPA supplementation in CC, there is evidence available regarding the lack of effect of EPA on tumour growth, and suggesting that its use in the prevention of cancer cachexia could be limited by the tumour type and growth pattern⁴⁷. An additional objective of this review was therefore to determine if tumour sites other than the pancreas have been considered. The lack of data allows this study only to list and state that other tumour sites have been included in trials using EPA supplements. Unfortunately it has not been possible to establish if there is a difference in effect between tumour sites following EPA supplementation.

Although EPA supplementation had positive effects on lean body mass, the lack of adequate symptom control and improvement of other nutritional variables may be a limiting factor in the therapeutic use of EPA supplements in patients with incurable progressive disease⁴¹. Bruera *et al* (S6)⁴¹ have also concluded that the use of fish oil as an alternative or complementary therapy does not help to improve subjective or objective manifestations of cancer cachexia/ anorexia.⁴¹ Quality of life, the outcome that could best address the impact that supplementation, either as fish oil capsules or as an enriched nutritional supplement, has on patients with cancer cachexia, was not adequately investigated and / or reported on in the studies included in this study.

Studies regarding the use of EPA supplementation have shown variable results, with few changes being significant. This could possibly be due to the limitations that many of the studies have with regards to the nature of the patient group and the rapid rate of disease progression with these patients, which will have a direct impact on drop-out rate and sample size and thus obscure results. Assessing the safety and efficacy of a product from individual studies with such limitations is difficult to establish, and for that reason one needs to consider a systematic review.

Systematic reviews or meta-analyses are increasingly being used to identify, appraise, synthesize and, if possible, combine the results of relevant studies to arrive at conclusions which can facilitate policy and decision-making with regards to the use of an intervention⁴⁸.

This study was anticipating being able to combine the existing research regarding the use of EPA supplementation in patients with cancer cachexia and to provide greater clarity with regards to its safety and efficacy. The small number of studies meeting the inclusion criteria and the lack of adequate data has unfortunately meant that this study could not quantitatively analyse the evidence and assess for publication bias. Furthermore, this study only included trials published in English and together with factors such as the variations in trial designs, type of supplements used and the dose

administration thereof, the strength and interpretation of the evidence in this study has been influenced. A further limitation relates to the statistical analysis that has been incorporated. It must be reiterated that the statistical results are merely suggestive and by no means indicative of the effect of EPA supplementation on the outcomes reviewed.

Although this study is unable to provide the quantitative evidence required to confidently advocate the use of EPA supplements in patients with cancer cachexia, it has certainly highlighted the difficulties and challenges that exist in managing the syndrome of cancer cachexia. The lack of significant effect of an intervention such as EPA, which shows so much promise, should not dissuade ongoing research on this topic. The evidence accumulated in this study should first of all emphasise the need for collecting more complete data. Had the data in this review not been so incomplete, the statistical analyses might have produced a very different result. Furthermore, this data could be used to initiate research in areas that may result in the more effective use of EPA supplements in the future.

Future considerations may include redirecting the use of EPA on specific tumour sites other than pancreatic, and reviewing the method, timing and route of administration of an oral EPA enriched nutritional supplement. These options can, however, only be implemented once there is a greater understanding of the mechanisms of cancer-associated wasting and the effect of intervention. A clearer definition of the different sub-groups of cancer cachexia, will make it possible to identify and characterize those patients who will be more likely to benefit from an intervention such as an EPA enriched nutritional supplement^{18, 49}.

Greater success may be achieved if the ENS is given earlier in the course of illness to prevent weight loss rather than waiting until it is too late and the manifestations of cancer cachexia are too severe to be reversed³⁹. Earlier intervention may have a greater impact on maintaining well-being and functional status and thus play a role in preserving quality of life⁴⁹.

A further suggestion regarding the future role of EPA supplementation is within the field of combination therapy^{33, 39}. There are already current trials looking at the use of EPA enriched nutritional supplements in patients receiving chemotherapy⁵⁰. There is also the possibility of combining pharmacologic management of cancer cachexia with EPA supplementation. Individualised dietary counselling has been found to promote the maintenance of adequate dietary intake and body weight, resulting in a marked reduction in the incidence and severity of anorexia and diarrhoea and improved quality of life⁵¹. Another recommendation could therefore be that greater emphasis is needed on improving dietary counselling and education with regards to dietary intervention and the use of EPA supplements.

Ultimately it is also necessary to explore quality of life aspects in cancer patients in more detail.

There is little information available in the literature regarding the impact of cancer cachexia on body image and quality of life⁵². Furthermore, it is important that, irrespective of the type of intervention used and the improvement in medical parameters it may produce, evaluating the impact that the method of intervention has on the cancer patient is not overlooked⁵³. A lot of emphasis has been placed parameters such as achieving weight gain or improving anorexia but the actual patient benefit of such parameters is unclear⁴⁹. Addressing the use of oral supplementation in cancer patients in more detail will definitely have an impact of the success and efficacy of any form of intervention.

CONCLUSION

Although much of the data collected and analysed in this review are suggestive of the beneficial effects of EPA supplementation, there remains a significant lack of substantial evidence and conclusive statistical analysis to confirm that EPA supplementation, either as an enriched nutritional supplement or as fish oil capsules, is a safe and effective method of intervention in the management of patients with cancer cachexia. Future research should be directed at strengthening this evidence and considering alternatives to improve the efficacy of a supplement that possesses anti-tumour and anti-cachectic properties and has the potential to improve quality of life for patients with cancer cachexia.

CHAPTER 5: REFERENCES

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CHAPTER 6: APPENDICES

Appendix 6.1 Ethical approval

15 March 2004

Ms T Klopper
C/o Prof D Labadarios
Department of Human Nutrition

Dear Ms Klopper

RESEARCH PROJECT : "SAFETY AND EFFICACY OF N-3 ENRICHED NUTRITIONAL SUPPLEMENTS IN THE MANAGEMENT OF CANCER CACHEXIA"
PROJECT NUMBER : N04/03/051

It is my pleasure to inform you that the abovementioned project has been approved by the Manager: Research Development and Support (Tygerberg), in accordance with the authority given to him by the Committee for Human Research, and that you may start with the project. This approval will however be submitted at the next meeting of the Committee for Human Research for ratification, after which we will contact you again.

Notwithstanding this approval, the Committee can request that work on this project be halted temporarily in anticipation of more information that they might deem necessary to make their final decision.

In future correspondence, kindly refer to the above project number.

I wish to remind you that patients participating in a research project at Tygerberg Hospital will not receive their treatment free, as the PAWC does not support research financially.

The nursing staff of Tygerberg Hospital can also not provide extensive nursing aid for research projects, due to the heavy workload that is already being placed upon them. In such instances a researcher might be expected to make use of private nurses instead.

Yours faithfully



CJ VAN TONDER
RESEARCH DEVELOPMENT AND SUPPORT (TYGERBERG)
CJVT/ejvt

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Appendix 6.2– Characteristics of references that could not be retrieve

STUDY ID	AUTHOR	YEAR	REASON FOR EXCLUSION
S15	Tisdale MJ	2001	Failed request
S29			Not requested
S35	Mantovani G, et al	2003	Failed request
S36	Zurcher	2002	Not in English
S40	Barber MD, et al	2002	Failed request
S43	Dewey A, et al	2004	Currently recruiting for study
S48 – S52 & S55 – S58	Fearon KCH	1999/2000	Multicentre trial, although complete –no results available yet
S53	Ahmedzai S	2000	Failed request
S59	Fearon KCH	1999	Failed request
S62	Read J	2004	Current trial. Combined with chemotherapy
S70	Barber MD, et al	1999	Failed request
S96	Moses AWG, et al	2002	Failed request

Appendix 6.3 – The inclusion and exclusion of studies

STUDY ID	Population	Intervention		Outcome							Study design	Incl / excl	Reason for exclusion	
		n-3 supple	n-3 enriched nutritional supple	Weight	App / diet intake	Body Compo / En Ex	Tumour / APR	Perform status	Quality of Life	Adverse Effects				
S1	Adults with solid tumours													
S2												E	Commentary on S6	
S3	X		X	X	X	X			X		RCT	I		
S4												E	Review article	
S5												E	Review article	
S6	X	X		X	X			X	X	X	RCT	I		
S7												E	Review article	
S8												E	Review article	
S9												E	Review article	
S10	X		X				X				P2	I		
S11												E	Review article	
S12												E	Review article	
S13	X	X		X				X		X	P1	I		
S14												E	Review article	
S15												E	Could not be retrieved	
S16												E	Review article	
S17	X	X				X					RCT	I		
S18												E	Review article	
S19												E	Review article	
S20	X	X		X		X	X	X		X	P2	I		

STUDY ID	Population	Intervention		Outcome							Study design	Incl / Excl	Reason for exclusion	
		n-3 supple	n-3 enriched nutritional supple	Weight	App / diet intake	Body Compo	Tumour / APR	Perform status	Quality of Life	Adverse Effects				
S21	X		X	X	X	X						P1	I	
S22		X		X						X		P1	I	
S23	X		X	X	X	X	X	X				P1	I	
S24													E	Review article
S25													E	Review article
S26	-	X								X			E	Animal study
S27													E	Review article
S28	X	X					X					P1	I	
S29														
S30		X										RCT	E	Animal study and no required outcome
S31	X	X		X		X	X					P2	I	
S32													E	Review article
S33		X		X								RCT	E	Animal study
S34													E	Review article
S35													E	Could not be retrieved
S36													E	Not English
S37													E	Commentary on topic
S38													E	Review article
S39													E	Commentary
S40													E	Could not be retrieved

Study ID	Population	Intervention		Outcome							Study design	INCL / EXCL	Reason for exclusion	
		n-3 supple	n-3 enriched nutritional supple	Weight	App / diet intake	Body Compo	Tumour / APR	Perform status	Quality of Life	Adverse Effects				
	Adults with solid tumours	n-3 supple	n-3 enriched nutritional supple									RCT / P1 / P2 trial		
S41													E	Review article
S42													E	Review article
S43													E	Currently recruiting – no results
S44													E	Review article
S45													E	Review article
S46													E	Letter
S47													E	Sys review
S48													E	No results yet
S49													E	No results yet
S50													E	No results yet
S51													E	No results yet
S52													E	No results yet
S53													E	Unable to locate published study, no response from author
S54													E	
S55													E	No results yet
S56													E	No results yet
S57													E	No results yet
S58													E	No results yet
S59													E	No results yet

STUDY ID	Population	Intervention		Outcome							Study design	INCL / EXCL	Reason for exclusion	
		n-3 supple	n-3 enriched nutritional supple	Weight	App / diet intake	Body Compo / En exp	Tumour / APR	Perform status	Quality of Life	Adverse Effects				
S60	X		X	X			X					P2	I	
S61		X											E	Animal study
S62													E	Current trial / chemotherapy
S63	X	X		X					X			P2	I	
S64													E	Abstract of S3
S65													E	Abstract of S3
S66													E	Abstract of S79
S67													E	Animal study
S68	X		X	X	X				X	X		RCT	E	Not meeting criteria
S69													E	Animal study
S70														Requested but not received
S71	X	X		X		X	X					P2	I	
S72										X			E	Animal study
S73													E	Review article
S74													E	Abstract
S75													E	Abstract S76
S76													E	Talk
S77	X	X		X		(X)		(X)				P1	E	Not meeting criteria
S78													E	Review article, 1993
S79	X		X	(X)	(X)	X		X				RCT	I	

STUDY ID	Population	Intervention		Outcome							Study design	INCL / EXCL	Reason for Exclusion	
		n-3 supple	n-3 enriched nutritional supple	Weight	App / diet intake	Body Compo	Tumour / APR	Perform status	Quality of Life	Adverse Effects				
S80	X												E	n-3 supple not used
S81													E	Review article
S82													E	Review article
S83													E	Review article
S84													E	Abstract of 21
S85													E	Review article
S86	X			X		X	X					P1	E	No supple used
S87	X											P1	E	n-3 supple not used, no required outcomes
S88													E	Animal study
S89													E	Animal study
S90													E	For lit r/v
S91	X	X		X			X	X				RCT	I	
S92													E	For lit r/v
S93														
S94													E	Abstract of S71
S95	-	X		X									E	Animal study
S96														
S97													E	Abstract & 1988

Appendix 6.4 Bibliographic information and study identification numbers of the excluded studies

STUDY ID	AUTHOR	YEAR	REASON FOR EXCLUSION
S2	Belda IC, et al ⁵⁴	2003	Commentary on S6
S4	Jho BS, et al ⁵⁵	2003	Review article on n-3 fatty acids
S5	Tisdale MJ ⁵⁶	2003	Review article on cancer cachexia
S7	Hardman WE ⁵⁷	2002	Review article on n-3 fatty acids
S8	Tisdale MJ ⁵⁸	2002	Review article on cancer cachexia
S9	Tisdale MJ ⁵⁹	2002	Review article
S11	Barber MD ²⁴	2001	Review article on fish-oil enriched nutritional supplementation
S12	Fearon KCH ²¹	2001	Review article on cancer cachexia
S14	Tisdale MJ ⁶⁰	2001	Review article on cancer cachexia
S16	Babcock T, et al ³⁰	2000	Review article on n-3 fatty acids
S18	Barber MD, et al ¹⁰	2000	Review article on cancer cachexia
S19	Tisdale MJ ²³	2000	Review article on cancer cachexia
S24	Barber MD, et al ³¹	1998	Review article on fatty acids
S25	Tisdale MJ ²²	1999	Review article on wasting and cachexia
S26	Griffini P, et al ⁶¹	1998	Animal study
S27	Puccio M, et al ¹³	1997	Review article on cancer cachexia
S30	Tisdale MJ ⁶²	1996	Animal study
S32	Karmali R A, et al ⁶³	1996	Review article on n-3 fatty acids and cancer cachexia
S33	Hudson EA ⁶⁴	1994	Animal study
S34	Tisdale MJ ⁶⁵	1993	Review article / > 10 years ago
S37	Unknown ⁶⁶	2001	Commentary on fish oil
S38	Fearon KCH ²⁷	2001	Review article
S39	Unknown ⁶⁷	1998	Commentary on cancer cachexia
S41	Mantovani G, et al ⁵³	2001	Review article on cancer cachexia
S42	Barber MD ²⁰	2002	Review article on cancer cachexia
S44	Ross JA, et al ⁶⁸	1999	Review article on n-3 fatty acids
S45	Tisdale MJ ⁶⁹	1998	Review article on cachectic factors
S46	Wigmore SJ, et al ⁷⁰	1994	Letter
S47	Piotrowski P ⁷¹	2002	Commentary
S54	Fearon KCH		Protocol of S13
S61	Beck SA, et al ⁷²	1991	Animal study and > 10 years ago
S64	Fearon KCH, et al ⁷³	2001	Abstract of S3
S65	Von Meyenfeldt M, et al ⁷⁴	2002	Abstract of S3
S66	Moses AWG, et al ⁵	2001	Abstract of 79
S67	Tisdale MJ ³²	1990	Animal study and >10 years ago
S68	Jatoi A ⁵⁰	2004	Neo adjuvant treatment allowed – not meeting criteria
S69	Hussey HJ ⁶	1999	Animal study
S72	Costelli P, et al ⁴⁷	1995	Animal study
S73	Simopoulos AP ³³	2003	Review article on n-3 fatty acids
S74	Kirk HJ, et al ⁷⁷	2002	Abstract, not humans
S75	Voss AC ⁷⁸	1999	Abstract of S76
S76	Voss AC ⁷⁹	1999	Talk
S77	Gogos CA ⁸⁰	1995	Not meeting criteria
S78	Tisdale MJ ⁶¹	1993	Review article & > 10 years
S80	Barber MD ⁸²	2004	No supplement used – not meeting criteria
S81	Fearon KCH ²⁹	2002	Review article on n-3 fatty acids
S82	Barber MD, et al ¹¹	2000	Review article on cancer and metabolism
S83	Fearon KCH, et al ⁸³	1999	Review article on cancer cachexia
S84	Barber MD, et al ³⁴	1999	Abstract of S21
S85	Barber MD, et al ⁸⁵	1998	Review article on n-3 fatty acids
S86	Wigmore SJ, et al ⁸⁶	1997	No supplements used – not meeting criteria
S87	Falconer JS ⁸⁷	1994	n-3 supple not used - not meeting criteria
S88	Whitehouse AS, et al ⁸⁸	2001	Animal study
S89	Sauer LA, et al ⁸⁹	2000	Animal study
S90	Ovesen L, et al ⁹⁰	1993	For literature review
S92	Ovesen L, et al ¹⁷	1993	For literature review
S93	Barber MD, et al ⁹¹	1998	Abstract
S94	Barber MD, et al ⁹²	1997	Abstract of S71
S95	Tisdale MJ ³²	1990	Animal study and > 10 years ago
S97	Holroyde CP, et al ⁹³	1988	Abstract and > 10 years ago

Appendix 6.5 Bibliographic information and study identification numbers of the included studies

STUDY ID	AUTHOR	TITLE	JOURNAL	YEAR	SOURCE
S3	Fearon KCH, et al ³⁵	Effect of a protein and energy dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer	Gut	2003	Medline / Ovid / Zetoc / Internet
S6	Bruera E, et al ⁴¹	Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: A double-blind placebo-controlled study	J of Clinical Oncology	2003	Medline / CINAHL / Cochrane / Internet
S10	Barber MD ³⁴	Effect of a fish-oil enriched nutritional supplement on metabolic mediators in patients with pancreatic cancer cachexia	Nutrition and Cancer	2001	Medline / Embase / CINAHL / Zetoc / internet
S13	Barber MD ⁴²	Tolerance and Incorporation of a high-dose eicosapentaenoic acid diester emulsion by patients with pancreatic cancer cachexia	Lipids	2001	Medline / Zetoc / Internet
S17	Zuijdgeest-Van Leeuwen SD ⁴⁵	Eicosapentaenoic acid ethyl ester supplementation in cachectic cancer patients and healthy subjects: effects on lipolysis and lipid oxidation	Clinical Nutrition	2000	Medline / Embase / Zetoc
S20	Wigmore SJ ⁴³	Effect of oral eicosapentaenoic acid on weight loss in patients with pancreatic cancer	Nutrition and Cancer	2000	Medline / Cinahl / Zetoc / Internet
S21	Barber MD ⁴⁶	Metabolic response to feeding in weight-losing pancreatic cancer patients and its modulation by a fish-oil-enriched nutritional supplement	Clinical Science	2000	Medline / Zetoc / Internet
S22	Burns PC ³⁸	Phase I clinical study of fish oil fatty acid capsules for patients with cancer cachexia: Cancer and Leukemia Group B Study 9473	Clinical Cancer Research	1999	Medline / Embase / Internet
S23	Barber MD ⁴⁰	The effect of an oral nutritional supplement enriched with fish oil on weight loss in patients with pancreatic cancer	British Journal of Cancer	1999	Medline / Zetoc / Internet
S28	Wigmore SJ ³⁴	Down-regulation of the acute phase response in patients with pancreatic cancer cachexia receiving oral eicosapentaenoic acid is mediated via suppression of interleukin-6	Clinical Science	1997	Medline / Zetoc
S31	Wigmore SJ ³⁵	The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer	Nutrition	1996	Medline / Zetoc / Internet
S60	Barber MD ³⁶	Fish-oil enriched nutritional supplement attenuates progression of the acute-phase response in weight-losing patients with advanced pancreatic cancer	Journal of Nutrition	1999	Zetoc / Internet
S63	Burns CP ³⁹	Phase II study of-dose fish oil capsules for patients with cancer-related cachexia	Cancer	2004	Clinicaltrials.gov / Internet

STUDY ID	AUTHOR	TITLE	JOURNAL	YEAR	SOURCE
S71	Barber MD ⁹⁷	Eicosapentaenoic acid attenuates cachexia associated with advanced pancreatic cancer	International congress on...	1997	Zetoc
S79	Moses AWG ¹⁹	Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids	British Journal of Cancer	2004	Zetoc
S91	Gogos CA ⁴⁴	Dietary Omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy	Cancer	1998	Hand searching references

Appendix 6.6 Study quality assessment tool - guidelines

STUDY QUALITY ASSESSMENT TOOL - GUIDELINES

For each study, the following questions need to be answered:

1. Was the study described as randomised (this includes the use of words such as randomly, random, and randomisation)?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Scoring the answers:

- 1 point is allocated for each 'yes' answer
- 0 points are allocated for 'no' answers

Additional points can be allocated as follows:

Question 1

- An additional point can be allocated if the method to generate the sequence of randomisation was described and if it was appropriate

Question 2

- An additional point can be allocated if the method of double blinding was described and it was appropriate

Deduction of points can occur as follows:

Question 1

- A point can be deducted if the method of randomisation was described but it was inappropriate
- For example; patients allocated alternately, according to date of birth, or hospital number

Question 2

- A point can be deducted if the study was described as double blind but the method of blinding was inappropriate

1 Guidelines for assessment

1.1 Randomisation

A method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of

receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

2. Double blinding

A study must be regarded as double blind if the word 'double blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned.

3. Withdrawals and dropouts

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

4. Quality assessment

Once a total score for each study has been calculated, the quality of each study can be ascertained. A score of 3 and above will be considered as good quality study whereas a score below 3 will be regarded as a poor quality study.

Appendix 6.7 Study quality assessment tool

STUDY QUALITY ASSESSMENT TOOL

2 STUDY ID NUMBER _____

REVIEWER _____

QUESTION 1: Was the study described as randomised (this includes the use of words such as randomly, random, and randomisation)?

Select answer and specify reason for selection

SCORE

1
YES _____

1
NO _____

Has the method of randomisation been specified and is it appropriate?

1
YES _____

1
NO _____

Has the method of randomisation been specified and is it **IN**appropriate?

1
YES _____

1
NO _____

SCORE FOR Q1 _____

QUESTION 2: Was the study described as double blind?

Select answer and specify reason for selection

SCORE

1

YES

1

NO

Has the method of double blinding been described and is it appropriate?

1

YES

1

NO

Has the method of double blinding been described and is it **IN**appropriate?

1

YES

1

NO

SCORE FOR Q2 _____

QUESTION 3: Was there a description of withdrawals and dropouts?

1

YES

1

NO

SCORE FOR Q3 _____

TOTAL SCORE _____

STUDY QUALITY _____

Appendix 6.8 – The results of the study quality assessment of the included studies

Study ID	Question 1 score	Question 2 score	Question 3 score	TOTAL SCORE	QUALITY
S3	2	2	1	5	GOOD
S6	2	2	1	5	GOOD
S10	0	0	1	1	POOR
S13	0	0	1	1	POOR
S17	1	1	1	3	GOOD
S20	0	0	1	1	POOR
S21	0	0	0	0	POOR
S22	0	0	1	1	POOR
S23	0	0	0	0	POOR
S28	0	0	0	0	POOR
S31	0	0	0	0	POOR
S60	0	0	0	0	POOR
S63	0	0	1	1	POOR
S71	0	0	1	1	POOR
S79	2	2	0	4	GOOD
S91	1	0	0	1	POOR

Appendix number 6.9.1 –Data extraction: Characteristics of included trials

ID	POPULATION		INTERVENTION			OUTCOME MEASURES USED	DROP-OUT (%)	TRIAL PERIOD (wks)
	SIZE (n=#)(*)	TYPE	n-3 SUPPLE (n=#)(*)	n-3 ENRICHED NUTR SUPPLE (n=#)(*)	PLACEBO (n=#)(*)			
S3	200(110)	Pancreas		95(50)	105 (60)	Weight Body composition Dietary Intake Quality of life	15 (b/line) – 7.5% 8C ; 7E 52 (4wks) – 26% 27C ; 25E 90 (8wks) – 45% 45C ; 45E	8 weeks
S6	91(60)	Mixed	46 (30)		45 (30)	Appetite , Nausea Tiredness dietary intake weight Body composition functional status	16 – 35%	2 weeks
S10	20(18)	pancreas		20 (18)	No controls	Hormone and metabolic indicators weight	2 – 10%	3 weeks
S13	5(5)	pancreas	5 (5)		No controls	Weight Performance status Adverse effects	0%	8 weeks
S17	17 (7)	Mixed	9 (3)		8 (4)	Lipolysis Lipid oxidation Weight Dietary intake	10 (59%) 4C ; 6E	12 weeks

(*) represents the number of patients remaining at the end of the trial

ID	POPULATION		INTERVENTION			OUTCOME MEASURES USED	DROP-OUT (%)	TRIAL PERIOD (wks)
	SIZE (n=#)(*)	TYPE	n-3 SUPPLE (n=#)(*)	n-3 ENRICHED NUTR SUPPLE (n=#)(*)	PLACEBO (n=#)(*)			
S20	26 (14)	Pancreas	26 (14)		No controls	Anthropometry Body composition Performance status Toxicity , Dietary intake	5 – 4 wks (19%) 10 – 8wks (38%) 12 – 12 wks (46%)	12 weeks
S21	16	Pancreas		16	6 (baseline study)	Weight Body composition Energy expenditure Dietary intake	Not reported	3 weeks
S22	25 (22)	Mixed	25(22)		No controls	Weight Toxicity	3 – (12%)	8 weeks
S23	20 (13)	Pancreas		20 (13)		Anthropometry Body Composition Nutritional Intake , Appetite Energy Expenditure Acute Phase Response Performance Status	2 – 3wks (10%) 7 – 7wks (35%)	7 weeks
S28	6	Pancreas	6			APR	Not reported	4 weeks
S31	18	Pancreas	18			Weight Body composition Energy expenditure Acute phase response	0	3 months

(*) represents the number of patients remaining at the end of the trial

ID	POPULATION		INTERVENTION			OUTCOME MEASURES USED	DROP-OUT (%)	TRIAL PERIOD (wks)
	SIZE (n=#)(*)	TYPE	n-3 SUPPLE (n=#)(*)	n-3 ENRICHED NUTR SUPPLE (n=#)(*)	PLACEBO (n=#)(*)			
S60	36	Pancreas	N/A	18	18 – supportive care	Acute phase proteins Weight	Not reported	Not reported
S63	43 (10)	Mixed	43 (10)			Weight Quality of life	33 (76%)	1.2 months (median) 0.5 days – 3.1 months
S71	27 (9)	pancreas	27 (9)			Weight APR Energy expenditure	5 – 0 wks (18%) 0 – 4 wks (0%) 9 – 8 wks (33%) 11 – 12 wks (40%) 18 – 24 weeks (66%)	24 weeks
S79	24	Pancreas		9(7)	15(12)	Energy expenditure Weight Dietary Intake Body Composition	5 – 8 wks (21%)	8 weeks
S91	60	Mixed	30		30	Weight Cytokine production Performance Status	4 (6.25%)	40 days

(*) represents the number of patients remaining at the end of the trial

Appendix number 6.9.2.1 –Data extraction: Summarising the evidence – Population characteristics of the Treated group

STUDY ID	TREATED PATIENTS							
	Size before	Size after	M:F	Supple	Tumour Site	Age (yrs)	% wt loss (prior to trial)	Period of wt loss (mo)
S3	95	50	54:41	ENS	pancreas	67	17.9	6
S6	46	30	10:20	capsules	7 GU 2 Breast 2 unknown 11 GI 6 Lung 1 h&n 1 sarcoma	63±9.1	16.0±11	
S10	20	18	10:10	ENS	Pancreas	62	17.9	x
S13	5	5	x	capsules	pancreas	x	x	x
S17	9	3	8:1	capsules	4 GI 1 pancreas 1 rectal 1 renal 1 breast 1 lung	64	13±4	6
S21	16	x	10:6	ENS	Pancreas	63	17.7	x
S23	20	13	10:10	ENS	Pancreas	62	17.9	x
S28	6	x	5:1	Capsule	pancreas	58±5	12.7±3.2	7.3±1.7

STUDY ID	TREATED PATIENTS							
	Size before	Size after	M:F	Supple	Tumour	Age (yrs)	% wt loss	Period of wt loss (mo)
S31	18	18	x	capsules	pancreas	x	x	x
S20	26	14	12:14	capsules	pancreas	56	13	4
S22	25	22	12:10	capsules	4 pancreas 9 lung 2 cervical 1 sarcoma 1 rectal 1 breast 1 hepatocellular 1 renal 1 CLL 1 neuroendocrine	64	x	x
S60	18	x	x	ENS	Pancreas	64	17.9	x
S71	27	9	13:14	capsules	pancreas	58	14	4 mo
S79	9	7	6:3	ENS	pancreas	65	21	6 mo
S91	30	x	17:13	Capsule	6 breast 10 GI 5 lung 4 liver 5 pancreas	58±4	6.7±0.8 – 13.3 ± 0.7	x

STUDY ID	TREATED PATIENTS							
	Size before	Size after	M:F	Supple	Tumour	Agyrs)	% wt loss	Period of wt loss (mo)
S63	43	10	29:14	capsules	8 colorectal 9 lung 8 unknown 2 sarcoma 2 breast 2 gastric 2 renal 2 neuroendocrine 2 myelodysplastic 1 pancreas 1 anal 1 CLL 1 h&n 1 hepatic 1 myeloma	67	2.7	1

Appendix number 6.9.2.2 – Data extraction: Summarising the evidence – Population characteristics of the Control group

STUDY ID	CONTROL PATIENTS					
	Size before	Size After	M:F	age	% wt loss	Tumour
S3	105	60	56:49	68	17.1	Pancreas
S6	45	30	7:23	64.6±9.4	15.6±8	4 GU 4 breast 4 unknown 10 GI 5 lung 1 haematologic 2 sarcoma
S10	-	-	-	-	-	-
S13	-	-	-	-	-	-
S17	8	4	5:3	64±5	10±5	1 oeso 1 pancreas 1 breast 1 cervical 1 carcinoid 1 unknown 1 lung 1 mesothelioma
S20	-	-	-	-	-	-
S21	6	Baseline study only	3:3	54	0	none
S22	-	-	-	-	-	-
S23	-	-	-	-	-	-
S28	-	-	-	-	-	-
S31	-	-	-	-	-	-
S60	18	×	×	60	11.8	pancreas

S63	-	-	-	-	-	-
S71	-	-	-	-	-	-
S79	15	12	4:11	70	19	pancreas
S91	30	x	19:11	57±4	5.8±0.7 – 14.6±2.1	7 breast 11 GI 6 lung 3 liver 3 pancreas

Appendix number 6.9.3 – Details of the type and dose of EPA supplements used

STUDY ID	TYPE OF n-3 SUPPLEMENT USED	RECOMMENDED INTAKE PER DAY (grams EPA / d)	ACTUAL INTAKE PER DAY (grams EPA/ d)
S3	ENS	2 x 237ml of supplement / d – (2.2g EPA)	1.4 x 237ml / d - (1.54g EPA) (70% of recommendation)
S6	Capsules	18 x 1000mg capsules – (3.24g EPA)	Mean of 9.8 capsules per day (1.76g EPA) (54% of recommendation)
S10	ENS	2 x 237ml cans – (2.2g EPA)	1.25 – 2.0 cans per day, median – 1.9 cans per day (1.4 – 2.2g EPA ; median 2.1g EPA) (62.5 – 100% of recommendation – 95% median)
S13	95% EPA diester liquid emulsion	Dose escalation study 25ml emulsion/d (4.5g EPA) – 200ml emulsion (36g EPA) Dose increased over 8 weeks and then maintained	2 pts = 100ml/d (18g EPA) 1 pt = 150ml / (27g EPA) 2pts = 200ml/d (36g EPA) – 1 week only then reduced dose
S17	EPA 95EE	6g of EPA capsules	>90% compliance ~ > 5.4g EPA capsules
S20	>95% EPA capsules	1g/ d – week1 2g / d – week 2 4g/ d – week 3 6g/d – weeks 4 - 12	Not reported
S21	ENS	2 x 237ml cans – (2.2g EPA)	1.25 – 2.0 cans per day, median – 1.9 cans per day (1.4 – 2.2g EPA ; median 2.1g EPA) (62.5 – 100% of recommendation – 95% median)
S22	Capsules	0.1g/kg/d to start and escalated at 2 week intervals if tolerated	0.3g / kg / d was the MTD 0.113g EPA / kg / day

STUDY ID	TYPE OF SUPPLEMENT USED	RECOMMENDED INTAKE PER DAY (grams EPA / d)	ACTUAL INTAKE PER DAY (grams EPA / d)
S23	ENS	2 x 237 ml cans – (2.2g EPA)	1.2 – 2.0 cans per day, median – 1.9 cans per day 1.3 – 2.0g EPA, median 2.1g EPA
S28	>95% EPA capsules	1g/ d – week1 2g / d – week 2 4g/ d – week 3 6g/d – weeks 4 - 12	1g/ d – week1 2g / d – week 2 4g/ d – week 3 6g/d – weeks 4 - 12
S31	Capsules (MaxEPA)	2 – 16g fish oil (0.34 – 2.72g EPA) Dose escalated over 12 weeks	12g fish oil / day (2g EPA/d)
S60	ENS	2 x 240ml cans – (2.18g EPA)	Not reported
S63	Capsules	0.15g / kg – (0.067g EPA / kg)	0.15 – 0.2g / kg (0.067 – 0.086g EPA / kg / d)
S71	Capsules	1g/ d – week1 2g / d – week 2 4g/ d – week 3 6g/d – weeks 4 Maintenance dose – 6g/d EPA	All did dose escalation 5 x continued: 12 – 16g/d (2.2 – 2.9g EPA / d) 22 x continued: 12g / d (6g EPA / d)
S79	ENS	2 x 237ml cans / d (2.2g EPA)	1.9 x 237ml /d
S91	Capsules	18g fish oil / d (18 x 170mg EPA)	Not reported

Appendix 6.9.4 – Weight change

STUDY ID	INTERVENTION		WEIGHT (kg)						WEIGHT CHANGE (Median – kg)	COMMENT / EFFECT
			BEFORE		DURING		AFTER		Median kg	
			E	C	E	C	E	C		
	Experimental (E)	Control (C)								
S3	ENS	NS	60.3	61.4	60.05	61.03	59.8	60.66	E: -0.25 kg / mo C: -0.37 kg / mo	p = 0.74 Not significant Compared to the rates of weight loss at baseline – significant attenuation of wt loss at 4 & 8 wks (p < 0.001)
S10	ENS	-		-	-	-		-	Median wt gain of 1kg	Only change in weight reported
S21	ENS	-	55.2	-	-	-	56.2	-	Median wt gain of 1kg – 3wks	p = < 0.05 significant
S23	ENS	-	55.2	-	56.2	-	57.2	-	+1.0 – 3wks +2.0 – 7 wks	p = 0.024 p = 0.033 significant
S60	ENS	Supportive care	55.0	58.5					E: ↑ 1kg / 4 wk C: ↓ 2.8 kg / 4 wk	Significant More details requested but not received
S79	ENS	-							0.0	Not significant Details requested but not received
S28	Capsules	-								NOT MEASURED
S13	Emulsion	-								Not reported

STUDY ID	INTERVENTION		WEIGHT (kg)						WEIGHT CHANGE (Median – kg)	COMMENT / EFFECT
			BEFORE		DURING		AFTER		Median kg	
			E	C	E	C	E	C		
	Experimental (E)	Control (C)								
S6	Capsules	Olive oil	60.8	61.1	-	-	60.83	60.21	E: 0.03 ± 2.8 C: -0.89 ± 3.8	Not significant
S17	Capsules	Oleic acid capsules	67 ± 10	63 ± 10					Not measured due to high drop –out rate by end of trial, therefore unable to draw any conclusions	
S20	Capsules	-	66.8	-	66.0 – 4wks 65.2 – 8wks	-	65	-	0: -2.0 kg / mo 4: +0.5 kg / mo 8: +0.2 kg / mo 12: +0.3 kg / mo	p < 0.0005 significant
S22	Capsules	-	62	-	-	-	Not specified	-	Not specified	Weight change was significantly associated with time on treatment. P = 0.028
S31	Capsules	-	62	-	63	-	62	-	0.3 kg / mo	Not significant
S63	Capsules	-	64	-				-	↓ 0.8 kg	Significance not stated
S71	Capsules	-	68.8	-	66.0 – 4wks 65.2 – 8wks	-	64.5 – 12wks 62.2 – 24wks	-	0: -2.2 kg / mo 4: +0.75 kg / mo 8: +0.2 kg / mo 12: +0.3 kg / mo 24: +0.1 kg / mo	Significant rate of weight loss at 4wks, no significant change thereafter. Change in median body weight not significant either
S91	Capsules	Placebo							No change in body weight	More details requested but not received

Appendix 6.9.5.1 – Body composition - lean body mass

STUDY ID	INTERVENTION		BODY COMPOSITON (LBM –KG)						CHANGE IN LBM (kg)	COMMENT / EFFECT
			BEFORE		DURING		AFTER			
	Experimental (E)	Control (C)	E	C	E	C	E	C		
S6	Capsule	Olive oil	24	23.7	-	-	24.49	23.15	E: +0.49 ± 6.2 kg C: -0.55 ± 3.9 kg	Not significant
S3	ENS	NS	43.3	43.4	43.57	43.52	43.84	43.64	E: +0.27 kg / mo C: +0.12 kg / mo	p = 0.88 not significant
S21	ENS	-							median 0.75kg (+ 0.1 – 1.6kg)	Significant p < 0.05 Only change in LBM reported
S23	ENS	-	41.5	N/A	42.5	N/A	43.4	N/A	3 wk: +1.0 (0.6 ± 1.4) 7 wk: +1.9 (1.0 ± 3.0)	p = 0.0064 p = 0.0047 Significant changes
S79	ENS	NS							E: 0.3 kg C: 0.6 kg	NOT REPORTED
S10	ENS									NOT MEASURED
S13	emulsion									NOT MEASURED
S17	Capsules	Oleic acid								NOT MEASURED
S20	Capsules	-								NOT MEASURED
S22	Capsules	-								NOT MEASURED
S28	Capsules	-								NOT MEASURED
S31	Capsules	-								NOT MEASURED
S60	Capsules	Supp care								NOT MEASURED
S63	Capsules	-								NOT MEASURED
S71	Capsules	-								NOT MEASURED
S91	Capsules	Placebo								NOT MEASURED

Appendix 6.9.5.2 – Body composition - Fat mass

STUDY ID	INTERVENTION		BODY COMPOSITON (FM – % / kg)						CHANGE IN FM (kg)	COMMENT / EFFECT
			BEFORE		DURING		AFTER			
	Experimen tal (E)	Control (C)	E	C	E	C	E	C		
S21	ENS	-	28.1%	-			28.1%	-	Unchanged 0.0 kg	Not significant
S23	ENS	-	14.5 kg	-	14.3 kg	-	14.7 kg		3 wk: -0.2 (-0.8 ± 0.9) 7 wk: +0.2 (-0.8 ± 2)	Not significant
S6	Capsule	Olive oil							Measured but no details reported	
S10	ENS	-								NOT MEASURED
S60	ENS	Supp care								NOT MEASURED
S3	ENS	NS								NOT MEASURED
S79	ENS	NS								NOT MEASURED
S13	emulsion	-								NOT MEASURED
S17	Capsules	Oleic acid								NOT MEASURED
S20	Capsules	-								NOT MEASURED
S22	Capsules	-								NOT MEASURED
S28	Capsules	-								NOT MEASURED
S31	Capsules	-								NOT MEASURED
S63	Capsules	-								NOT MEASURED
S71	Capsules	-								NOT MEASURED
S91	Capsules	Placebo								NOT MEASURED

Appendix 6.9.5.3 – Body composition - % body water

STUDY ID	INTERVENTION		BODY COMPOSITON (% body water)						CHANGE IN % BODY WATER	COMMENT / EFFECT
			BEFORE		DURING		AFTER			
	Experimental (E)	Control (C)	E	C	E	C	E	C		
S20	Capsules	-	50.9	-	49.5(4) 49.3(8)	-	49.1(12)	-	-1.8%	Not significant
S31	Capsules	-	56	-	55	-	55	-	0 / 1mo / 3mo	Not significant
S23	ENS	-	52.9	-	53.0	-	52.8	-	3wk: +0.1 (-0.3 ± 1.9) 7wk: -0.1 (-0.4 ± 1.5)	Not significant
S6	Capsules	Olive oil							Measured but no details reported	
S3	ENS	NS								NOT MEASURED
S10	ENS	-								NOT MEASURED
S21	ENS	-								NOT MEASURED
S60	ENS	Supp care								NOT MEASURED
S79	ENS	NS								NOT MEASURED
S13	emulsion	-								NOT MEASURED
S17	Capsules	Oleic acid								NOT MEASURED
S22	Capsules	-								NOT MEASURED
S28	Capsules	-								NOT MEASURED
S63	Capsules	-								NOT MEASURED
S71	Capsules	-								NOT MEASURED
S91	Capsules	Placebo								NOT MEASURED

Appendix 6.9.6 – Energy expenditure

STUDY ID	ASSESSMENT TOOL USED	INTERVENTION		2.1.1 REE (kcal/d / kcal / kg /d)						COMMENT / EFFECT
				BEFORE		DURING		AFTER		
		Experimental (E)	Control (C)	E	C	E	C	E	C	
S21	Indirect Calorimetry	ENS	-	1354 / 23.9	-			1295 / 23.5	-	<i>p</i> > 0.1 Significant <i>p</i> < 0.05
S23	Indirect Calorimetry	ENS	-	1339 / 24.2	-	1303 / 24	-			<i>p</i> = 0.18 Significant <i>p</i> = 0.025
S79	Indirect Calorimetry	ENS	NS	1387				1386		- 1 kcal / d <i>p</i> < 0.05
S17	Indirect Calorimetry	Capsules	Oleic acid	- / 22.3	- / 23.4	- / 22.5	- / 23.8			NO CHANGE
S31	Indirect Calorimetry	Capsules		- / 25	-	- / 24	-	- / 26	-	0 / 1 / 3 mo Not significant
S71	Indirect Calorimetry	Capsules	-	1815 / 23.4	-	1570 / 22.8				<i>p</i> = 0.17 0 / 1 mo Not significant <i>p</i> = 0.15
S3		ENS	NS							NOT MEASURED
S10		ENS	-							NOT MEASURED
S60		ENS	Supp Care							NOT MEASURED
S6		Capsules	Olive oil							NOT MEASURED
S13		Emulsion	-							NOT MEASURED
S20		Capsules	-							NOT MEASURED
S22		Capsules	-							NOT MEASURED
S28		Capsules								NOT MEASURED
S63		Capsules	-							NOT MEASURED
S91		Capsules	Placebo							NOT MEASURED

Appendix 6.9.7.1 - Dietary intake - energy intake

STUDY ID	ASSESS TOOL USED	INTERVENTION		DIETARY INTAKE (kcal / day)						CHANGE IN INTAKE (kcal/d)	COMMENT / EFFECT
				BEFORE		DURING		AFTER			
				E	C	E	C	E	C		
		Experimental (E)	Control (C)								
S3	3 day food diaries	ENS	NS	1504	1613	-	-	1281	1237	E: -223 C: -376	$p \leq 0.001$ $p \leq 0.001$
S23	3 day food diary	ENS		1450	-	1798 (3 wks)	-	-	-	+372 (median)	$p = 0.0016$ Significant increase
S79	3 day diet dairy	ENS	NS	1574	1814	-	-	2048	1980	474	$p < 0.05$
S6	3 day food records	Capsules	Olive oil	1386	1349	-	-	-	-	E: 51 C: -57	Not significant Not significant
S17	Diet records	Capsules	Oleic acid	1964 ± 634	1459 ± 485	-	-	2098.6 ± 765	1546.2 ± 374	E: 134.6 C: 87.2	7 Day period
S20	Not specified	Capsules	-	1777	-	1828	-	-	-	+51	
S21	3 day food diary	ENS									Details not reported
S10		ENS	-								NOT MEASURED
S60		ENS	Supp care								NOT MEASURED
S13		Emulsion	-								NOT MEASURED
S22		Capsules	-								NOT MEASURED
S28		Capsules	-								NOT MEASURED
S31		Capsules	-								NOT MEASURED
S63		Capsules									NOT MEASURED
S71		Capsules									NOT MEASURED
S91		Capsules	Placebo								NOT MEASURED

Appendix 6.9.7.2 – Dietary intake - protein intake

STUDY ID	ASSESS TOOL USED	INTERVENTION		DIETARY INTAKE (g/day)						CHANGE IN INTAKE (g/d)	COMMENT / EFFECT
				BEFORE		DURING		AFTER			
		Experimental (E)	Control (C)	E	C	E	C	E	C		
S3	3 day food diaries	ENS	NS	60	63	-	-	52	46	E: -8 C: -17	$p \leq 0.05$ $p \leq 0.001$
S79	3 day diet diary	ENS	NS	57	73	-	-	84	77	27	$p < 0.05$
S6	Visual analog scale 3 day food records	Capsules	Olive oil								NOT MEASURED Details not available
S10		ENS	-								NOT MEASURED
S21	3 day food diary	ENS	-								NOT REPORTED
S23	3 day food diary	ENS	-		-		-	-	-		NOT MEASURED
S60		ENS	Supp care								NOT MEASURED
S13		Emulsion	-								NOT MEASURED
S17	Diet records	Capsules	Oleic acid								NOT MEASURED
S20		Capsules	-		-		-	-	-		NOT MEASURED
S22		Capsules	-								NOT MEASURED
S28		Capsules	-								NOT MEASURED
S31		Capsules	-								NOT MEASURED
S63		capsules	-								NOT MEASURED
S71		Capsules	-								NOT MEASURED
S91		Capsules	Placebo								NOT MEASURED

Appendix 6.9.8 – Appetite

STUDY ID	ASSESS TOOL USED	INTERVENTION		APPETITE						CHANGE IN APPETITE (median)	COMMENT / EFFECT
				BEFORE		DURING		AFTER			
		Experimental (E)	Control (C)	E	C	E	C	E	C		
S6	VAS	Capsules	Olive oil	57.5	66.5					E:-9.8 C:-9.0	Not significant Details not reported
S23	Numerical rating scale	ENS	-	5	-	6 (3wk)	-	6 (7wk)	-		3wk: <i>p</i> = 0.001 significant 7wk: not significant
S3		ENS	NS								NOT MEASURED
S10		ENS	-								NOT MEASURED
S13		Emulsion	-								NOT MEASURED
S17		capsules	Oleic acid								NOT MEASURED
S20		capsules	-								NOT MEASURED
S21		ENS	-								NOT MEASURED
S22		Capsules	-								NOT MEASURED
S28		Capsules	-								NOT MEASURED
S31		Capsules	-								NOT MEASURED
S60		ENS	Supp care								NOT MEASURED
S63		Capsules	-								NOT MEASURED
S71		Capsules	-								NOT MEASURED
S79		ENS	NS								NOT MEASURED
S91		Capsules	Placebo								NOT MEASURED

Appendix 6.9.9 – Functional status

ID	ASSESSMENT TOOL USED	INTERVENTION		FUNCTIONAL STATUS SCORE						CHANGE	COMMENT / EFFECT
				BEFORE		DURING		AFTER			
		Experimental (E)	Control (C)	E	C	E	C	E	C		
S3	Karnofsky (0-100)	ENS	NS	74.9	73.9						Not significant – 4 & 8 wks not reported
S79	Physical Activity Level (PAL =TEE/REE)	ENS								E: 0.18 C: 0.01	Only change reported
S23	Karnofsky (0-100)	ENS	-	85	-	95	-	95	-	3wks: +10 7wks: +10	p = 0.0047 p = 0.046
S6	Karnofsky (0-100) EFAT (0-30)	Capsules	Olive oil	69.7 4.9	63.3 5.8	- -	- -	69.7 5.2	56.4 6.0	E:0.0 ;C:-6.9 E: 0.2 ; C:0.3	Change not significant Change not significant
S13	Karnofsky (0-100)	Emulsion	-								NOT REPORTED
S20	WHO Performance status	Capsules	-	1	-	1(4wk) 1(8wk)	-	0	-		Not significant
S63	FAACT FACT-G	Capsules	-							3.3 (-140 – 18.2) 1.9 (-7.8 – 13.5)	Only change reported
S91	Karnofsky (0-100)	Capsules	Placebo	77 / 51	72 / 54			- / 72	- / -	NOT REPORTED	Well nourished / malnourished Significant increase in malnourished group
S10		ENS	-								NOT MEASURED
S21		ENS	-								NOT MEASURED
S60		ENS	Supp care								NOT MEASURED
S17		Capsules	Oleic acid								NOT MEASURED
S22		Capsules	-								NOT MEASURED
S28		Capsules	-								NOT MEASURED
S31		Capsules	-								NOT MEASURED
S71		Capsules	-								NOT MEASURED

Appendix 6.9.10 – Acute phase response

ID	MEASUREMENT	INTERVENTION		CRP (mg /L)						COMMENT / EFFECT
				BEFORE		DURING		AFTER		
		Experimental (E)	Control (C)	E	C	E	C	E	C	
S23	Serum CRP	ENS	-	10	-	10(3wk)	-	10(7wk)	-	No change / Not significant
S60	Serum CRP	ENS	Supportive care	<5	11					Only baseline data reported
S17	Serum CRP	Capsules	Oleic acid	37	37	-	-	41	31	Not significant
S20	Serum CRP	Capsules	-							Not specified – only no. with increased CRP levels stated
S28	Serum CRP	Capsules	-	11.0	-		-	0.8(4wk)		Significant change
S31	Serum CRP	Capsules	-	15	-	10(4wk)	-	16(12wk)	-	4 wk: p < 0.002 12 wk: not significant
S71	Serum CRP	Capsules	-							B/Line: 36% ↑ 4wk:25%↑ CRP (p> 0.05) 12wk: 37% ↑ CRP Changes in CRP levels were significantly negatively correlated with changes in weight (r= -0.28, p< 0.04)

ID	MEASUREMENT	INTERVENTION		CRP (mg /L)						COMMENT / EFFECT
				BEFORE		DURING		AFTER		
		Experimental (E)	Control (C)	E	C	E	C	E	C	
S3		ENS	NS							NOT MEASURED
S79		ENS	NS							NOT MEASURED
S10		ENS	-							Although ARP measured, no CRP
S21		ENS	-							NOT MEASURED
S13		emulsion	-							NOT MEASURED
S6		Capsules	Olive oil							NOT MEASURED
S22		Capsules	-							NOT MEASURED
S63		Capsules	-							NOT MEASURED
S91		Capsules	Placebo							CRP NOT MEASURED

Appendix 6.9.11 – Adverse effects and quality of life

STUDY ID	ASSESSMENT TOOL USED	INTERVENTION		QUALITY OF LIFE SCORE				ADVERSE EFFECTS	EFFECT
				BEFORE		AFTER			
		Experimental (E)	Control (C)	E	C	E	C		
S3	<i>EuroQol EQ – 5D index Eurocol EQ – 5D vas EORTC – QLQ-C30 EORTC – QLQ – C30</i>	<i>ENS</i>	<i>NS</i>					<i>None reported</i>	<i>Q of L NOT reported</i>
S6		Capsules						Belching x 2 Nausea x2 Vomiting x 1 Constipation x 1	Q of L NOT MEASURED
S13		Capsules						Sensation of fullness x3 Steatorrhea x2 Nausea x 1 Abdominal pain x 2	Q of L NOT MEASURED
S20		Capsules	-					Nausea x3 Steatorrhea x2 Taste Others – not specified	Q of L NOT MEASURED
S22		Capsules	-					Taste x 10 Body smell x 6 Belching x 15 Flatulence x 9 Nausea x 2 Diarrhoea	Q of L NOT MEASURED

STUDY ID	ASSESSMENT TOOL USED	INTERVENTION		QUALITY OF LIFE SCORE				ADVERSE EFFECTS	EFFECT
				BEFORE		AFTER			
		Experimental (E)	Control (C)	E	C	E	C		
S23		ENS	-					Steatthorea x 3	Q of L NOT MEASURED
S31		Capsules	-					Taste Diarrhoea	Q of L NOT MEASURED
S63	FAACT	Capsules						Nausea x11 Taste x19 Belching x9 Flatulence x9 Emesis x8 Diarrhoea x7 Body smell x4 Dyspepsia x2	Q of life not reported
S60		ENS						Not reported	Q of L NOT MEASURED
S10		ENS						NOT REPORTED	Q of L NOT MEASURED
S21		ENS						NOT REPORTED	Q of L NOT MEASURED
S79		ENS						NOT REPORTED	Q of L NOT MEASURED
S28		Capsules	-					NOT REPORTED	
S71		Capsules						NOT REPORTED	Q of L NOT MEASURED
S91		Capsules						NOT REPORTED	Q of L NOT MEASURED
S17		Capsules						NOT REPORTED	NOT MEASURED